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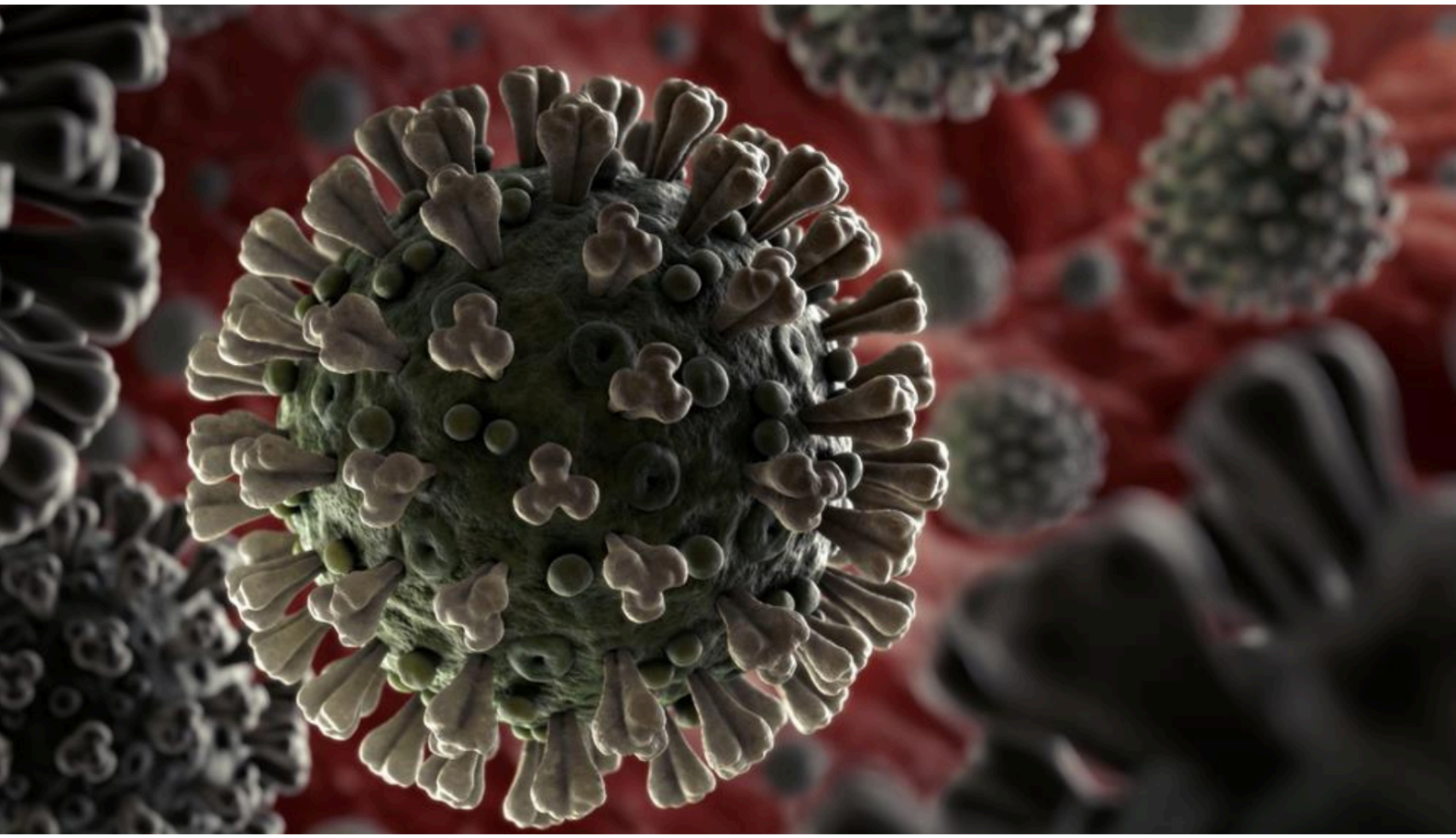

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3D Vector Reconstruction of the Atlas from Anatomical Sections of Korean Visible Human at the Laboratory of Clinical and Digital Anatomy of Paris Descartes University

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Abstract
Aim: Carry out a 3D vector reconstruction of the atlas from the anatomical sections of the "Korean Visible Human" for educational purposes. Material and methods: The anatomical subject was a 33-year-old Korean man who died of leukemia. It measured 164 cm and weighed 55 kg. This man donated his body to science. Her body was frozen and cut into several anatomical sections after an MRI and CT scan. These anatomical sections were made using a special saw called a 0.2 mm thick cryomacrotome. Thus 8,100 cuts were obtained. Only the sections numbered 780 to 860 were used for our study. A segmentation by manual contouring of the different parts of the atlas was done using the software Winsurf version 3.5 on a laptop PC running Windows 7 equipped with a Ram of 8 gigas. Results: Our 3D vector model of the atlas is easy to manipulate using the Acrobat 3DPDF interface. The atlas accessible in a menu can be displayed, hidden or made transparent, and 3D labels are available as well as educational menus for learning anatomy. Conclusion: This original work constitutes a remarkable educational tool for the anatomical study of the atlas and can also be used as a 3D atlas for simulation purposes for training in therapeutic gestures.

Keywords: 3D Vector Modelling, Atlas, Digital Anatomy, Korean Visible Human

1. Introduction

Training in human anatomy is essential at all stages of medical practice: clinical examination, interpretation of medical images and surgery are based on knowledge of the anatomy of the human body. The acquisition of these skills is first theoretical then practical with dissection. Unfortunately, the provision of subjects for this stage of

learning by dissection remains problematic, in general in the countries of the South and in particular in Mali, sometimes letting certain professionals start their careers with little experience in this field.

Sectioned images of the human body are very useful because of their high resolutions and natural colors compared to CT scans and magnetic resonance imaging (Ackerman *1990)*. The images available include those from the Visible Human Project (VHP, male and female) conducted in the United States (Ackerman *1990)*; the Chinese human "Visible" (CVH, man and woman) (Cho Z. 2009); the Chinese virtual human (VCH, man and woman) (Cho, Calamate & al 2012.); and the Korean “Visible” woman (VK; whole male body, male head, and female pelvis) (Chung, Shin, Brown P & al *2015*).

The sectioned images of the VHP, CVH and VK males were used in several ways: for the creation of atlases (Dai, Chung, Qu & al *2012*), navigation software (Kim, Choi, Jeong & al *2008*) ; (Park, Chung, Shin & al *2013*) and the virtual dissection software (Park, Chung, Hwang & al *2005*) and allowed access free and free to three-dimensional models in PDF atlas files (Park, Chung, Hwang & al *2005*). In addition, cross-sectional images of VK have been used so that the radiology dose conversion coefficients are calculated virtually (Park, Chung, Hwang & al *2006*). However, the use of prepared female sectioned images has been limited for the following reasons:
- In VHP images, degeneration of the uterus and ovaries was observed because the subject was post-menopausal (59 years), and the lateral edges of the two arms could not be used due to the subject's overweight.
The image quality was not optimal due to the limited performance of the digital camera and the personal computer used (Park, Chung, Shin & al *2009*) ; (Quackenbush, Ratiu, Kerr & al 1996)
- In addition to this, gaps in the images appeared in the digital atlases.

In CVH and VCH images, small pixel size images (> 0.1 mm) and 24 bits color were made, but the colors of the living body could not be represented because a fixative had been injected into the body and a red dye was infused into the arteries (Schiemann, Freudenberg, Pflesser & al *2000*). If there were high-quality sectional images of a whole male body, they would be very useful, like images of female bodies.

It is in this context that we initiated this work which is part of our science thesis on 3D vector reconstruction of the ventral region of the neck from anatomical sections of Korean Visible Human (KVH). This article deals with the 3D vector reconstruction of the atlas that is part of the cervical region.

2. Materials and Methods

Our study was carried out in the Development Research, Imaging and Anatomy Unit (URDIA) EA 4465 in the Clinical and Digital Anatomy laboratory of the University of Paris Descartes.

The anatomical sections of a 33-year-old Korean man who died of leukemia who donated his body were made in 2010 after an MRI and CT scan. A cryomacrotome made it possible to make cuts of 0.2 mm thick on the frozen body, ie 8,100 cuts. (Figure 1)

Only the sections numbered 780 to 860 were used for our study (Figure 2).

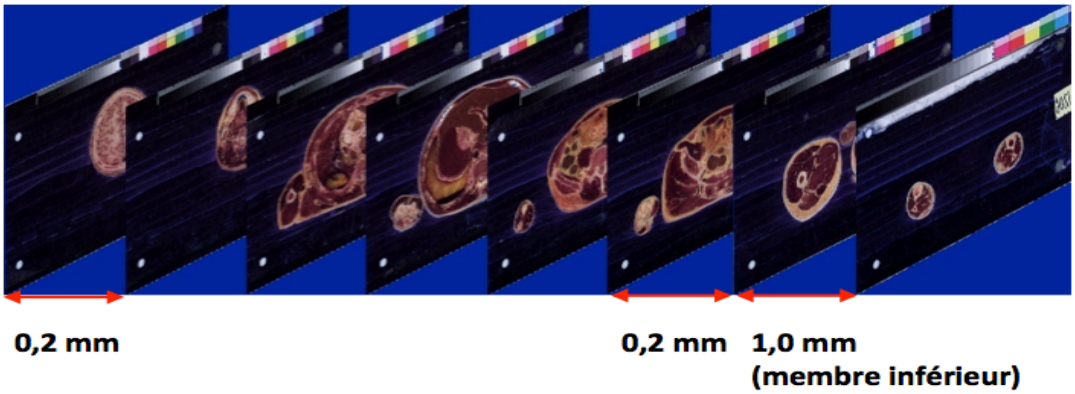

Figure 1: showing photographs of KVH anatomical sections

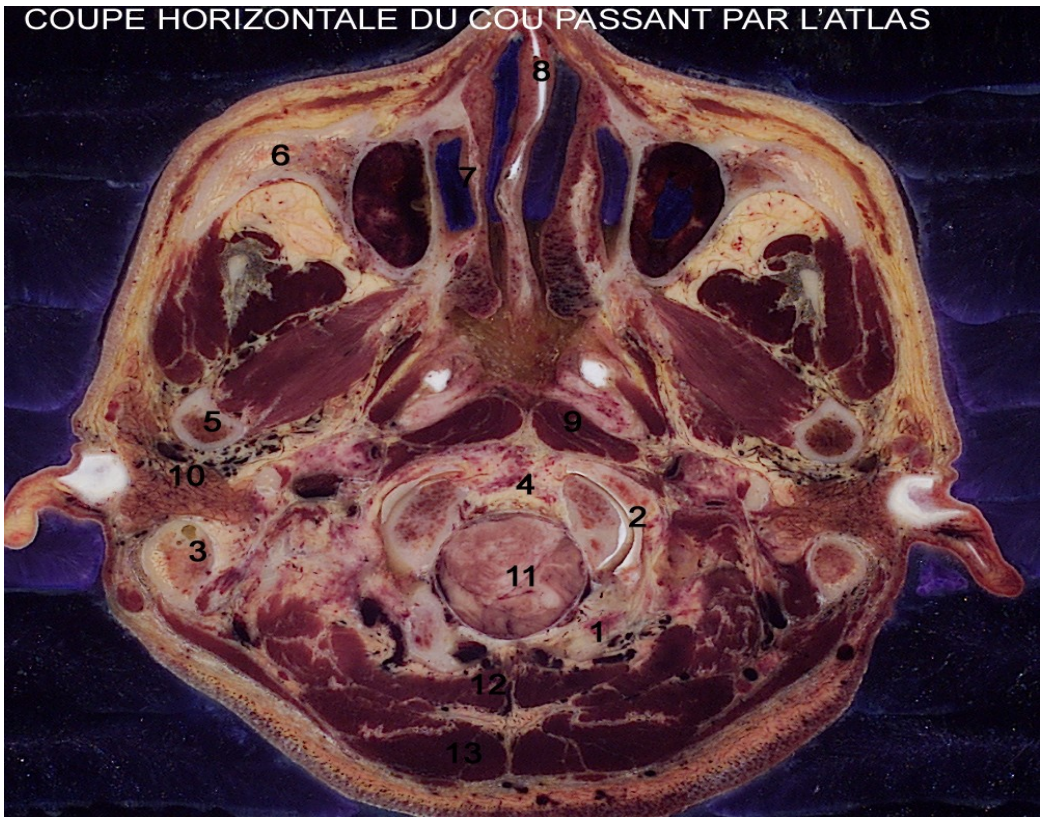

Figure 2: horizontal anatomical section passing through the first cervical vertebra or atlas

1. Occipital; 2. Occipito-atloid joint ; 3. Mastoid process; 4. Upper extremity of the odontoid process; 5. Mandible, 6. Zygomatic process 7. Nasal cavity; 8. Partition of the nasal cavity; 9. Anterior rectus muscle 10. Parotid gland; 11. Elongated marrow; 12. Semi-spiny muscle of the head; 13. Trapezius muscle.

A segmentation by manual contouring of the different parts of the atlas was done using the software Winsurf version 3.5 on a laptop PC running Windows 7 with a Ram of 8 gigas (Figure 3)

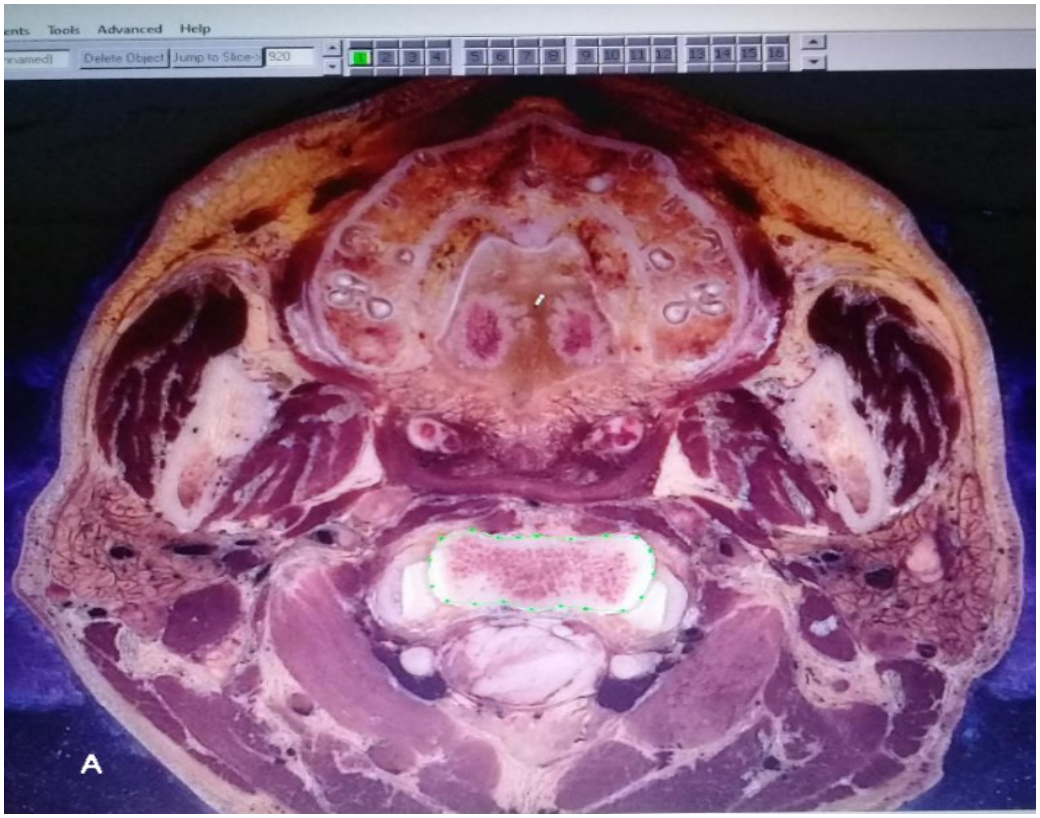

Figure 3: contouring the atlas on an anatomical section (2D) from Winsurf using the "pencil".

3. Result

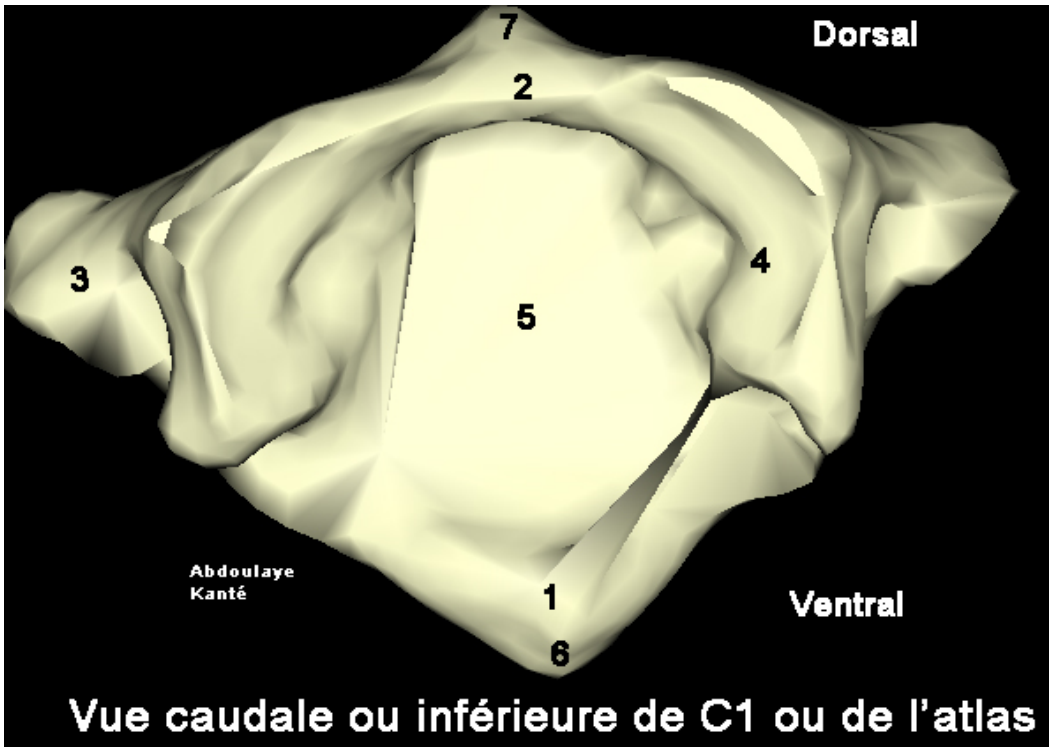

Figure 4: 3D vector reconstruction of the atlas with Winsurf software: caudal view

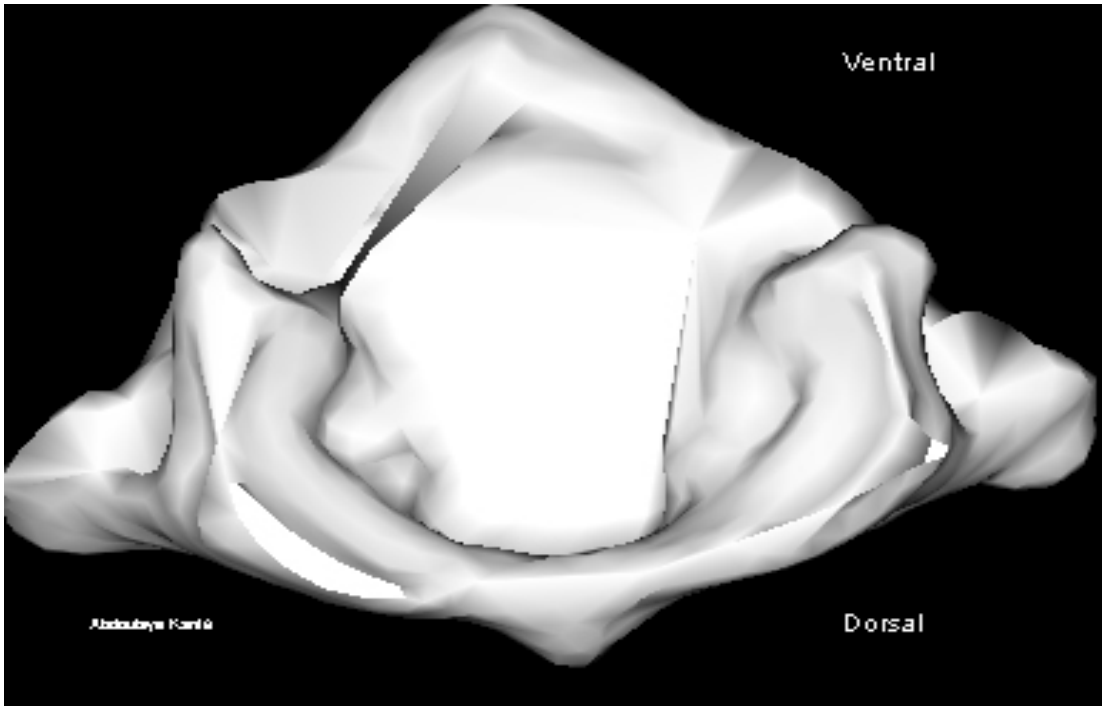

Figure 5 3D vector reconstruction of the atlas with Winsurf software cranial view

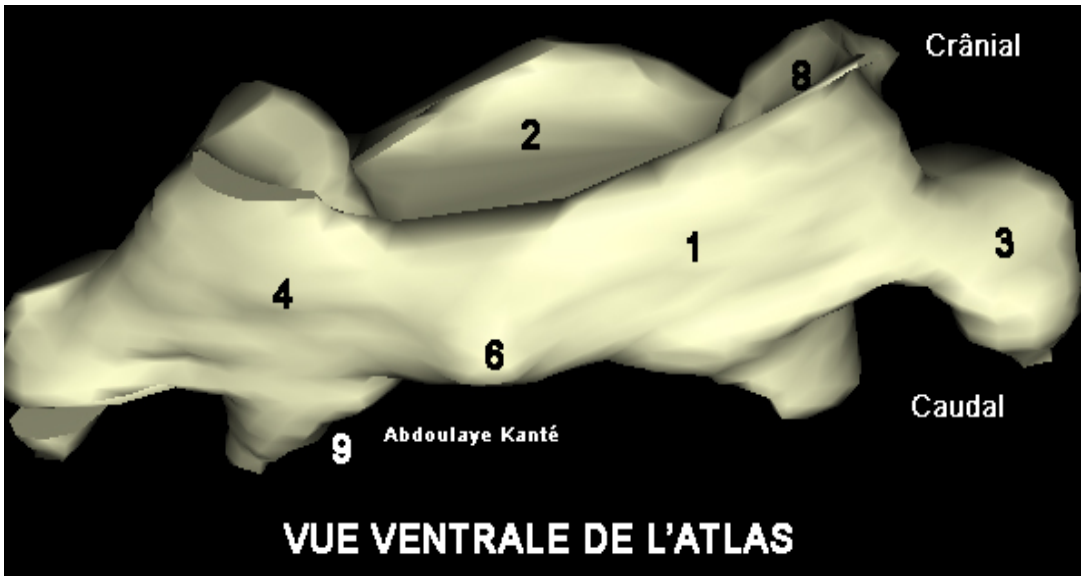

Figure 6 :3D vector reconstruction of the atlas with Winsurf software :ventral view

1.Belly arch; 2. Dorsal arch; 3. Transversal process; 4. Lateral weights; 5. Vertebral foramen; 6. Belly tuber; 7. Back tubercle; 8. Cranial articular facet; 9. Caudal articular facet.

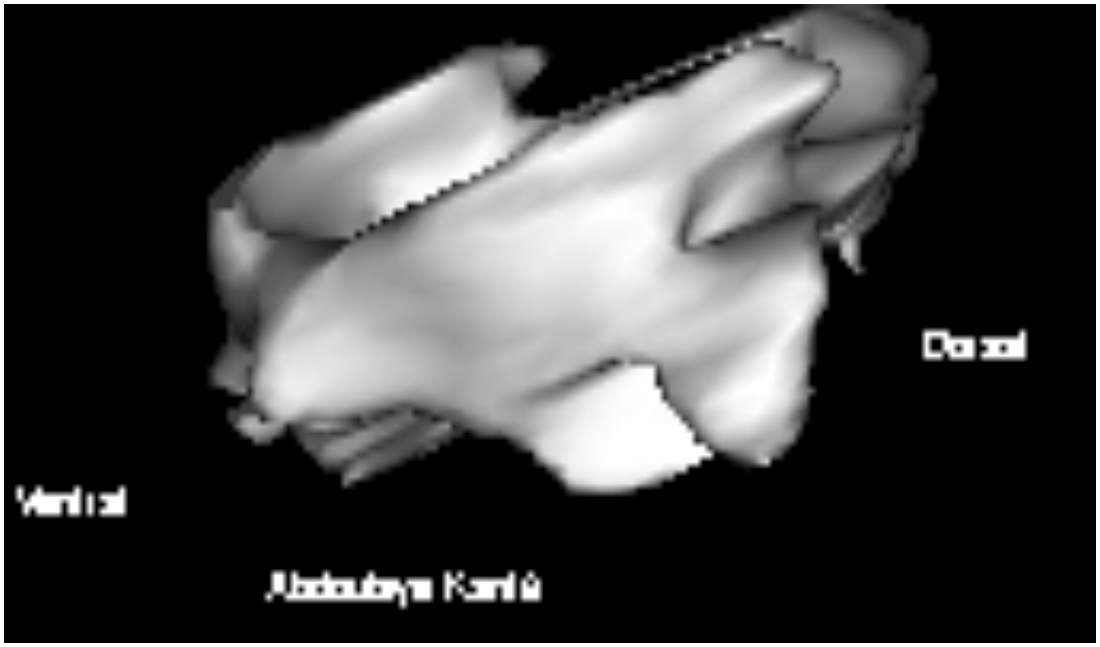

Figure 7 : D vector reconstruction of the atlas with Winsurf software : lft side view

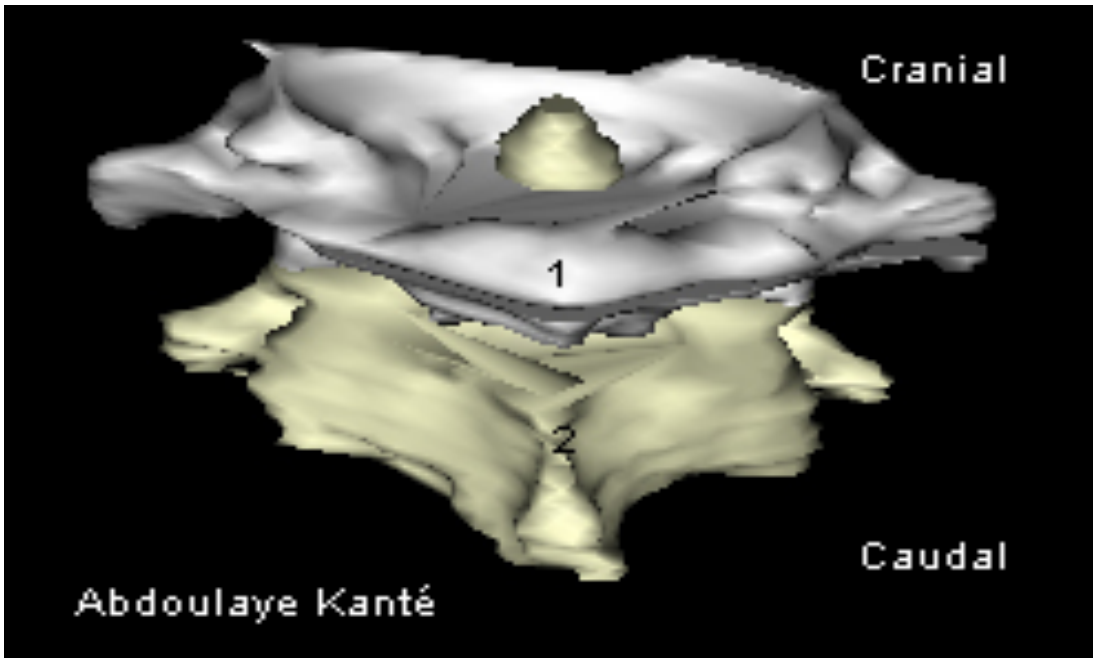

Figure 8 : 3 vector reconstruction of the atlas articulated with the axis with the Winsurf software :dorsal view

1. Atlas ; . Axis

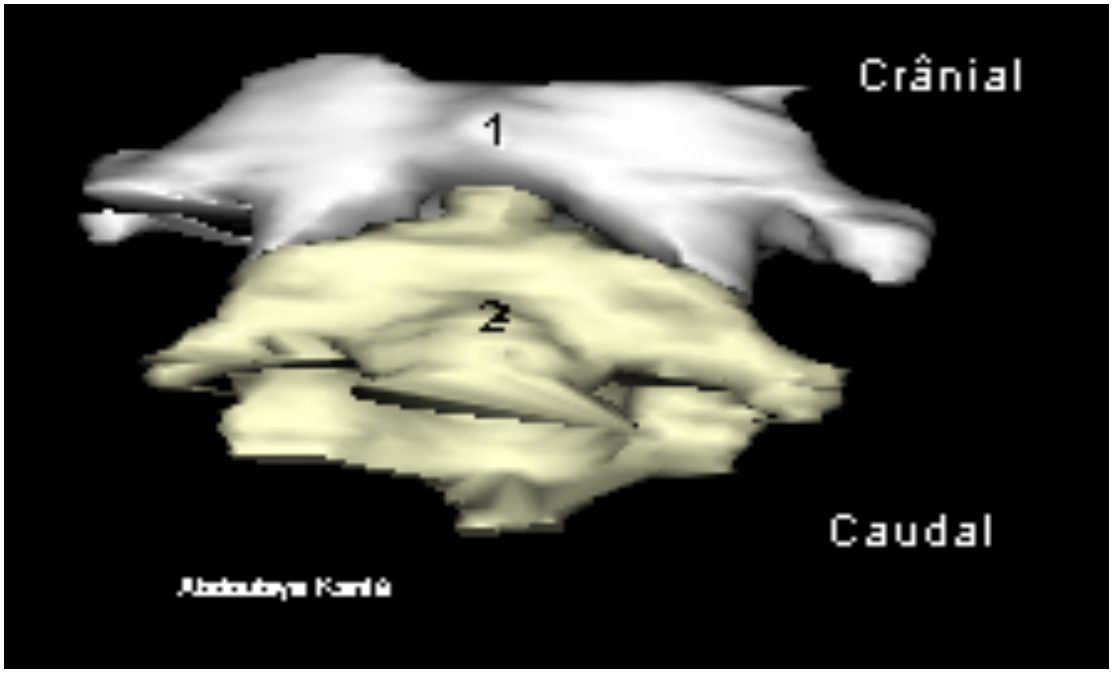

Figure 9 :3D vector reconstruction of the atlas articulated with the axis with the Winsurf software ventral view

1. Atlas 2. Axis

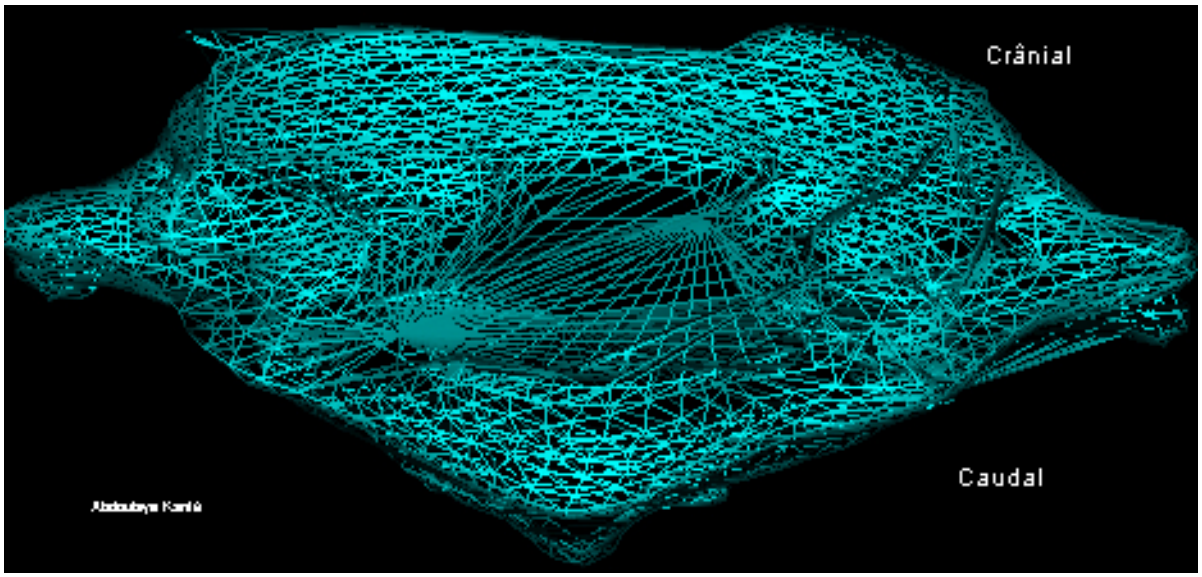

Figure 10 :3D vector reconstruction of the atlas articulated with the axis with the Winsurf software wireframe representation

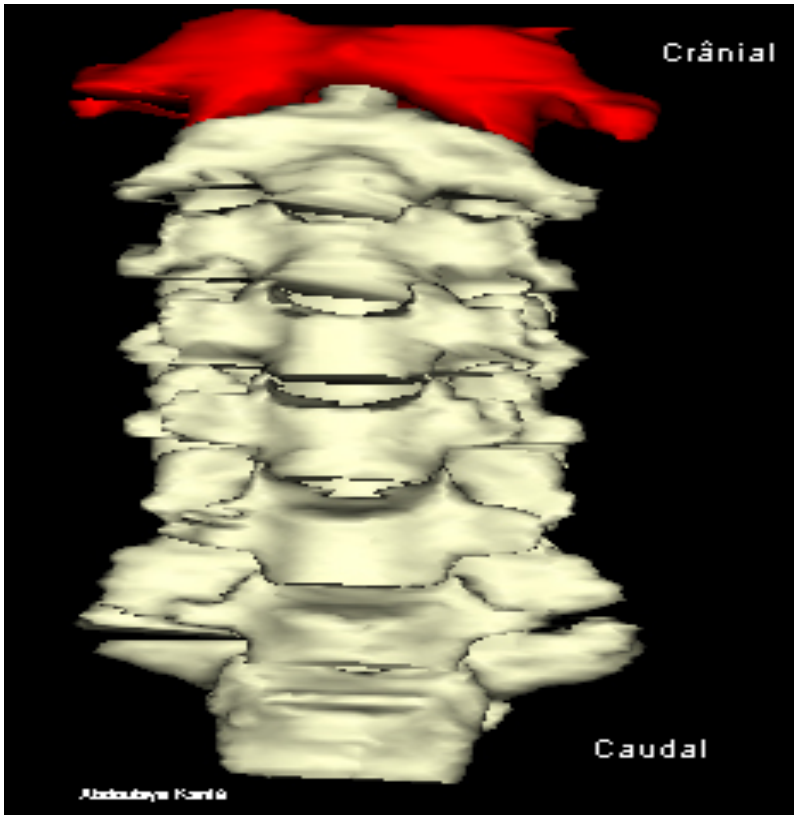

Figure 11 3D vector reconstruction of the atlas in red with the other cervical vertebrae with Winsurf software :ventral view

4. Discussion

This article was made from the anatomical sections of Korean Visible Human in order to achieve in the best possible way, a dynamic and detailed 3D atlas of the atlas.

Our work t,herefore c,onsisted in recognizing the anatomical structures of the atlas on these sections and in a more tedious work of contouring in order to obtain the most realistic models possible. Our methodology is quite similar to that of the Korean team, which used segmentation instead of manual contouring. (Figure 12)

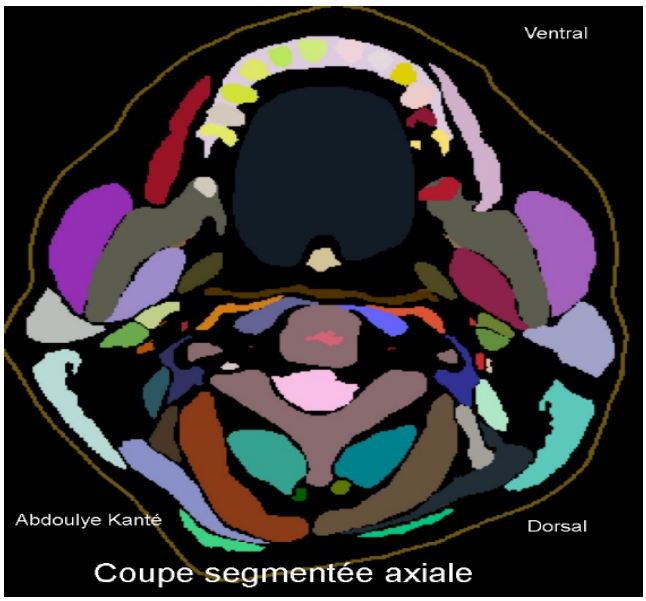

Figure 1 : segmented section used by the Korean team

The advantage of this work is essentially based on the fact that the entire contouring work and therefore the entire 3D vector reconstruction of the atlas, was carried out using real sections of the human body. This results in a major increase in the precision and reliability inherent in the results presented above.

Indeed, reconstructions of the atlas from digital procedures such as CT scans can prove to be somewhat disappointing in the sense that certain structures are absent and others that are difficult to distinguish. In contrast to this process, this contouring work is based on a manual, analog segmentation process under our supervision and not that of an automaton, which reduces the risk of anatomical errors in reconstruction.

The second advantage is based on the fact that better precision as well as the possibility of individualization of the different parts of the atlas favors a massive application in the university field thus participating in a better understanding by medical students and other fields. In addition, it is essential to underline that this application is not restricted to the university field but can also be the support of a “Surgical Training” thus allowing a continuous training of the surgeons and a fortiori an improvement of their aptitude in their practices daily.

Finally, it is clear that "Winsurf" and Acrobat 3D PDF are particularly easy to use software which is not the case with other 3D modeling and manual segmentation software. In addition, they offer fairly wide ranges of textures which further increase the realism that we can bring to our final work.

Although the "Winsurf" software made it possible to reproduce the typical cervical vertebra fairly faithfully, there are nevertheless some shortcomings.

The main disadvantage of this software is the time required to achieve the desired result. Indeed, this is a tedious contouring work of several months on several anatomical sections where sometimes only the section-by-section analysis was possible. To this are added the various objects that had to be created in order to be able to individualize the edges of the atlas, which increased the number of cuts to which it was necessary to return each time.

Unfortunately, there is no miracle cure allowing a reduction of this working time if it is not a great motivation and an unprecedented personal investment.

Conclusion

Our 3D vector modeling of the atlas is a remarkable educational tool for teaching the anatomy of the atlas and can also be used as a 3D atlas for simulation purposes for training in therapeutic gestures.

Conflicts of interest :
The authors do not declare any conflict of interest concerning the publication of this document.

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Combined Effects of Fatigue Indicators on the Health and Wellbeing of Workers in the Offshore Oil Industry

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Abstract
Offshore workers are exposed to a unique combination of factors that may impact negatively on well-being. This paper describes results from a survey of fatigue, health and injury amongst seafarers and installation personnel working in the UK sector of the offshore oil industry. Potential stressors and fatigue- related variables (e.g. noise, working hours, and shift) were considered in terms of their combined effects on subjective outcome measures. Median splits of these variables were summed to create a 'total fatigue indicators' score. A quartile split of this variable was entered into a series of analyses of covariance (ANCOVA), co-varying age, education and socio-economic status (SES) and stratifying for occupational group (i.e. seafarers or installation personnel). Total fatigue indicators demonstrated a linear effect on depression, cognitive failures, social functioning, lack of/poor quality sleep, fatigue, and the home-work interface. Effects were more pronounced amongst installation personnel than seafarers. This is possibly due to fundamental differences in shift systems between the two groups of offshore workers. No significant effects were observed for injury frequency, prescribed medication or smoking and alcohol consumption. Results suggest that exposure to a combination of stressors has a significantly greater negative effect on health than any of these factors in isolation.

Keywords: Psychology, Occupational Medicine, Epidemiology, Fatigue; Combined Effects

1. Introduction

The purpose of the present paper is to describe a survey that was carried out to determine the extent of fatigue and poor health offshore. The term 'offshore' refers in this instance, to all personnel employed in the UK sector of the offshore oil industry, who work tours of duty between two and four weeks in length, either on installations or on support and supply vessels. It was hoped that this might provide some indication, not just of injury likelihood, but of chronic problems that may occur as a result of working in an offshore environment.

Extreme weather conditions, noisy working environments and demanding work and rest patterns may all contribute to fatigue and poor health offshore (Parkes 1997, 1998). Furthermore, major economic, structural and technological changes have taken place within the industry in recent years, often resulting in reduced manning, increased workload and job insecurity (e.g. Collinson 1998). All of these factors, either alone or in combination, may have a negative impact on the health and well-being of offshore workers.

A number of studies of stress and health offshore have been undertaken in recent years, yet fatigue is rarely examined specifically. Furthermore, surveys are for the most part limited to offshore installation personnel. What is apparent from the self-reported data however, is that increased workload, long hours, poor quality or lack of sleep and boredom do indeed contribute to poor mental health and fatigue offshore (Parkes 1997, Parker et al. 1997). However, some studies have failed to demonstrate significantly poorer levels of health amongst installation personnel, and have therefore concluded that they are no worse off than their onshore counterparts (Gann et al. 1990).

The current survey was designed to identify all aspects of the working environment that may impact on the health and general well-being of personnel employed in all sectors of the offshore oil industry. By drawing comparisons between installation workers and seafarers, it is hoped that risk factors inherent in these diverse occupations can be reduced, and in some cases eliminated. Previous research (e.g. Smith et al. 2000, 2001) has shown the relationship between exposure to one or more occupational hazards (e.g. noise, shift work) and poor health to be linear. In light of this, the purpose of the present analyses was to examine the impact of workplace factors in combination, as individuals in an offshore environment are likely to be exposed to a number of negative factors at any one time.

2. Material and methods

2.1 Survey Content

The main aim of the survey was to assess the work and rest patterns of seafarers and offshore installation workers. More specifically, to assess the extent to which working hours, shift patterns and time spent offshore were associated with fatigue, accidents and injuries, and poor physical and mental health of crewmembers. The questionnaire was designed to encompass all aspects of life offshore. It was divided into the following three sections:

1.Offshore**:** included questions relating specifically to work patterns, and subjective measures of attitudes towards work.

2. On leave: included subjective measures of health, wellbeing and health-related behaviours such as eating, drinking, smoking and exercise.

3. Life in general: included a number of standardised scales of wellbeing, such as the General Health Questionnaire (GHQ: Goldberg 1972), the Profile of Fatigue-Related Symptoms (PFRS: Ray 1991), the Cognitive Failures Questionnaire (CFQ: Broadbent et al. 1982) and the MOS Short Form Health Questionnaire (SF-36: Ware et al. 1993).

2.2 Participants/Procedure

The questionnaire was distributed to the home addresses of members of the seafaring officer's union, NUMAST and the installation worker's union, MSF. Secondly, questionnaires were distributed to seafarers onboard offshore oil support vessels operating in the UK sector, by visiting researchers. A short version of the questionnaire was sent to a group of onshore workers, as a control for items specifically relating to fatigue. Results were also compared with normative data from three other sources: a sample of 93 onshore workers who participated in a study of workplace stressors, (Smith et al. 2001), a random sample (N=8092) of the working population taken from the Welsh Health Survey (The National Assembly for Wales 1998), and data (N=3220) from the Bristol Health and Safety at Work Study (All three control groups served as comparative norms for scores on the health and well-being scales, e.g. GHQ, CFQ, SF-36 - Smith et al. 2000).

2.3 Response rate

1600 questionnaires were sent out to NUMAST members and 563 were returned (35.2% response rate). 1800 questionnaires were sent to MSF members and 388 were returned (21.6% response rate). 53 questionnaires were returned by offshore support crew and 93 questionnaires were sent to onshore controls and 71 were returned (76.3% response rate).

3. Results

Potential stressors and fatigue related variables (e.g. high levels of noise, long working hours and rotating versus fixed shifts) were considered in terms of their combined effects on outcome measures (i.e. subjective reports of physical and psychological health). ANCOVAs were carried out on offshore groups only as the sample size in the onshore control group was deemed insufficient.

3.1 Statistical Methods

Median splits of potential stressors were examined in pairs [Where 1=1ow exposure, 2=high exposure.], and summed to create a 'total fatigue indicators score'. These comprised 'number of hours worked per week', and the following working hours and physical hazards variables: night work, shift work, unsociable hours, breathing fumes/harmful substances, touching/handling harmful substances, ringing in the ears, background noise, vibration and motion sickness [Responses to all working hours and physical hazards variables were scored from 1-4: 1=never,2=seldom, 3=sometimes, 4=often.]. Median splits of the following items relating to job demand [Taken from Siegrist's Effort-Reward Imbalance Model (1996): 1=Not at all distressed, 4=Very distressed.] were also included:

- 'I have constant time pressure due to a heavy workload'
- 'I have many interruptions and disturbances in my job'
- 'I have a lot of responsibility in my job'
- 'I am often under pressure to work overtime'
- 'I have experienced or expect to experience an undesirable change in my work'
- 'My job promotion prospects are poor'
- 'My job security is poor' and
- 'I am treated unfairly at work'

Shift schedule was split into two categories (i.e.'fixed or rotating') as was shift length (i.e. 'long' versus 'short'). These items were also included in the 'total fatigue indicators score'. A quartile split of this composite variable was then entered into a series of analyses of co-variance (ANCOVA) co-varying age, education and socio- economic status (SES) and stratifying for occupational group (i.e. seafarers or installation personnel).

3.2 Descriptive Statistics

The seafarers had a mean age of 43.7 years (s.d.=9.55), the installation workers 45.6 years (s.d.=7.8) and the onshore controls 39.2 years (s.d. = 12.29). The seafarers and installation workers did not differ in terms of marital status or education. Over 75% of the seafarers were in senior ranks compared to 20% of the installation workers. This is not surprising as the seafarers were contacted through the officers' union. The shift systems and the work hours of the seafarers and installation workers are shown in Table 1.

3.3 Shift Systems

There were several major differences in the work and leave systems reported by seafarers and installation workers. For example, the most common work/leave cycle for seafarers is the 4 weeks-on, 4 weeks-off cycle. However, less than 1% of workers on offshore installations work this system. Over 3/4 of installation personnel work a 2 weeks-on, 2-weeks off schedule. Furthermore, seafarers appear more likely than installation personnel to work fixed shifts.

3.4 Work Hours

There were also significant differences in work hours within these shift systems: more than twice as many installation respondents as seafarers work 12-hour shifts. As the nature of seafaring often demands personnel to 'keep watch', 6 hours-on, 4-off and 4-on, 4-on and 8-off systems are common. However, despite these differences in shift patterns between the two offshore groups, both report significantly higher weekly hours than onshore workers. It is also evident that offshore personnel tend to do more hours of overtime per day than onshore workers (N.B. mean additional daily hours were higher still in the seafaring group than amongst installation workers).

Table 1: Shift systems and working hours

	Seafarers %	Installation workers %	Control Group %
4 week schedule	65.7	0.8	-
2 week schedule	1.2	78.1	-
12 hour shifts	41.4	87.5	-
Fixed shifts	75.1	48.5	-
>60 hours a week	93.0	93.3	5.8
3-5 hours overtime	24.5	17.8	9.8
2-3 days to adjust	50.1	43.6	-
12 hours on 12 off	41.4	86.9	-
6 hours on 6 off	22.4	12.4	-
4 hours on 8 off	18.1	-	-
4hours on 4 off	0.2	-	-

3.5 Adjustment to Shift Systems and Work Hours

A significant proportion of respondents in both offshore groups reported feeling 'below par' on returning to their vessel/installation after a period of leave, although this was more marked in the case of installation workers (reported by 44.6% as opposed to 25.2% of seafarers). Furthermore, approximately half of all respondents felt that adjusting to life offshore took at least 2-3 days. Perhaps of more concern, is the fact that 45.1% of seafarers and 63.7% of installation workers felt their performance to be affected during this period of adjustment.

3.6 *Mental and Physical Fatigue*

Table 2 shows the percentage of workers in each group who reported feeling very or extremely tired at the end of their working day.

Table 2: Mental and physical fatigue of the different groups of workers

	Mentally tired (very/extremely) %	Physically tired (very/extremely) %
Seafarers	52	39
Installation workers	62	52
Control group	48	54

As is evident from the graph, those who work in an offshore environment are more likely to report feeling mentally tired at the end of the working day than onshore workers. This pattern was reversed for physical tiredness.

3.7 Fatigue-Related Incidents

The percentage of respondents who report being involved in at least one fatigue-related incident was highest amongst installation workers (reported by12.9% of respondents, as compared to 6.6% of seafarers and 10.1% of controls). However, the proportion of respondents reporting involvement in 3-4 fatigue-related incidents was very similar across all three groups.

3.8 Further Analysis: Analyses of covariance

Where pairs of stressors were examined in combination, there was evidence to suggest that exposure to two hazards resulted in reduced wellbeing compared to exposure to a single hazard. However, this was not the case for all combinations studied. If one takes GHQ scores as an example of a typical outcome variable, there were no additive effects of background noise and night work (main effect of noise: $F[1, 849] = 15.34, p<.0001$), background noise and unpredictable hours (main effect of noise: $F[1, 845] = 15.26$, $p<.0001$) night work and exposure to hazards (main effect of hazards: $F[1, 848] = 5.78$, $p<.02$), night work and level of responsibility (main effect of responsibility: $F[1, 848] = 30.35$, $p<.0001$) and night work and unfair treatment (main effect of unfair treatment: $F[1, 849] = 48.65$, $p<.0001$).

However, additive effects were observed for the following example pairings: 'long/unsociable working hours' and noise (Workhours: $F[1, 842] = 17.56$, $p<.0001$; Noise: $F[1, 842] = 8.76$, $p<.0001$) and shift schedule and time pressure (Shift: $F[1, 789] = 4.27$, $p<.04$; Time pressure: $F[1, 789] = 29.68$, $p<.0001$). Table 3 shows the mean GHQ scores for each of these groups.

Table 3: Mean GHQ scores (s.d.s in parentheses) for different combinations of hazards

Noise and working hours	Low noise/low hours	Low noise/high hours	High noise/low hours	High noise/high hours
	1.13 (2.22)	1.51 (2.34)	1.66 (2.56)	2.55 (3.15)
Shifts and time pressure	Fixed shift/low pressure	Rotating shift/low pressure	Fixed shift/high pressure	Rotating shift/high pressure
	1.14 (2.21)	1.54 (2.34)	2.08 (2.80)	2.99 (3.33)

The means in Table 3 suggest a linear relationship between combinations of hazards and mental health. In order to further test this, and to determine whether greater variance in wellbeing could be explained, a 'total fatigue indicators score' was calculated across all possible hazards.

3.9 *Total Fatigue Indicators Score*

Significant effects of the composite fatigue indicators score were found on virtually all subjective measures of health and well-being, including mental health (GHQ Score $F[1, 739] = 35.38$, $p<.0001$), cognitive failures (CFQ $F[1,723] = 29.62$, $p<.0001$), fatigue (PFRS fatigue $F[1, 732] = 43.37$, $p<.0001$), physical functioning (SF-36 physical functioning $F[1, 735] = 5.55$, $p<.0001$), social functioning (SF-36 social functioning $F[1, 732] = 36.32$, $p<.0001$), job stress ($F[1, 732] = 53.38$, $p<.0001$), life stress ($F[1, 737] = 7.17$, $p<.0001$), lack of sleep ($F[1, 735] = 25.66$, $p<.0001$), poor quality sleep ($F[1, 739] = 34.31$, $p<.0001$), physical ($F[1, 745] = 31.32$, $p<.0001$) and mental fatigue ($F[1, 744] = 38.93$, $p<.0001$), and aspects of the home-work interface, including: 'problems at work make you irritable at home' ($F[1, 728] = 9.55$, $p<.0001$) and 'job takes up too much energy' ($F[1, 731] = 34.65$, $p<.0001$). Means and standard deviations for the outcome measures are shown in Table 4.

Table 4: Mean outcome scores (sds in parentheses) for the 4 quartiles of the total fatigue indicators score (high scores = reduced wellbeing apart from social functioning where high scores = better wellbeing)

Outcome	1st Quartile	2nd Quartile	3rd Quartile	4th Quartile
GHQ	0.59 (1.28)	1.25 (2.09)	2.22 (2.75)	3.17 (3.44)
CFQ	32.50 (11.85)	36.62 (11.79)	40.40 (13.20)	44.13 (13.65)
SF-36 Social Functioning	94.31 (14.14)	88.24 (17.67)	80.10 (22.16)	72.62 (22.68)
Poor quality sleep	1.97 (0.75)	2.36 (0.83)	2.55 (0.86)	2.80 (0.88)

Job stress	1.95 (0.78)	2.40 (0.94)	2.64 (0.90)	3.08 (0.95)
Physical Fatigue	2.08 (0.62)	2.32 (0.65)	2.50 (0.66)	2.72 (0.68)
Mental fatigue	2.22 (0.66)	2.55 (0.67)	2.77 (0.64)	2.93 (0.71)
Irritable at home due to problems at work	1.32 (0.50)	1.53 (0.60)	1.76 (0.60)	1.67 (0.65)

3.10 Injuries and Health-Related Behaviours

No significant effects of the total fatigue indicators score were observed for injury frequency, use of prescribed medication or smoking and alcohol consumption.

3.11 Occupational group

Installation workers were significantly worse for the following outcomes: GHQ (Occupational Group: $F[1, 711] = 25.28$, $p<.0001$), SF-36 social functioning ($F[1, 709] = 10.46$, $p<.001$), PRFS fatigue ($F[1, 709] = 11.94$, $p<.001$), physical fatigue ($F[1, 720] = 6.42$, $p<.01$), mental fatigue ($F[1,720] = 13.02$, $p<.0001$), job stress ($F[1, 708] = 4.42$, $p<.04$), life stress ($F[1, 712] = 8.25$, $p<.004$), lack of sleep ($F[1, 720] = 25.07$, $p<.0001$),'problems at work make you irritable at home' ($F[1, 704] = 30.18$, $p<.0001$) and 'job takes up too much energy' ($F[1, 704] = 37.69$, $p<.0001$).

3.12 *Demographics*

Functioning on the following measures was found to deteriorate with age: CFQ (F 1, 706] = 6.52, $p<.01$), SF-36 physical functioning ($F[1, 712] = 24.99$, $p<.0001$) and physical fatigue ($F[1, 720] = 5.09$, $p<.01$). Low socio-economic status was associated with increased life stress ($F[1, 712] = 4.51$, $p< .03$), mental fatigue ($F[1, 720] = 3.95$, $p<.05$) and 'problems at work make you irritable at home' ($F[1, 704] = 4.81$, $p<.03$). Low educational status negatively influenced mental fatigue only ($F[1, 720] = 4.18$, $p<.04$).

3.13 *Summary of Findings*

These results suggested that physical and psychosocial hazards in the offshore environment combine additively to produce a linear effect on a wide range of health and wellbeing outcome measures. Furthermore, this effect was more marked when a range of stressors were combined additively (as opposed to studying pairs of hazards). They did not however, appear to demonstrate these effects on health-related behaviours or injury frequency. The pattern of significance suggested that installation workers were worst off on the majority of outcome measures (as compared to both seafarers and onshore norms), and not surprisingly, that cognitive ability and physical functioning deteriorate with age.

4. Discussion

These results clearly demonstrate that exposure to a combination of workplace stressors has a significantly greater negative impact on subjective measures of health and well-being than any one 'hazard' in isolation. Furthermore, installation workers appear worse off in terms of wellbeing than their seafaring counterparts. This may be explained in part by the differences in shift systems between the two groups: installation workers tend to work fast rotating as opposed to fixed shifts, which have previously been demonstrated to be the most detrimental shift pattern in terms of health and performance (e.g. Wilkinson, 1992). This idea requires further clarification however: future research in the area might therefore wish to investigate this issue.

There are a number of problems inherent in the type of methodology used in this study. It was not possible to determine causal relationships from a cross- sectional survey. Although the results suggest

that working in an offshore environment is detrimental to health, the possibility that poor health may lead to a more negative perception of working patterns cannot be ruled out. Individual differences such as negative affectivity may create reporting biases amongst those who seem to be most affected. These difficulties could be overcome in future by employing longitudinal or intervention studies, although an approach of this nature might prove difficult to implement from a practical point of view. Co-varying negative affectivity may provide a more suitable alternative (see Smith et al. 2001).

As part of a research project examining fatigue and health amongst the seafaring population (Smith et al. 2001), onboard studies of the relationships between working patterns and objective performance, sleep and physiological parameters were carried out. It is hoped that this approach will lead to a clearer picture of the effects of life offshore on the workforce, which will enable policy makers and commercial organisations to follow a common standard of best practice.

The current research highlights the potential for fatigue in an offshore environment. Although it was not clear in this instance what the consequences of this might be in terms of injury and accident causation, future research should seek to examine this link as the environmental, financial and personal costs of such a causal relationship are potentially devastating. It is already clear that a revision of working practices within the industry would greatly improve the wellbeing of the workforce.

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3D Vector Reconstruction of the Brain from Anatomical Sections of Korean Visible Human at the Laboratory of Clinical and Digital Anatomy of Paris Descartes University

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Abstract
Aim: Carry out a 3D vector reconstruction of the brain from anatomical sections of the "Korean Visible Human" for educational purposes. Material and Methods: The anatomical subject was a 33-year-old Korean man who died of leukemia. It measured 164 cm and weighed 55 kg. This man donated his body to science. Her body was frozen and cut into several anatomical sections after an MRI and CT scan. These anatomical sections were made using a 0.2 mm thick cryomacrotome. Thus 8,100 cuts were obtained. Only the sections numbered 500 to 700 were used for our study. Manual contouring of the different parts of the brain was done using Winsurf version 3.5 software on a laptop PC running Windows 7 with an 8-gigabyte Ram. Results: Our 3D vector model of the brain is easily manipulated using the Acrobat 3DPDF interface. The different brain parts accessible in a menu can be displayed, hidden or made transparent, and 3D labels are available as well as educational menus for learning anatomy. Conclusion: This brain reconstruction constitutes a remarkable educational tool for the anatomical study of the brain and can also be used as a 3D atlas for simulation purposes for training in therapeutic gestures.

Keywords: Three-Dimensional Anatomy, Korean Human Visible, Brain Modeling, Virtual Reality, 3D Reconstruction, Virtual Dissection, Surgical Simulation, Surgical Training

1. Introduction

Training in human anatomy is essential at all stages of medical practice: clinical examination, interpretation of medical images and surgery are based on knowledge of the anatomy of the human body. The acquisition of these

skills is first theoretical then practical with dissection. Unfortunately, the provision of subjects for this stage of learning by dissection remains problematic, in general in the countries of the South and in particular in Mali, sometimes letting certain professionals start their careers with little experience in this field.

Sectioned images of the human body are very useful because of their high resolutions and natural colors compared to CT scans and magnetic resonance imaging (Ackerman *1990)*. The images available include those from the Visible Human Project (VHP, male and female) conducted in the United States (Ackerman *1990)*; the Chinese human "Visible" (CVH, man and woman) (Cho Z. 2009); the Chinese virtual human (VCH, man and woman) (Cho, Calamate & al 2012.); and the Korean "Visible" woman (VK whole male body, male head, and female pelvis) (Chung, Shin, Brown P & al *2015*).

The sectioned images of the VHP, CVH and VK males were used in several ways: for the creation of atlases (Dai, Chung, Qu & al *2012*), navigation software (Kim, Choi, Jeong & al *2008*) ; (Park Chung, Shin & al *2013*) and the virtual dissection software (Park, Chung ,Hwang & al *2005*) and allowed access free and free to three-dimensional models in PDF atlas files (Park, Chung, Hwang & al *2005*). In addition, cross-sectional images of VK have been used so that the radiology dose conversion coefficients are calculated virtually (Park, Chung, Hwang & al *2006*). However, the use of prepared female sectioned images has been limited for the following reasons:
- In VHP images, degeneration of the uterus and ovaries was observed because the subject was post-menopausal (59 years), and the lateral edges of the two arms could not be used due to the subject's overweight.

The image quality was not optimal due to the limited performance of the digital camera and the personal computer used (Park, Chung, Shin & al *2009*) ; (Quackenbush, Ratiu, Kerr & al 1996)
- In addition to this, gaps in the images appeared in the digital atlases.
In CVH and VCH images, small pixel size images (> 0.1 mm) and 24 bits color were made, but the colors of the living body could not be represented because a fixative had been injected into the body and a red dye was infused into the arteries (Schiemann, Freudenberg, Pflesser & al *2000*). If there were high-quality sectional images of a whole male body, they would be very useful, like images of female bodies.
It is in this context that we initiated this work in order to reconstruct the brain from the anatomical sections of Korean Visible Human (KVH).

2. Materials and Methods

Our study was carried out in the Development Research, Imaging and Anatomy Unit (URDIA) EA 4465 in the Clinical and Digital Anatomy laboratory of the University of Paris Descartes.
The anatomical sections of a 33-year-old Korean man who died of leukemia who donated his body were made in 2010 after an MRI and CT scan. A cryomacrotome made it possible to make cuts of 0.2 mm thick on the frozen body, ie 8,100 cuts. (Figures 1)

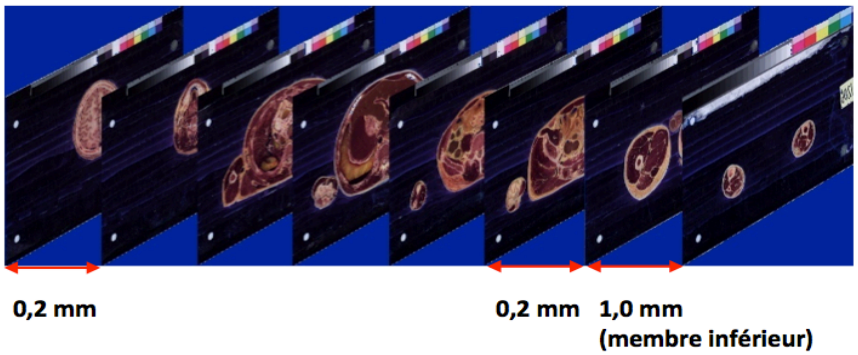

Figure 1: showing photographs of KVH anatomical sections

Only the sections numbered 500 to 700 were used for our study (Figure 2).

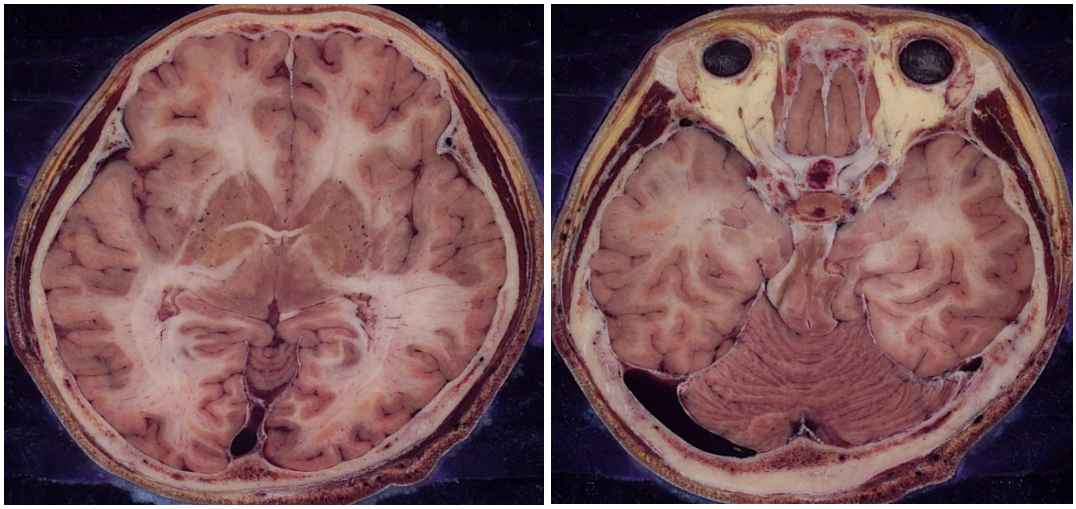

Figure 2 horizontal anatomical sections (2D) passing through the brain**.**

A segmentation by manual contouring of the different parts of the brain was done using the software Winsurf version 3.5 on a laptop PC running Windows 7 with an Ram of 8 gigas (Figure 3)

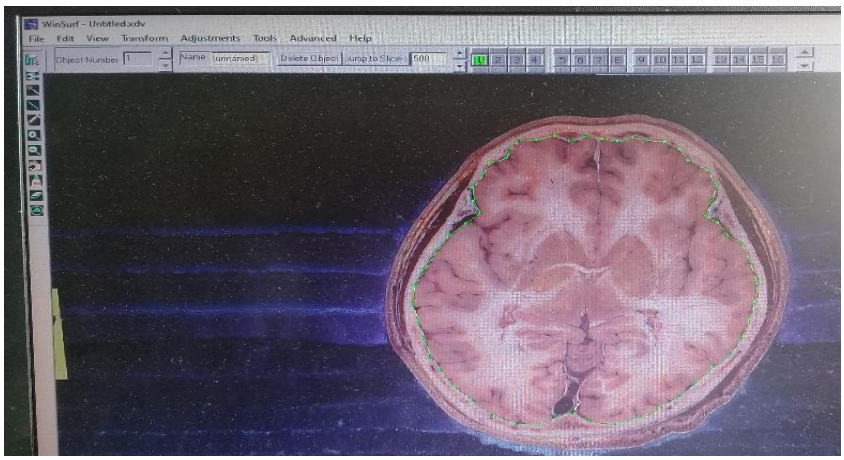

Figure 3: interface screen of the Winsurf® software (version 3.5) to draw the limits of the brain (green line and dots) on anatomical section number 500. This is done with the pen tool using the green channel.

3. Result

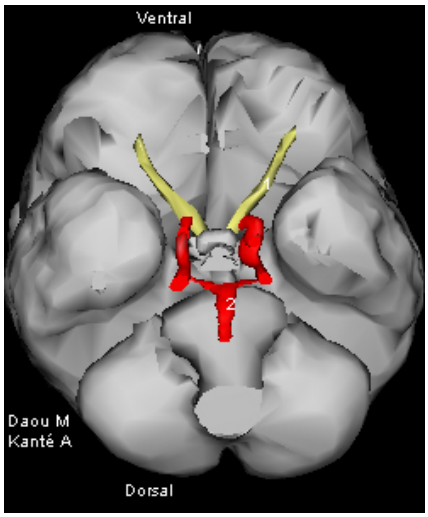

Figure 4 3D vector reconstruction of the brain showing the optic nerves (1) and the arterial circle of the brain (2) with Winsurf software caudal view

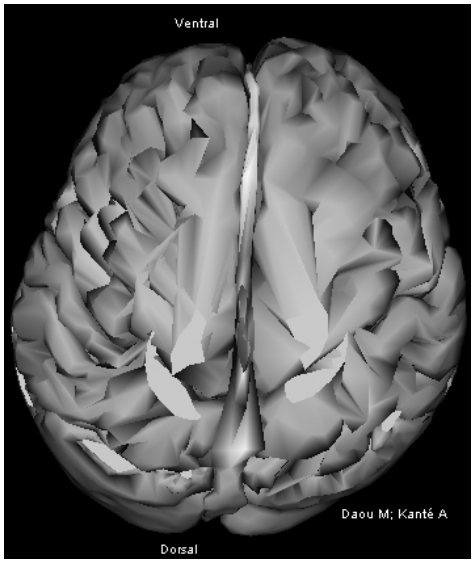

Figure 5 :3D vector reconstruction of the brain with Winsurf software : cranial view

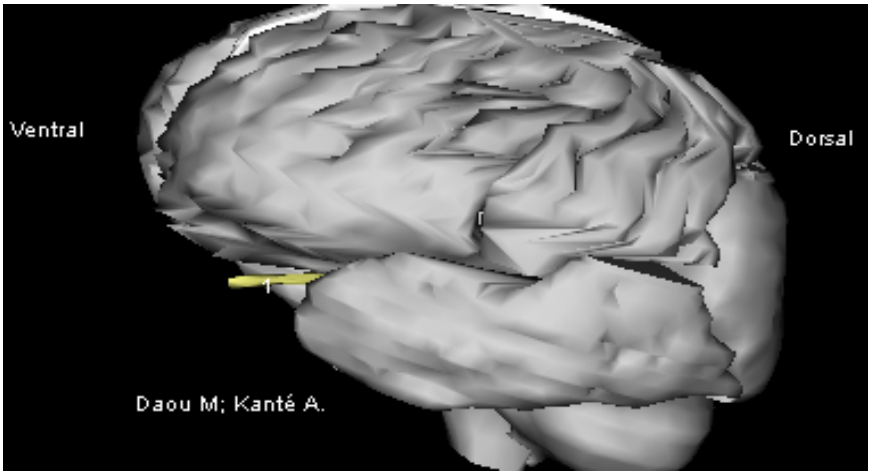

Figure 6 : D vector reconstruction of the brain showing the optic nerve (1) with Winsurf software : eft side view

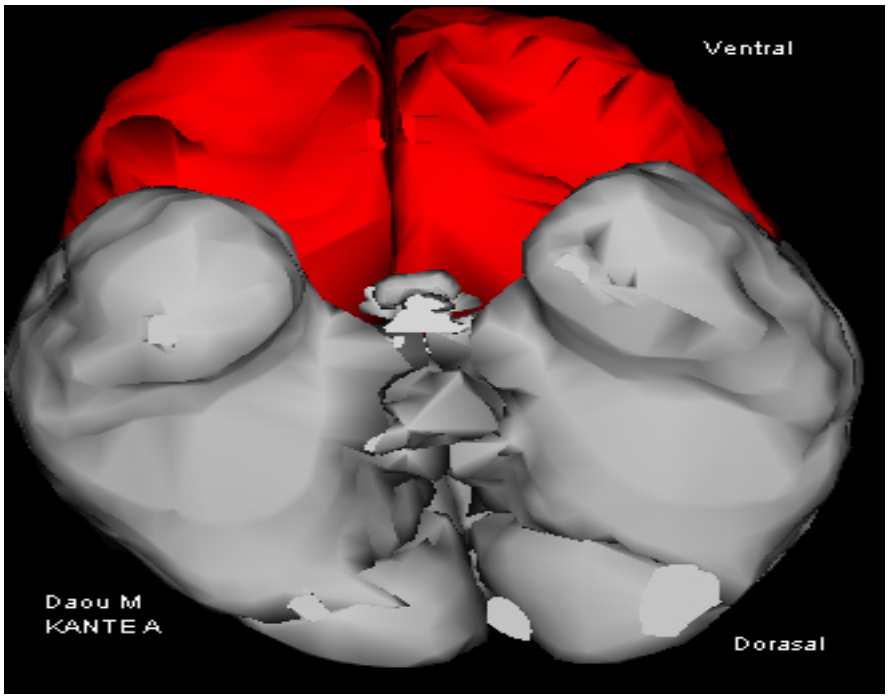

Figure 7 : D vector reconstruction of the brain showing the frontal lobes with Winsurf software : cudal view

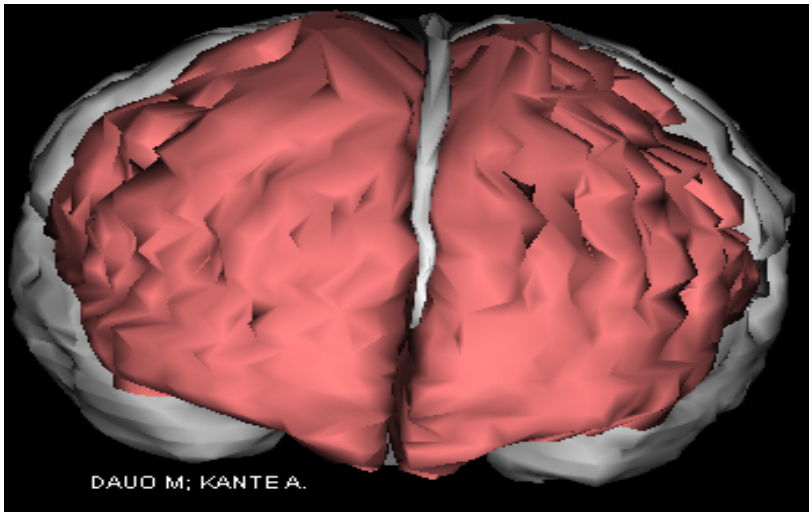

Figure 8 : 3 vector reconstruction of the brain showing the frontal lobes with Winsurf software : vntral view

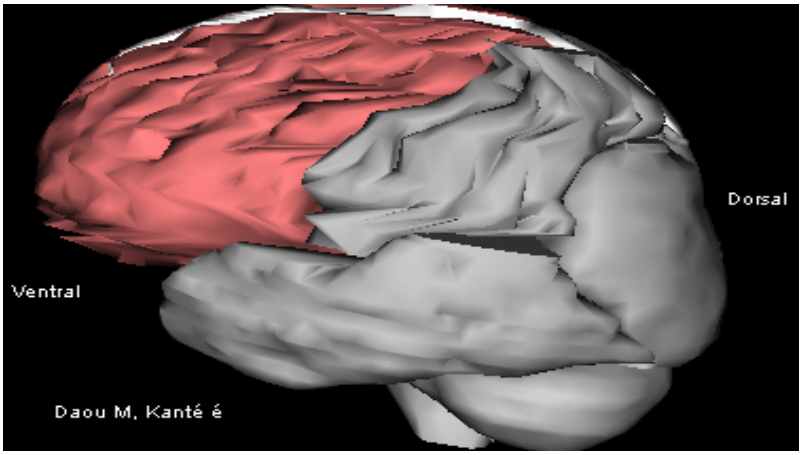

Figure 9 : D vector reconstruction of the brain showing the left frontal lobe with Winsurf software.

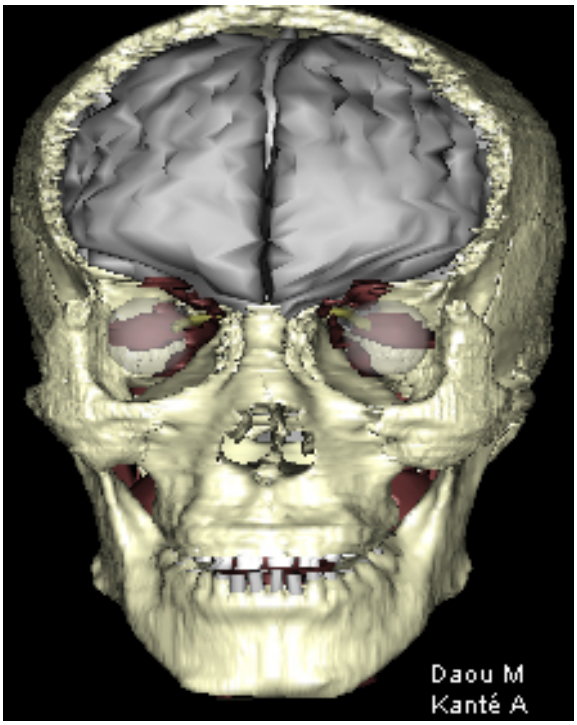

Figure 10 : D vector reconstruction of the brain showing the frontal lobes in the skull with Winsurf software.

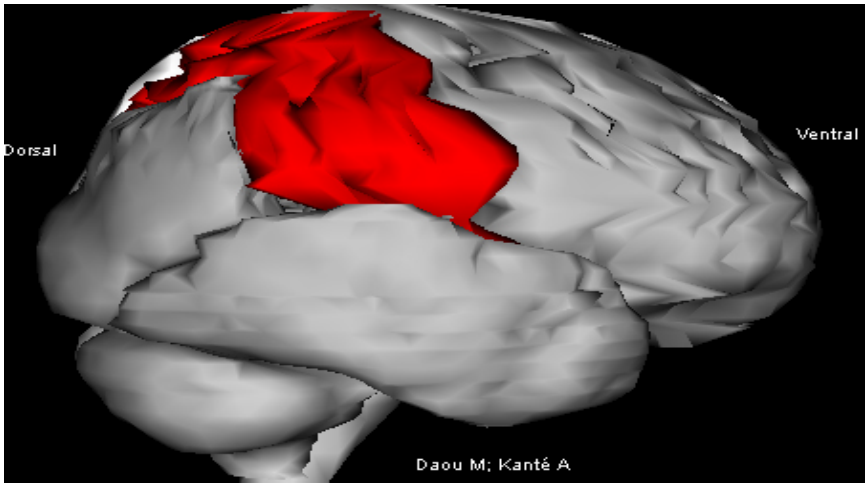

Figure 11 : 3 vector reconstruction of the brain showing the right parietal lobe with Winsurf software.

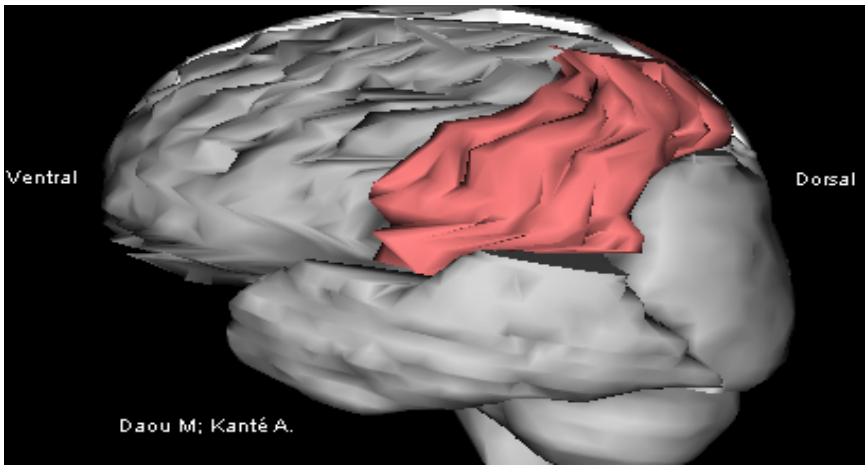

Figure 12 : 3Dvector reconstruction of the brain showing the left parietal lobe with Winsurf software.

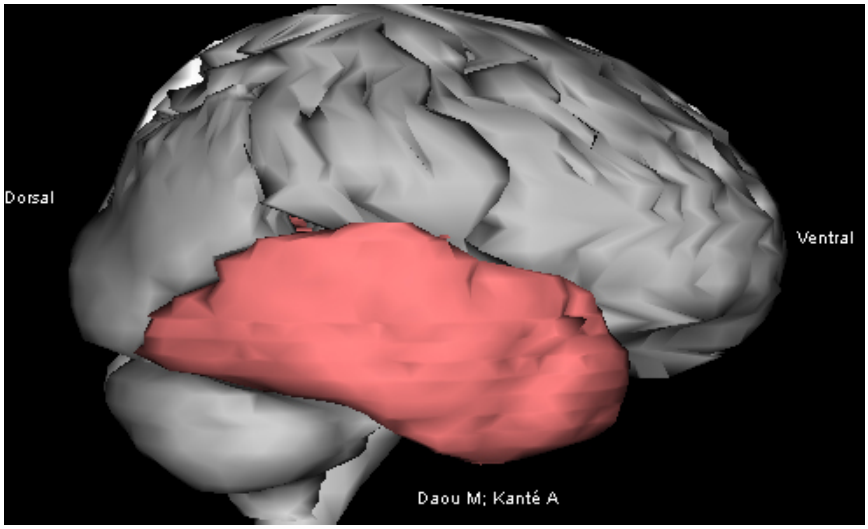

Figure 13 : 3Dvector reconstruction of the brain showing the right temporal lobe with Winsurf software.

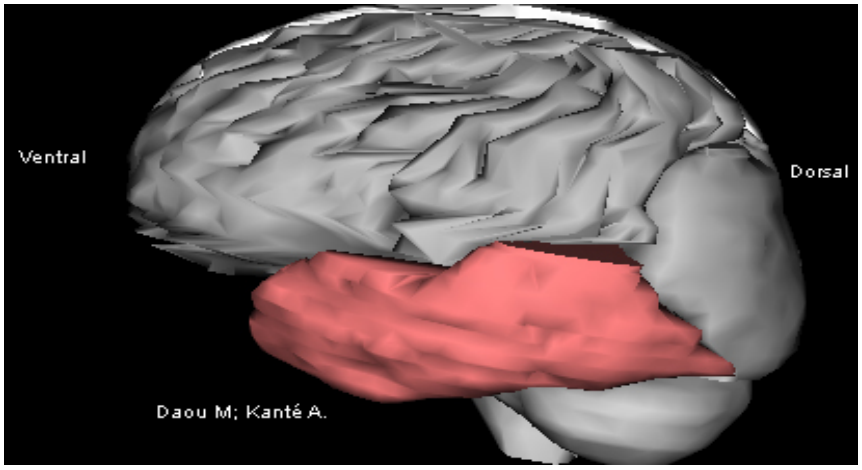

Figure 14 : 3Dvector reconstruction of the brain showing the left temporal lobe with Winsurf software.

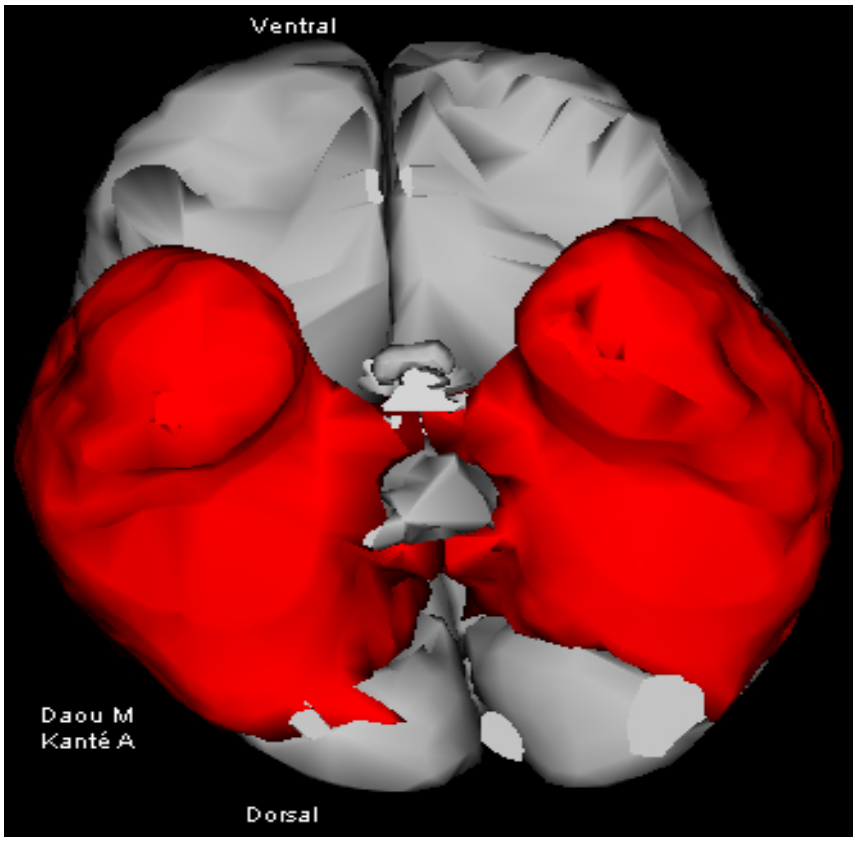

Figure 15 : 3Dvector reconstruction of the brain showing the temporal lobes with Winsurf software. Caudal view

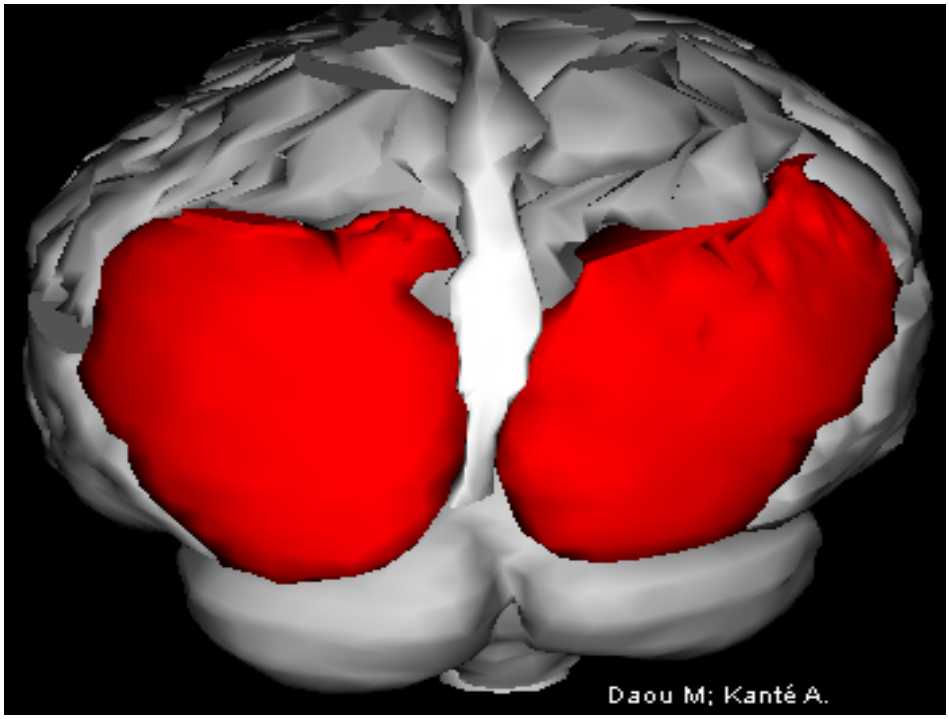

Figure 16 : 3D vctor reconstruction of the brain showing the occipital lobes with Winsurf software.

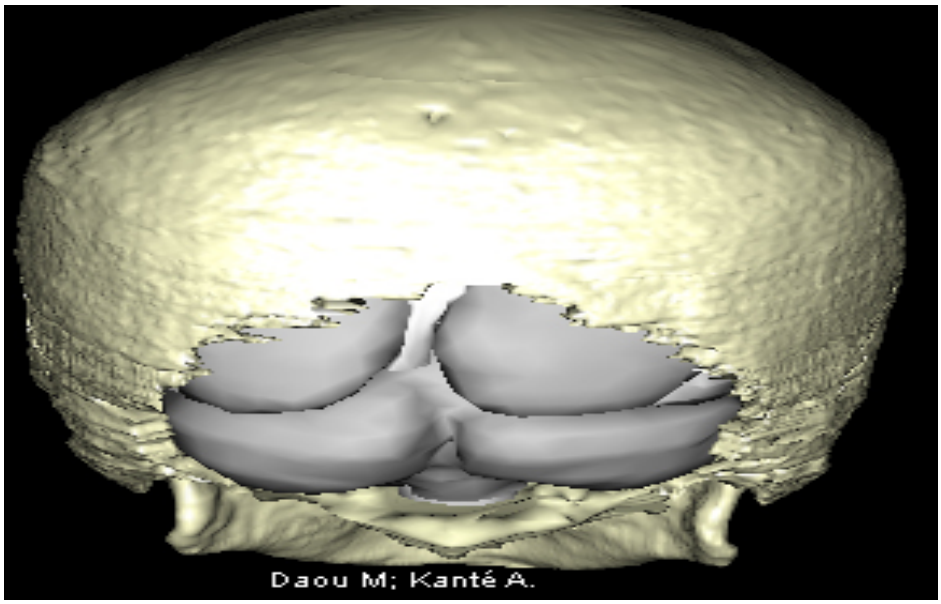

Figure 17 : 3D vctor reconstruction of the brain showing the occipital lobes in the skull with Winsurf software.

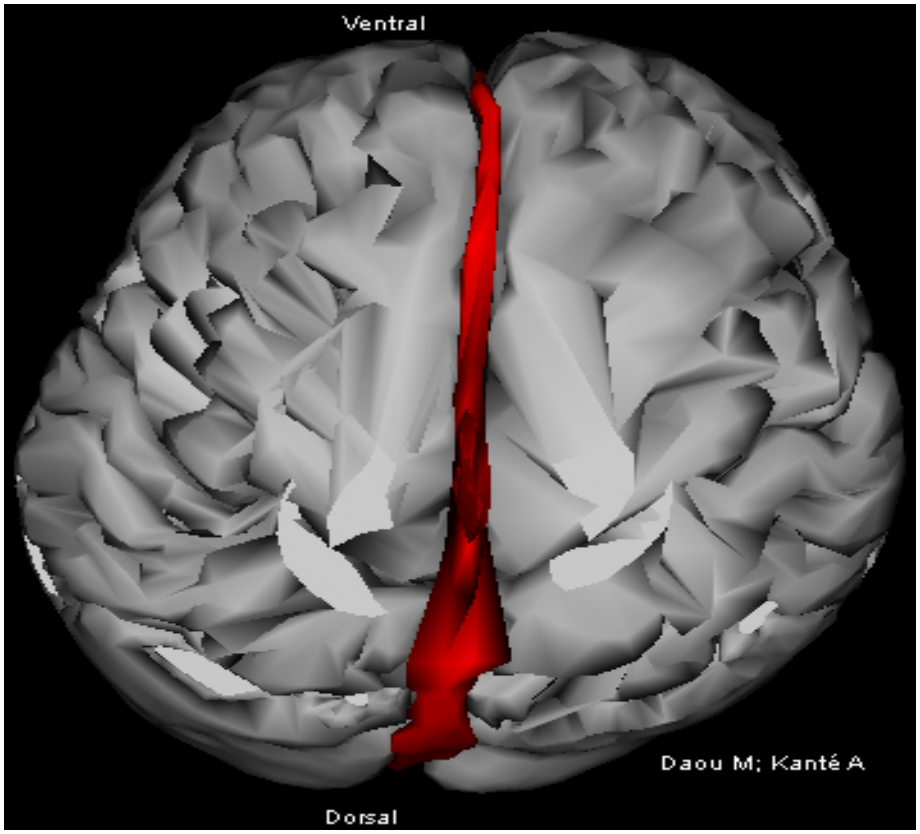

Figure 18 : 3D vetor reconstruction of the brain showing the brain scythe with Winsurf software.

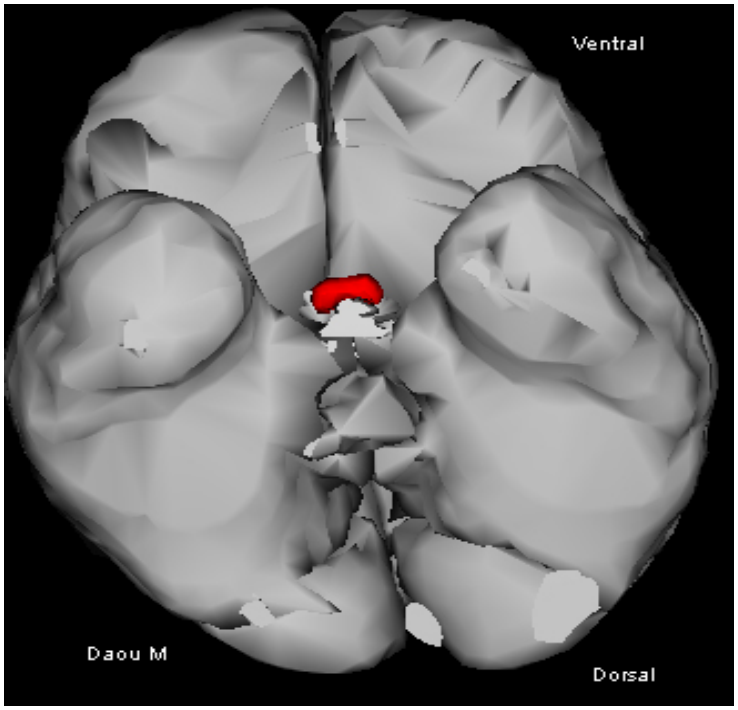

Figure 19 : 3D vetor reconstruction of the brain showing the pituitary gland with Winsurf software : cauda view

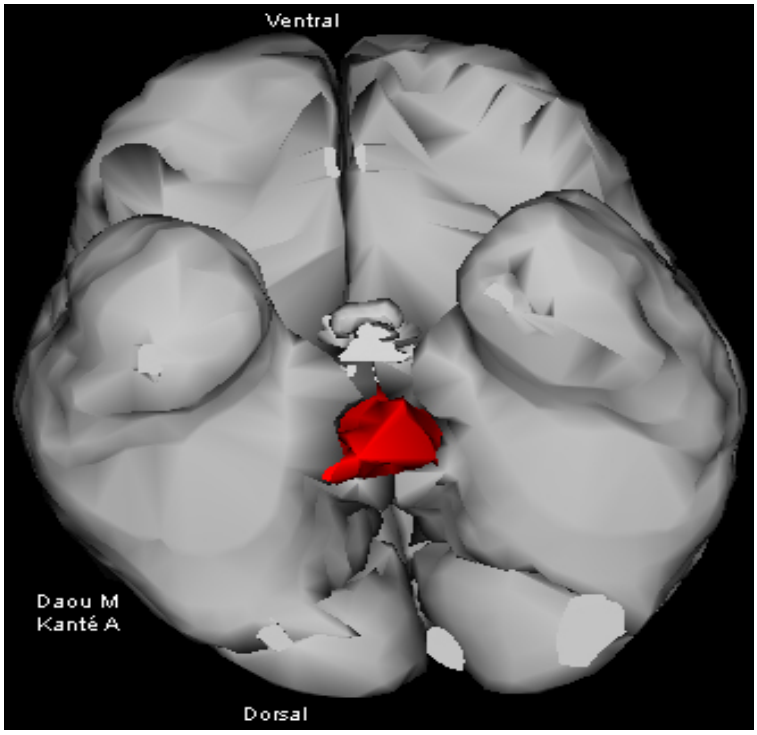

Figure 20 : 3D vecor reconstruction of the brain showing the thalamus e with Winsurf software : caudalview

4. Discussion

This article was made from anatomical sections of Korean Visible Human in order to achieve in the best possible way, a dynamic and detailed 3D atlas of the brain. Our work therefore, consisted, in recognizing the anatomical structures of the brain on these sections and in a more tedious work of contouring in order to obtain the most realistic models possible. Our methodology is quite similar to that of the Korean team, which used segmentation instead of manual contouring (Figures 21).

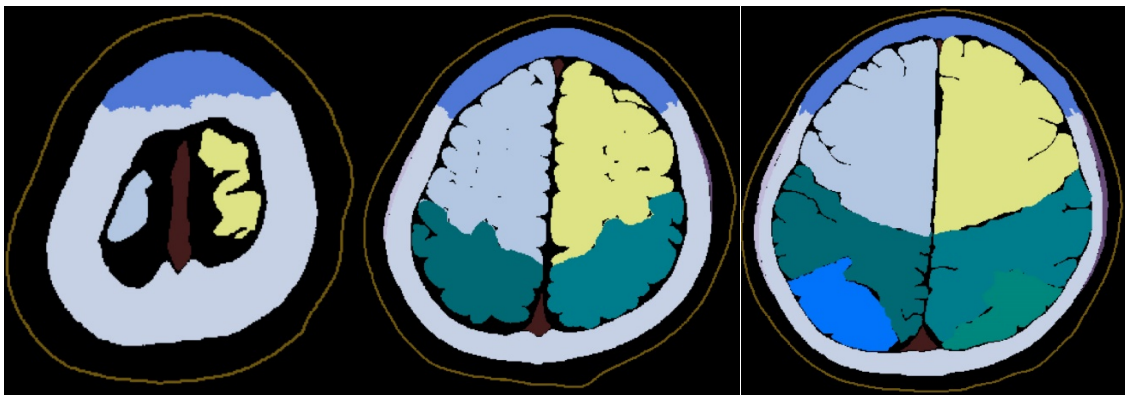
Figure 21 : segented sections used by the Korean team

The advantage of this work is mainly based on the fact that the entire contouring work and therefore the entire 3D vector reconstruction of the brain, was carried out using real sections of the human body. This results in a major increase in the precision and reliability inherent in the results presented above.

Indeed, reconstructions of the brain from digital procedures such as CT scans may prove to be somewhat disappointing in the sense that certain structures are absent and others that are difficult to distinguish. In contrast to this process, this contouring work is based on a manual, analog segmentation process under our supervision and not that of an automaton, which reduces the risk of anatomical errors in reconstruction.

The second advantage is based on the fact that better precision as well as the possibility of individualization of the different parts of the brain promotes a massive application in the university field thus contributing to a better understanding by medical students and other fields. In addition, it is essential to underline that this application is not restricted to the university field **but can also be the** support of a "Surgical Training" thus allowing a continuous training of the surgeons and a fortiori an improvement of their aptitude in their practices daily.

Finally, it is clear that "Winsurf" and Acrobat 3D PDF are particularly easy to use software which is not the case with other 3D modeling and manual segmentation software. In addition, they offer fairly wide ranges of textures which further increase the realism that we can bring to our final work.

Although the "Winsurf" software made it possible to reproduce the brain fairly faithfully, there are nevertheless some shortcomings.

The main disadvantage of this software is the time required to achieve the desired result. Indeed, this is a tedious contouring work of several months on several anatomical sections where sometimes only the section-by-section analysis was possible. To this are added the different objects that had to be created in order to be able to individualize the edges of the brain, which increased the number of cuts to which it was necessary to return each time.

Unfortunately, there is no miracle cure allowing a reduction of this working time if it is not a great motivation and an unprecedented personal investment.

Conclusion

Our 3D vector modeling of the brain is a remarkable educational tool for teaching the anatomy of the brain and can also be used as a 3D atlas for simulation purposes for training in therapeutic gestures.

Conflicts of interest: The authors do not declare any conflict of interest concerning the publication of this document.

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Diagnostic Accuracy of Ultrasound in the Detection of Malignant Focal Solid Breast Lesions Taking Biopsy as a Gold Standard

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Abstract
Background: Now a day's breast cancer is one of the most common causes of deaths and the most malignant condition among women. Objective: To determine diagnostic accuracy of ultrasound in detection of malignant focal solid breast lesions taking biopsy as a gold standard. Material and methods: This Cross-sectional analytical study was conducted at the department of radiology and pathology of Life Line Hospital. Duration of the study was 9 months after the aproval of synopsis. Ultrasound system (Toshiba Xario) with linear transducer, frequency ranging 7 to 14 MHZ. All 78 participants were scanned while observing international standards of American institute of ultrasound in medicine (AIUM) guidelines for breast sonography. Results: Total 78 females with solid breast lesions were included in this study, out of them 28 (35.90%) were found in right while 50(64.10%) in left side. The distribution of breast lesions in Upper outer quadrant, Lower outer quadrant, Upper inner quadrant, and Lower inner quadrant were 50 (64.10%), 45 (57.49%), 13 (16.67%), 16 (20.51%) and 4 (51.13%) respectively. Mean of the depth to width D/W ration in malignant was 0.78±0.098 (0.42-0.93), while in benign was 0.52±0.141(0.35-0.85). there was a significant difference between the D/W ratio of benign and malignant solid breast lesion. The specificity, sensitivity, positive predictive value, negative predictive value, and diagnostic accuracy of ultrasound while taking histopathology as gold standard were 94.74%, 95.24%, 98.18%, 86.96%, and 94.87% respectively. Conclusion: Ultrasound can differentiate benign and malignant solid breast lesion to a great extent. With the application of this sonographic criteria in the cases of solid breast lesion before biopsy for histologic examination the number of unwanted biopsies will be reduced to a great extent.

Keywords: Solid Breast Lesion, Breast Cancer, Biopsy, Sonography, Noninvasive Method.

Introduction

Cancer is a dreadful condition that is characterized by uncontrollable growth of the cells in organ or from site from where cells are originating[1,2]. Cancer of the breast is most malignant condition of the breast and among women is the 2nd most common type of cancer.[3] Breast cancer starts to develop in the tissues of the breast or may begin in the lobes or ducts.[4] If the spread of the cancerous cell is not controlled timely, the division continuously takes place and ultimately results in the development of a lump or tumor.[5] The incidence rate of the breast cancer mortality in females is 20%.[6] It mostly affects the women more than 50years of age, but it can also find in young age too. The commonest site that is affected with the tumor is upper outer quadrant (60%).[7] The causes of the breast cancer include hormonal causes, when the cells come in contact with estrogen hormone or genetic factors like gene mutation.[8] The risk factors of breast cancer are as follows: start of menopause in late age of life, no breast feeding, women who deliver their 1st child in age of 30 years or above, having no children, women who have breast cancer in family history, use of contraceptive pills, being obese after menopause, smoking, alcohol or lack of exercise etc.[9] The following are the signs and symptoms of the breast: formation of the new lump in the breast or underarm, swelling or thickening of the affected part of breast, formation of the mass with hard or irregular borders, dimpling or irritation of the breast skin, appearance of skin flakes or redness in the breast or nipple area, pain in the nipple area, discharge from the nipple other than breast milk, change in the size and shape of the breast etc.[10] According to the classification of W.H.O the carcinoma of breast is invasive and no-invasive carcinoma.[11] Invasive carcinoma is further classified into invasive ductal carcinoma is the most commonly found carcinoma (80%), invasive lobular carcinoma is next to the invasive ductal carcinoma and found almost 10%, mucinous carcinoma seen in 2% population, medullary carcinoma in 5% of affected women, papillary carcinoma in 1%, tubular carcinoma in 1%, adenoid cyst carcinoma, apocrine carcinoma, secretory carcinoma, inflammatory carcinoma and metaplastic carcinoma.[11] Non-invasive carcinoma is further classified into ductal carcinoma in situ (DCIS) (25 – 70%), lobular carcinoma in situ (LCIS) (25 – 35%) and Paget's disease (1 -2%) of nipple (without any mass).[11] Ductal carcinoma in situ originates from the terminal duct lobular units. The patient will complaint of mass, pain and discharge.[12] They are mostly ipsilateral. Different types of ductal carcinoma of situ can be find including: papillary subtype, cribriform subtype, solid subtype, comedo subtype (Figure # 1).[12] Lobular carcinoma in situ starts to originate from the lobules, the milk-producing glands at the end of the breast ducts.[13] There are no significant clinical signs and symptoms of this type. And no microcalcifications are seen on the mammogram. They are mostly bilateral.[13] Paget's disease of nipple is a condition which resembles the eczema especially of the nipple and areola. Breast lump posterior to the areola with hyperplasia of all layers of the epidermis can be found in this type. Thickening of the epidermis can be sequenced by the ulceration of skin. Staging of the Paget's disease is divided into with mass or without mass with good prognosis because it is slow in growth and can be diagnosed early.[14] Although breast cancer could be diagnosed with histopathology but Ultrasound with the modern advancement in hardware and software has the potential give some clue regarding it. Most of the breast solid lesion are benign in nature but due to the fear of breast cancer there are numerous benign cases undergo unwanted invasive biopsy procedures. If the sonographic criteria is applied to the breast masses for its nature and initial differentiation is made, this way the number of unwanted biopsy procedures could be reduced.

Material and methods

This Cross-sectional analytical study was conducted at the department of radiology and pathology of Life Line Hospital. Duration of the study was 9 months after the aproval of synopsis. Ultrasound system (Toshiba Xario) with linear transducer, frequency ranging 7 to 14 MHZ. All 78 participants were scanned while observing international standards of American institute of ultrasound in medicine (AIUM) guidelines for breast sonography. Inclusion criteria was female patients age 16 years and above. Having symptoms in unilateral or bilateral breast like lump, Swelling, Nipple discharge, Redness and pain for four weeks. All the patients having breast mass with the request of ultrasound and biopsy. Patients with previous breast surgery and The patient who is already on medication for breast cancer were excluded.

Results

Out of 78 patients mean age was 51.4231, minimum was 19, maximum was 81 and std. deviation was 14.79515. Total 78 females with solid breast lesions were included in this study, out of them 28 (35.90%) were found in right while 50(64.10%) in left side. Quadrant-wise distribution of solid breast lesions was summarized in both the breasts as 50 (64.10%), 45 (57.49%), 13 (16.67%), 16 (20.51%) and 4 (51.13%) in Upper outer quadrant, Lower outer quadrant, Upper inner quadrant, Lower inner quadrant respectively. Margins of the masses were Speculated in 27 (34.62%), Irregular in 17 (21.79%), Angular in 10 (12.82%), Micro lobulated in 1 (1.28%), Well defined in 15 (19.23%), Smooth in 7 (8.97%), and Macro lobulated in 1 (1.28%). A diverse echo-pattern was observed in all the solid breast lesions, which is summarized as; hypoechoic in 55 (70.50%), hyperechoic in 20 (25.64%), isoechoic in 2 (2.56%) and heterogeneous in 1 (1.28%) of all the individuals. There was vascularity (blood flow) in 55 (70.51%) while in 23 (29.49%) there was no vascularity out of the total solid breast lesions. on Ultrasound 55 (70.05%) were malignant, while 23 (29.05%) were benign. On biopsy out of 78 patients, 57 (78.08%) were malignant and 21 (26.92%) were benign. Comparison of the mean and standard deviation was done with independent sample t-test. Mean of the depth to width D/W ration in malignant was 0.78±0.098 (0.42-0.93), while in benign was 0.52±0.141(0.35-0.85). there was a significant difference between the D/W ratio of benign and malignant solid breast lesion. It was also observed that there is a great variation in the D/W ratio of benign as compared to malignant 0.141 and 0.098 respectively. The specificity, sensitivity, positive predictive value, and negative predictive value of ultrasound findings was calculated with the help of two by two table against histopathology (biopsy). The sensitivity was 94.74% (85.63-98.19), the specificity was 95.24% (77.33-99.15), the positive predictive value98.18% (90.39-99.68), the negative predictive value86.96% (67.87-95.46), and the overall diagnostic accuracy94.87% (87.54-97.99).

Discussions

Solid, palpable breast lesion is one of the most common cause of female anxiety and fear, while assuming that could be malignant. After breast pain, pulpable solid breast masses is the second commonest clinical presentation. careful physical examination along with various investigations can pinpoint the differential and can classify these masses either benign, malignant or equivocal.[15]

There are several causes of solid breast masses ranging from physiologic changes due to age or variation in hormone during normal menstrual cycle or pregnancy to the memory gland infection and surrounding tissue. Some of the most common causes of pulpable breast lesion are listed as; mastitis (an infection in breast tissue that most commonly affects women who are breast-feeding), fibroadenoma, fibrocystic breasts (lumpy or rope-like breast tissue), breast cysts, injury or trauma to the breast, intraductal papilloma (a benign, wartlike growth in a milk duct), lipoma (a slow-growing, doughy mass that's usually harmless), milk cyst (galactocele) — a milk-filled cyst that's usually harmless, and breast cancer, etc.[16]

A study was conducted in Agha khan university hospital, Karachi in 2018 to determine the sonographic negative predictive value of the breast lesion, which are morphologically benign. It was also aimed to know whether follow up could be an alternative to histopathology. For this purpose, they included 40 consecutive patients having 157 breast lesions which were declared benign with the help of ultrasonography. Amongst them 17 underwent histopathology and the result confirmed them as benign. The rest of the 140 lesions were followed for 2-years. Some of the remaining regressed in size while others remain benign. It was concluded that the negative predictive valued of the ultrasound is almost hundred percent.[17] To determine the negative predictive value of ultrasound in the estimation of tumor-free margins while taking biopsy as the gold standard, a study was conducted in 2017. All the 47 conveniently included patients were evaluate 54 breast lesions. ultrasound was performed for the detection of lesion and tumor-free margins in malignant lesion. Post-excision ultrasound was performed for the evaluation of lesion whether visualized or absent with localizing needle in situ, lesion dimensions, depth measurement between the superior margin of the lesion and its edge. All the masses were present on post-excision scan, amongst them 51.85% were documented as malignant while 48.14% as benign. Ultrasound declared all specimens as tumor-free margins. But only 2 lesions had spiculated margins and were proven to be invasive lobular carcinoma on histopathology. Therefore, the negative predictive value of the specimen sonography for margin detection was 92.8%. It was concluded that ultrasound of the excised breast

tumor specimen is a simple and reliable technique for confirmation of the tumor-free margins in non-palpable breast lesions.[18] In the current study 78 patients were conveniently included. Side of breast involved in solid breast lesions, quadrant of breast involved in the development of breast lesions, margins of various breast lesions, echopattern of the breast masses, vascularity of the breast masses, overall ultrasound findings to differentiate benign from malignant, and histopathology results to diagnose either the lesion is benign or malignant in the breast. Moreover, the sensitivity, specificity, positive predictive value and negative predictive value of ultrasound were checked against the histopathologic diagnosis.Detection of malignant breast cancer from benign without painful surgical biopsy requires accurate predictions and reliable diagnostic modalities. The controversial findings of equivocal lesions assessment results in unnecessary core or open breast biopsy. To determine the reliabilities the ultrasound feature of solid breast lesion a study was conducted in Agha khan university hospital, Karachi by Murad M; et al. Sonographic criteria was evaluated for the differentiation of benign and malignant breast masses in 100 participants after performing the histologic examination. The sonographic criteria interpreted by 2 experts of ultrasound, without knowledge of clinical history or histologic examination results. Then the sonographic features were compared with histologic results to determine the reliability of the sonography in benign or malignant nature of nodules. The sonographic appearances most likely to characterize benign solid breast masses were; a round or oval shape, well circumscribed depth to width (D/W) ratio smaller than 0.71. But the sonographic features of solid malignant breast lesions included irregular shape, spiculated margins and width (D/W) ratio greater than 0.71. If these three most reliable criteria had been strictly applied by the sonologist to differentiate benign from malignant pulpable breast masses then the number of unwanted biopsies will dramatically reduce and the overall cancer biopsy yield would have increased. It was concluded that ultrasound features can help differentiate benign from malignant solid breast lesions. However, operator dependency and operator knowledge are utmost important because ultrasound is more subjective rather than to yield objective results. Interobserver variability is important should be observed and cross checked before deferring the biopsy of solid breast lesions.[19]

In another study total 180 patients were included with 132 benign and 48 malignant. The accuracy of ultrasound results of the three observers were compared with gold-standard histopathology which yielded a result of 95.7%, 84.3% and 91.4% respectively[88]. In the current all of the above including vascularity were taken as variables and individually were checked for the differentiation of benign and malignant breast masses. The mean of the depth to width (D/W) ratio was compared benign and malignant breast lesions and a significant difference was found between them. It was calculated as 0.78±0.098 and 0.52±0.141 in malignant and benign respectively, which agree with previous studies as shown in table 15 and graph 9. The p-value of levene's test was 0.037, which means there was significant difference between both the means.

Conclusion

Ultrasound can differentiate benign and malignant solid breast lesion to a great extent. With the application of this sonographic criteria in the cases of solid breast lesion before biopsy for histologic examination the number of unwanted biopsies will be reduced to a great extent.

Recommendations

The reliability study should be performed on a large sample size to acquire more precise results.
The electrographic strain value should also be evaluated against the histopathology and should be added as a parameter in the sonographic criteria for the differentiation of solid benign and malignant breast lesions.

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Table 1: Descriptive Statistics of Age

Age	N	Minimum	Maximum	Mean	Std. Deviation
Total	78	19.00	81.00	51.4231	14.79515

Table 2: Comparison of the "Depth to width" (D/W) ratio mean and standard deviation with independent sample t-test

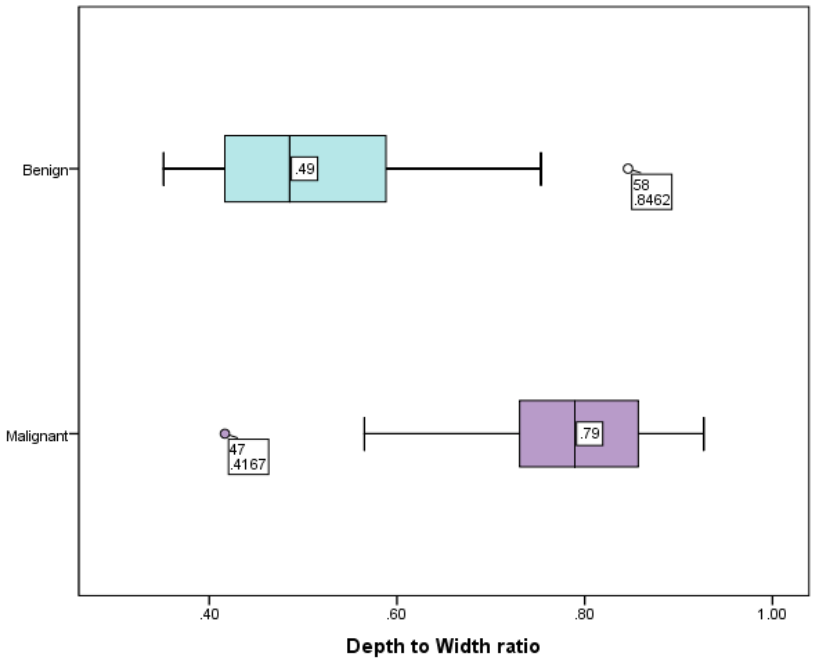
Group Statistics						
D/W Ratio	**Biopsy result**	**N**	**Mean**	**Std. Deviation**	**Minimum**	**Maximum**
	Malignant	57	0.78	0.098	0.42	0.93
	Benign	21	0.52	0.141	0.35	0.85
	Total	78	0.71	0.16	0.35	0.93

Table 3: Cross tabulation of ultrasound findings versus biopsy results with the help of two by two table to find our sensitivity, specificity, positive predictive value and negative predictive value

		Biopsy Findings			
		Malignant	**Benign**	**Total**	**P-value**
Ultrasound Findings	**Malignant**	54	1	55	0.00
	Benign	3	20	23	0.00
Total		57	21	78	0.00

Sensitivity = 94.74%
Specificity = 95.24%
Positive Predictive Value = 98.18%
Negative Predictive Value = 86.96%
Diagnostic Accuracy = 94.87%

Graph 1: Box-Plot for the comparison of mean of depth to width in benign and malignant cases



Figures

Figure 1: Well defined isoechoic solid lesion, with smooth margins, in the left breast at the upper outer quadrant, in retroarelora region, measures 1.07cm x 1.07cm, with no vascularity observed.

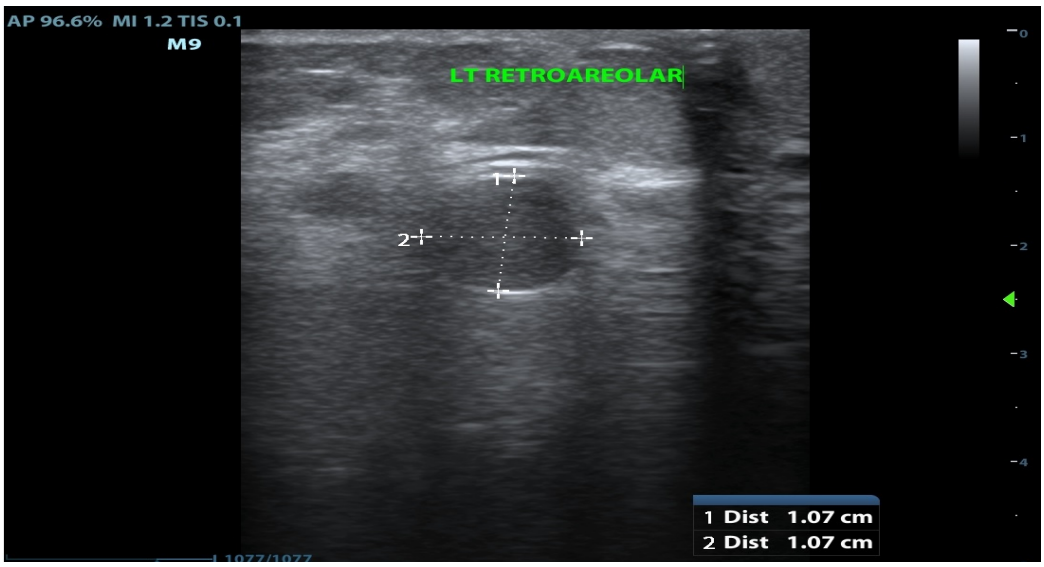
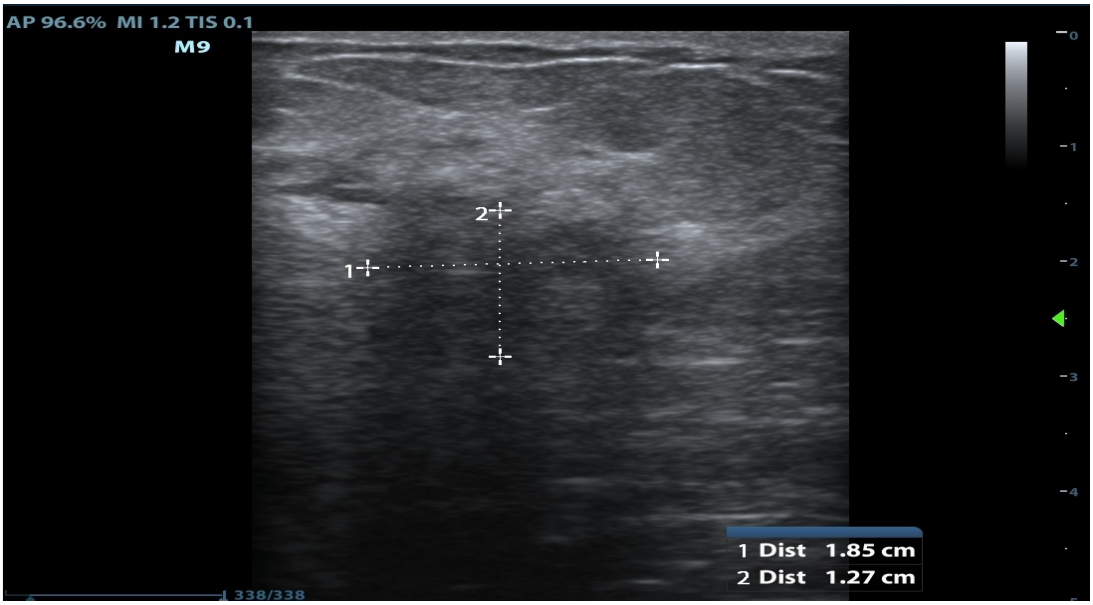


Figure II: Irregular hypoechoic solid lesion, in the left breast at the upper outer quadrant, measures 1.85cm x 1.27cm.



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Delusional Misidentification Syndromes: Psychopathology and Culture

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Abstract
Delusional misidentification syndromes constitute a number of disorders that involve a myriad of delusions related to the identity of self or other. The forms of delusion range from misattribution of identity related to self, other, as well as parts of the body. Although rare, these syndromes are encountered in a number of different forms by medical and psychiatric personnel, as well as other types of mental health workers. This is especially true since many of the syndromes have organic etiology and are treated via medical rather than psychological intervention. Nevertheless, delusional misidentification syndromes often co-exist with psychiatric issues which can be helped by concurrent psychological treatment. Given that identity is central to human beings and their cultures, it is not surprising that delusional misidentification is represented in a number of cultural beliefs. Some cultural expressions of delusional misidentification may function as coping mechanisms for anxiety over loss of identity or the trauma of infant mortality.

Keywords: Capgras Syndrome, Fregoli Delusion, Prosopagnosia, Alien Hand, Body Dysmorphic Disorder

1. Introduction

Psychiatric disorders that are related to the concept of misidentification are labeled together as delusional misidentification syndromes (DMS) and are somewhat rare. In these syndromes someone, or something, is incorrectly identified as a person, part of the body, place, or thing. Thoughts and attribution of thoughts are also misidentified, in many cases to the point of being delusional. Most of these syndromes are more often than not related to organic abnormalities of the brain, or they may be a combination of organic problems with psychological issues, or in rare instances, may be purely psychological. Many DMS are often associated with psychoses and have only rarely been reported in non-psychotic individuals. They are, nevertheless, fairly uncommon, occurring in about 4% of patients presenting with functional psychoses (Melca et al., 2013).

2. Capgras Syndrome

This is a misidentification syndrome where a person holds a delusion or belief that an acquaintance, typically a close family member, has been replaced by an identical looking imposter. This syndrome can be transient, developing very quickly after a brain injury, or can take a chronic form where the delusion is long standing. The syndrome is named after the French psychiatrist Joseph Capgras (1873-1950) who first described the disorder in a 1923 paper and used the term 'illusion of doubles' to describe a case of woman who had various doubles that had taken the place of people she knew. For some people with Capgras syndrome, even inanimate objects such as chairs and animals can be imposters. Often patients are so disturbed with seeing their doubles that they remove all mirrors from house. In some cases, if the Capgras sufferer can be convinced that one person is not an imposter, they will transfer the Capgras delusion to someone else (Sinkman, 2008).

Capgras Syndrome can also be co-morbid with other mental health and medical problems including; Alzheimer's disease, Cotard's syndrome, epilepsy, Farh's disease, Fregoli delusion, Hashimoto's hypothyroidism, incubus syndrome, neurodegenerative disease, Diogenes syndrome, and Parkinson's disease (Bourget & Whitehurst, 2004; Ceylan et al., 2010; Chiu, 2009; Donnelly et al., 2008; Fischer et al., 2009; Josephs, 2007; Mishra et al., 2009; Pande, 1981; Rodríguez et al., 2011; Yalin et al., 2008). Capras syndrome has also been associated with the administration of morphine and ketamine (Bekelman & Hallenbeck, 2006; Corlett et al., 2010) as well as with lithium toxicity (Nagasawa et al., 2012).

Since the time Capgras syndrome was first described (and even a bit before) a number of theoretical explanations have been put forth as to its origins. As might be expected many of the early theories were psychoanalytically based. A comprehensive account of these early conceptualizations of Capgras has been compiled by de Pauw (1994). In this article de Pauw notes that many of the psychoanalytic explanations are mutually incompatible. These psychoanalytic theories include; defense against unconscious homosexuality, a regression to the early stage of primary narcissism (which some writers believe was due to anxiety), and a novel resolution to the Oedipal and (especially) the Electra complexes. Psychodynamic explanations seemed to make sense because the people being replaced by imposters were almost always close family members. However, on closer scrutiny of the literature this argument falls apart as other people or things are often found to also be imposters; including doctors and nurses, as well as entire buildings and other inanimate objects. In general, according to de Pauw psychoanalytic explanations tend to be "generally post hoc and teleological in nature, postulating motives that are not introspectable and defense mechanisms that cannot be observed, measured, or refuted" (p. 158). He concludes that while the presence of brain injury also does not fully explain Capgras syndrome this may be due to a breakdown in the manner in which sensory information is brought into the brain and the way it is stored (and presumably retrieved). In another review of the psychoanalytic explanations of Capgras syndrome, Christodoulou, et. al. (2009) report that Capgras symptoms were originally thought of as psychological defense mechanisms against repressed desires. These authors also state that the psychoanalytic ideas of projection and splitting might play a role in Capgras syndrome. A person who is unable to integrate repressed or 'bad' aspects of themselves might project these on to another person who would take on these characteristics in the form of a double. It may be that mechanisms such as projection and splitting do play a role in DMS. Cerebral pathology may make it difficult for the sufferer to process information related to the identity of others leading to confusion and possibly the inability to integrate other people with identity, feelings, and memories. Projection and splitting could then be a defense mechanism that helps the Capgras sufferer make meaning of their confusion. These ideas deserve further study.

Another issue in the published case literature on Capgras syndrome is the focus on the delusion of the imposter to the exclusion of other aspects of the syndrome. Closer scrutiny often demonstrates other DMS and psychotic/schizophrenic symptoms in Capgras syndrome cases. Many patients suffer from a sort of expanded Capgras syndrome where there are many other delusions present. Some of these delusions may be somatic in nature, with the patient experiencing bizarre changes to their bodies that can seem strange and alien. Even the patient's sense of self can change and subject to delusion. These symptoms are reminiscent of schizophrenia and it is no surprise that some cases of Capgras syndrome have a co-morbid diagnosis of schizophrenia, usually of the paranoid variety. Upon closer examination it can become difficult to make a differential diagnosis between Capgras syndrome and schizophrenia in many sufferers. Or the Capgras symptoms may be another aspect of the schizophrenic illness. In fact, studies have shown that misidentification symptoms occur in a large number of cases of schizophrenia, maybe even as high as 40% (Sinkman, 2008). Capgras

patients can be prone to acts of violence, especially against people they have misidentified (Bourget & Whitehurst, 2004). Given the relation of Capgras to paranoid schizophrenia this makes sense.

Modern clinicians and researchers now believe that Capgras syndrome and other DMS have an organic basis, which is specifically related to cerebral dysfunction. Neuroimaging studies have shown that lesions in the right hemisphere of the brain are common among Capgras syndrome sufferers. Some studies have demonstrated bilateral damage to the hemispheres in Capgras syndrome patients (Bourget & Whitehurst, 2004). In one small study 81% of Capgras syndrome sufferers also had neurodegenerative disease, usually involving the Lewy body. As would be expected, these Capgras syndrome sufferers were older than Capgras patients without neurodegenerative disease. This latter group were also more likely to suffer from paranoid schizophrenia, schizoaffective disorder, methamphetamine abuse, or other cerebrovascular problems. All patients in the study with Capgras syndrome and Lewy body disease also experienced visual hallucinations (Josephs, 2007).

While structural deficit models of the brain related to Capgras syndrome and other DMS are important, these biological explanations are not able to extricate the meaning of the specific delusions for DMS patients, and do not explain why the mind of these individuals creates imposters and doubles (Christodoulou et al., 2009). Therefore, psychological and cognitive processes remain important lines of research into DMS.

There is evidence to support the idea that an emotional processing module in the brain, especially as it related to feelings of familiarity and unfamiliarity, and its connection to facial recognition is flawed in Capgras sufferers (Pacherie, 2009). This flaw in emotional processing can be demonstrated via facial recognition tasks and eye movement patterns (Brighetti et al., 2007; Grignon & Trottier, 2005; Walther et al., 2010). Similar differences in audio perceptions related to working memory have also been reported for Capgras syndrome sufferers (Papageorgiou et al., 2002). In one dramatic case a Capgras syndrome patient had sexual relations with his wife, thinking she was a ‘double’. He had no feelings of familiarity with his wife whatsoever and essentially felt as if he were having sex with a different woman; so much so that he even changed his sexual behavior. The authors (Antérion et al., 2008) note that this may be the only known documentation of a patient who was able to make his wife into his mistress!

Some researchers believe that DMS results from a breakdown of the cognitive process of identification, in which a small discrepancy in input of stimuli results in misidentification and a denial the other’s true identity. Other researchers characterize a two-factor model in which an abnormality prompts a delusional belief. A second abnormality prevents the sufferer from rejecting this delusional belief even in the presence of strong evidence to the contrary. It may be that the initial delusions come about when the DMS sufferer attempts to explain their odd abnormal perceptions (Christodoulou et al., 2009).

As might be expected the typical treatment for Capgras syndrome is anti-psychotic medications. However, when anti-psychotic medication is only partially effective or not effective, the use of electroconvulsive therapy has been shown to be helpful. This is especially the case when Capgras syndrome is co-morbid with Parkinson’s Disease (Chiu, 2009).

3. Fregoli Delusion

Another, related misidentification syndrome is Fregoli delusion. This syndrome is named after the Italian actor Leopoldo Fregoli, who often changed appearances and identities during his performances. This type of delusion occurs when a person believes that a number of different people are actually one person who has the ability to change their appearance. The different people are usually familiar and are often considered to be hostile or persecutory to the Fregoli sufferer. This delusion is often thought of as a variant of Capgras syndrome and it seems the underlying neuropathology is similar, usually involving lesions to the right hemisphere of the brain. It has been difficult however, to clearly trace the delusional misidentification directly to the organic pathology since the syndrome is so often comorbid with psychotic disorders (Mojtabai, 1994; Novakovic et al., 2010).

In addition to psychoses, Fregoli delusion has been associated with a number of other disorders. Bruggemann and Garlip (2007) report a case of erotomania combined with Fregoli delusion in a 24-year-old woman. This woman believed a colleague who was the target of her erotomania, appeared as other people. While they did not find any overt pathology, they did note EEG differences in the right temporal lobe. This woman, as is typical for people with Fregoli syndrome,

also suffered from psychotic symptoms such as imagining she had become pregnant by her colleague and that she was his fiancée. She was treated via psychotherapy and neuroleptic medication, which lessened her symptoms. When the patient stopped taking her medication her psychotic symptoms returned. The authors conclude that the Fregoli delusion was secondary to paranoid schizophrenia. Fregoli delusion has also been associated with bipolar schizoaffective disorder and Hashimoto thyroiditis (Ceylan et al., 2010).

Melca et. al. (2012) describe two patients with Capgras syndrome and Fregoli delusion who also suffered from treatment resistant obsessive-compulsive disorder (OCD). One of the two patients also was diagnosed with paranoid personality disorder while the other with pervasive developmental disorder. Both patients in the study exhibited varying amounts of insight related to their OCD. The authors speculate that there may be a relationship between OCD and DMS.

Fregoli delusion has also been associated with violent behavior. Delavenne & Garcia (2011) report on a case of a paranoid schizophrenic woman who was convinced that a boyfriend was able to appear as other people so he could follow her. This patient had an episode of violent behavior associated with her Fregoli delusion. She had stopped taking her anti-psychotic medication six months prior to her violent outburst. Facial recognition tests and a CT scan of her brain revealed no abnormalities. Even though she was put back on anti-psychotic medication, her delusions returned after 10 days.

4. Variants of Delusional Misidentification Disorder

One research study has reported that Capgras syndrome, Fregoli delusion, and psychoses can be distinguished from one another by observing facial recognition reaction times. Patients suffering from DMS took longer to perform facial recognition tasks than psychotic patients, with Fregoli patients taking longer than Capgras patients. This may indicate differences in underlying pathology among psychotic, Capgras, and Fregoli disorders (Walther et al., 2010). However, facial processing does not explain why there are various subtypes of DMS, why the subject of a delusional misidentification is visually identified correctly, and why some DMS patients report having multiple doubles (Christodoulou et al., 2009). Young (2010) compared patients with DMS with other non-delusional facial recognition disorders. He concluded that the patients' experience is an important factor in the genesis and maintenance of the DMS. Some writers, notably Christodoulou, view DMS as consisting of four subtypes: Capgras syndrome, Fregoli delusion, intermetamorphosis syndrome, and subjective doubles syndrome. As stated above, Capgras syndrome involves the delusion that someone close to the sufferer has been replaced by a double. Fregoli delusion involves the sufferer having the delusion that a familiar person, who is typically hostile or persecutory, is taking on the forms of strangers. Intermetamorphosis syndrome is where the sufferer believes a familiar person has become a stranger (like in Fregoli delusion) but this stranger is also physically and psychologically similar to the familiar person, interchanging with them. Finally, subjective doubles syndrome is where a person has the delusion that other people are physically transforming into them (Christodoulou et al., 2009; Christodoulou et al., 1995; Christodoulou, 1986; Shah, 2012; Young, 2010). Another way, perhaps to look at these is as two subtypes, with intermetamorphosis being a variant of Fregoli delusion and subjective doubles syndrome being a variant of Capgras syndrome (where the familiar person being replaced is oneself).

5. Prosopagnosia

Prosopagnosia is the official term for face blindness, a disorder in which a person is unable to recognize the faces of others. This is a neurological condition that is not related to other syndromes or illnesses and can be caused by injury to the brain or congenital abnormalities of the brain (Van Belle et al., 2011; Van den Stock et al., 2012). The condition derives from a dysfunction in the medial cerebral hemisphere, more specifically the fusiform gyrus area of the temporal lobe in Brodmann area 37. Disruption in nerve pathways in this region lead to problems of face recognition, while the ability to recognize of other aspects of people and things, as well as cognitive and emotional processing, remains intact. The lack of facial recognition may be related to an inability to perceive emotions from facial stimuli. The mechanism by which faces are not recognized may be related to a lack of emotion when the person with prosopagnosia sees the face of someone they know. This may lead to the perception that the person isn't who they appear to be, and in this sense, the person is misidentified.

People with prosopagnosia are thought to compensate for the inability to recognize faces by using other cues, such as parts or of the body, or characteristics such as movement, almost anything except visualizing the face. One research study indicates that auditory cues such as voice recognition may be an important way in which people with prosopagnosia recognize others (Hoover et al., 2010).

6. Alien Hand Syndrome

Alien hand syndrome is where the hand or arm of a person seems to have a life of its own. It is a neurological problem, but it is intertwined with psychological constructs such as will (Sacco & Calabrese, 2010). It is a rare condition that usually turns up after a stroke, though it can also result from other trauma to the area of the brain which controls limb function when neurological messages somehow get scrambled in meaning.

There are some variations of alien hand syndrome, but all types are thought to be related to lesions in the medial frontal lobe, the corpus callosum and the parietal areas of the brain. Alien hand syndrome has also been seen in patients with neurodegenerative diseases involving corticobasal degeneration (e.g. prion-disease) and may be a precursor to the expression of neurodegeneration (Sacco & Calabrese, 2010).

Patients suffering from alien hand syndrome experience their hand as being controlled by external forces and are often astonished and frustrated by the errant hand (Biran & Chatterjee, 2004). A typical clinical presentation of the syndrome is as follows:

> "*Two weeks after stroke onset, the patient started to present involuntary and intermittent movements of the right arm, irregular in speed and usually with a slow onset. Also, levitation of the right arm occurred. She did not always seem aware of the problem. Her right hand frequently stroked the bed, but she never looked at it or attempted to intervene to stop the movements. The patient failed to recognize the affected limb as her own, personifying it and expressing the idea that it was under someone else's control."* (Bartolo et al., 2011,p. 484)

It has been postulated that three factors contribute to the sense of alien-ness of the affected limb; 1. There is disinhibition of the affected limb and it is disproportionately reactive to environmental stimuli; 2. The limb is under less volitional control by the sufferer and engages in perseverative, stereotyped movements which are linked together; 3. The sufferer is cognitively intact to the level where they are aware that the movements are abnormal (Biran et al., 2006).

There is no known cure, but alien hand syndrome tends to disappear after a few weeks or months. This usually coincides with the fading of the stroke trauma. The estimated prevalence of alien hand syndrome could be as much as one out of 100 among stroke patients (Nowak et al., 2014).

The idea of the alien hand has made a few appearances in popular culture. The film *The Hands of Orlac* (Gréville, 1961) which was later released under the title *The Hands of a Strangler*, tells the story of a famous concert pianist who sufferers horrendous injuries to his hands in a car accident. Fortunately, new hands are able to be successfully transplanted allowing the pianist to resume his career. However, unbeknownst to the pianist, his new hands were taken from an executed murderer. The new hands seem to have a will of their own which manifests as a desire to strangle people to death.

Biran and Chatterjee (2004) point out an excellent example of alien hand syndrome in the film *Dr. Strangelove or: How I Learned to Stop Worrying and Love the Bomb* (Kubrick, 1964). In the film the main character Dr. Strangelove, brilliantly played by Peter Sellers, has a right hand that seems to have a mind of its own. Strangelove's hand sometimes tries to choke him by grasping his throat and other times involuntarily giving a Nazi salute. During these episodes Strangelove does his best to restrain his right hand with his left one.

Lastly, it would be remiss not to mention the television show The Addams Family (*The Addams Family*, 1964) and the later film remake (Sonnenfeld, 1991). The television show and the film depict an eccentric, if not, goth-like family that includes "Thing" who is a hand. Thing is fully autonomous and mysteriously animated appendage with a will of his own who seems to have done away with the need of body.

7. Cotard's Syndrome

Cotard's syndrome is another rare syndrome possibly related to misidentification. Debruyne et. al. (Debruyne, 2017; Debruyne et al., 2013; Debruyne et al., 2013) have published a number of excellent reviews of Cotard's syndrome which are summarized here. In this syndrome, which was first described by Jules Cotard in 1880, a person has the delusion that they somehow, in all or part, do not exist. This manifests as the person believing they are dead, or have lost their soul, or no longer have any organs, etc. Cotard initially characterized the disorder as consisting of anxious melancholia related to ideas of damnation or rejection, insensitivity to pain, delusions of bodily non-existence and immortality. Cotard's syndrome is not included in the DSM V as a specific diagnosis. This is due to its rarity and its conceptualization under other disorders – typically schizophrenic delusions and depression. There has not been systematic scientific research done on the syndrome with most of the literature consisting of case studies which may or may not include neuroimaging. One of the rare scientific studies done in the modern era used data reduction techniques to analyze 100 cases of Cotard's Syndrome. This resulted in three types of syndromes related to Cotard's syndrome. The first type consists of psychotic depression with features of anxiety, melancholia, delusions of guilt, and auditory hallucinations. The second type called Cotard's type I was associated with hypochondriacal and nihilistic delusions in the absence of clinical depression. The third type, Cotard's type II includes anxiety, depression, auditory hallucinations, nihilistic delusions, delusions of immortality, and suicidal behaviors (Berrios & Luque, 1995). Prevalence rates for Cotard's syndrome are difficult to determine because of diagnostic overlap with other disorders. A study in China of older adults with psychiatric issues found an overall prevalence rate of 0.57%, However, when only severely depressed older adults were examined the prevalence rate jumped to 3.2%. In the study cited above by Berrios and Luque (1995), the mean age of Cotard's patients was 52, however, the disorder has been found in people of all ages, including in rare instances, adolescents and children. Women seem to suffer from the disorder more than men.

Sahoo and Josephs (2017) report that Cotard's syndrome has been associated with a number of other morbidities with uni-polar and bi-polar depression being the most common, followed by psychosis. Other psychiatric disorders associated with Cotard's syndrome include voluntary starvation, hydrophobia, lycanthropy, and *folie a' deux* (shared psychotic disorder). A number of organic conditions have also been associated with Cotard's syndrome. These include dementia, developmental disability, typhoid fever, stroke, superior sagittal sinus thrombosis, brain tumors, Capgras syndrome, cerebral arteriovenous malformation, various types of epilepsy, migraine, multiple sclerosis, Parkinson's disease, brain injury, etc. The authors examined 14 patients with Cotard's syndrome and found it to be associated with frontal lobe volume and blood supply loss, and right-side and bi-lateral hemisphere lesions. Research on Cotard's syndrome has not definitively found a cause for the disorder but has generated some plausible theories as to its etiology.

Treatment for Cotard's syndrome can include both psychological and medical modalities, though the psychiatric treatments are more prevalent, psychotherapy, including behavior therapy, is also used with Cotard's syndrome patients. Psychiatric medications for Cotard's syndrome include antipsychotics, sometimes in combination with SSRI antidepressants (Chan et al., 2009; Moschopoulos et al., 2016) Electroconvulsive therapy (ECT) has been used successfully for Cotard's syndrome. This is especially true for type I Cotard's syndrome, while for type II antipsychotic medication is the preferred treatment (Madani & Sabbe, 2007). The above treatment regimens appear to have good outcomes.

With regard to expressions of Cotard's syndrome-like aspects in popular culture, there are many examples. Probably the most obvious would be people who consider themselves to vampires, werewolves or zombies. The cultural representations of this in literature, film, and television are too numerous to list.

8. Body Dysmorphic Disorder

It is also possible to understand some other syndromes as being related to DMS. For instance, body dysmorphic disorder (BDD)[1] is where a person has the delusion that a limb or limbs, or other parts of the body do not belong to them. Estimates of up about 2% of the population may suffer from BDD, while the prevalence may be higher among college students and clinical populations at around 5%. Outpatient psychiatric populations have been estimated to be 5.8% while

[1] In specific incidences BDD has been labelled apotemnophilia, body integrity disorder, and xenomelia. These terms have been used somewhat interchangeably in the research literature.

inpatient psychiatric populations could be as high as 7.4% (Hong et al., 2019). However, it seems safe to assume that more extreme cases, for instance where a person makes an attempt to amputate a limb, are far fewer. BDD is now included in the DSM V as a diagnostic category where it is defined as the alteration or removal of a body part because it is thought by the sufferer to be somehow abnormal. Many people with this disorder report that amputation of the body part makes them feel whole or complete. In some cases, the person with BDD has a wish or compulsion to live as an amputee or a disabled person (American Psychiatric Association, 2013). The first scientific study of the disorder occurred in 2005 when First and Fischer studied 52 subjects and were able to report some more specific characteristics of the disorder. Among the findings were that most individuals with the condition are men, there is a preference for amputation on the left side, and a preference for amputation of legs rather than arms (First & Fisher, 2011).

It is not known if BDD has an organic etiology, or if it is psychological, or both. Sedda and Bottini (2014) give an excellent review of 37 years of studies which includes both psychological and neurological approaches to the disorder. Early psychological approaches to understanding BDD examined sexual motives and concluded that the disorder represented a paraphilia. Explanations for BDD included ideas such as;

1. Body modification is a way for bisexual subjects to preserve their masculinity
2. The fear of losing a limb transmutes to an impulse to amputate so that a person can feel superior
3. A desire for amputation is a learned response reinforced by a rehearsal of experiences with images of amputation
4. A desire for amputation can be an eroticized hatred of the mother figure
5. A desire for amputation is a learned response in childhood from seeing someone with crutches or an amputation getting attention and being happy
6. Body modification is related to a psychotic disturbance where the person is told by voices to remove a limb.

First and Fischer believed that apotemnophilia (an older term denoting the severe urge to amputate a limb) should not be included in BDD because the individuals in their study did not perceive a defect in the limb they wanted to amputate and did not complain about its appearance. They felt that sexual motivations in apotemnophilia were secondary and that the disorder was more akin to gender dysphoria, where the sufferer identifies as a person without the limb. The authors proposed the use of the term body integrity identity disorder to capture the nuances of the disorder. Other researchers argued that the sexual aspects of the disorder were more relevant than identity issues (De Preester, 2013). Sedda and Bottini (2014) characterize the psychological literature succinctly:

> *"In summary, psychological/psychiatric explanations for the desire to amputate a healthy limb include two main hypotheses: a sexual compulsion, belonging to the paraphilic core, and an identity disturbance, paralleling gender identity disorder. At present, no new psychological/psychiatric explanations have been proposed.*" (p.1259)

Brang, McGeoch, and Ramachandran (2008) make the case that the specific form of BDD known as apotemnophilia is neurological disorder. They found that two patients with apotemnophilia had heightened skin conductance in limbs below where they wish to have an amputation. They concluded that this arises from a congenital dysfunction in the right superior parietal lobe and its connection to the insula. This area of the brain "receives and integrates input from various sensory areas and the insula to form a coherent sense of body image" (p. 1306). Indeed, there seems to be a trend in understanding BDD to be a neurologic disease, however, there have only been a limited number of studies with inconsistent methodology, so it the issue is far from settled (Sedda & Bottini, 2014).

Treatment for BDD runs the gamut of psychological and psychiatric solutions. With regard to psychotherapeutic treatments cognitive behavior therapy (CBT) seems to be the most common modality and is generally thought to be effective in treating BDD (Rasmussen et al., 2017). However, a number of authors state that CBT is not effective for everyone suffering from BDD (Hong et al., 2019; Weingarden et al., 2019).

One recent study found the electroconvulsive therapy was effective in eradicating the symptoms of BDD (Başgül et al., 2020).

A German study found there were a number of barriers to treatment. These included a lack of perceived need for treatment, shame, younger age, and a preference for cosmetic and medical treatment over psychiatric treatment. The authors also found a number of characteristics associated with BDD including high BDD symptom severity, poor patient insight into their condition, a previous suicide attempt related to patient appearance, a co-morbid eating disorder, and

current major depressive disorder. Interestingly, the majority of subjects in this study were female and their appearance concerns included a wide range of areas in decreasing order of prevalence – skin, nose, hair, breasts, mouth, genitals, eyes, muscularity, hands, legs, ears, stomach, buttocks, and other facial features. The authors state that there are effective treatments for BDD and advocate for a stepped treatment model that first provides information about the condition and its prevention followed by online CBT, smartphone treatment apps, or specialized face-to-face treatments (Schulte et al., 2020).

An Iranian study using single-subject methodology found that CBT improved patient's BDD symptoms as well co-morbid depression and disability (Abbarin et al., 2018). A case study of a single adolescent female patient found that intensive CBT and exposure/response prevention reduced levels of general anxiety and increased functioning (Neziroglu et al., 2018).

Greenberg et. al. (2019) found that greater readiness/motivation to change, greater treatment expectancy, better baseline BDD related insight, significantly predicted better outcomes with CBT among BDD patients.

Wilhelm et. al. (2019) compared CBT to supportive psychotherapy and found that both therapeutic modalities were effective in treating BDD, but that CBT had greater efficacy. Another small (n=10) 12-week study by the same group examined the use of smartphone based Cognitive Behavioral Therapy (CBT) for the treatment of BDD. The results indicated that this modality of CBT resulted in good response 90 days post treatment with measures of BDD severity decreasing along with improvement of in BDD insight, functional impairment, and quality of life (Wilhelm et al., 2020). Another study using internet-based CBT reported good outcomes in treating BDD patients as well (La Lima, 2018).

Weingarden et. al. (2019) studied the use of d-cycloserine augmented CBT in patients with BDD in a small clinical trial. The authors were looking for a way to enhance standard CBT which they reported as not always being effective with BDD. They found that CBT augmented with d-cycloserine significantly reduced BDD related stress.

A neurological-oriented treatment study found the BDD subjects had abnormal amygdala–temporal connectivity at rest compared to healthy controls as measured by MRI. The administration of intranasal oxytocin was found to reverse resting state abnormality (Grace et al., 2019).

Hong et. al. (2019) writes that BDD is typically treated using CBT and pharmacotherapies, but these are not always effective. The authors review current pharmacotherapies which include anti-depressants, fluoxetine, and suggest that novel treatments such as intranasal oxytocin, atypical antipsychotics and neuromodulation treatments such as transcranial magnetic stimulation hold promise for treating BDD.

Other novel psychotherapy treatments have been suggested for BDD patients but have not yet been implemented. Scandiffio (2018), studied the feasibility of using two Japanese forms of psychotherapy – Morita therapy and Naikan therapy – for treating BDD sufferers using a manualized approach. He had five experts judge whether the use of these therapeutic modalities alone or as an adjunct to CBT would be beneficial. The judges tended to think these therapies could be beneficial.

BDD is a dramatic disorder that has been subject to being sensationalized. For instance, The Jerry Springer Show aired an episode titled "*I'm Happy I Cut Off My Legs*" on November 2, 2006 (TV.com, n.d.)[2]. In this episode a transsexual woman named Sandra describes in detail how she amputated both of her legs. Sandra describes how from an early age her legs just didn't feel right and that after she amputated them (using a handheld electric saw) she felt relieved as if a weight was lifted from her. To make the show even more sensational Springer has Sandra confront a man who was born without legs who berates her for being ungrateful for having legs to begin with. What Sandra describes is a textbook example of BDD. It is too bad that the show didn't explore her transition from being a man to a woman, since gender dysphoria is considered to be a separate diagnosis from BDD, and Sandra would be the rare case where it might be possible to study the intersection of both syndromes. The Jerry Springer Show aired an update with Sandra on January 17, 2007 in which she re-enacted the amputation of her legs from her trailer home.

[2] Unfortunately, the official site of the Jerry Springer Show (*Videos - The Jerry Springer Show*, n.d.) doesn't keep episodes this old on the site. In order to see this episode, it is necessary to search YouTube.com where it can usually be found posted.

9. Neuro-Psychoanalysis and Delusional Misidentification Disorders

While organic disturbances may cause delusional syndromes, the delusions themselves may play a role in repairing a damaged ego or sense of self. Freud (1924) believed that delusions served this function and were a compromise when some aspect of external reality overwhelms the ego's ability to function in it. The delusion puts a sort of band-aid over the inability of the ego to deal with external reality. However, reality continues to try to manifest itself so the delusion must be constantly renewed in a defensive fashion. This idea fits well with the neuropathology of DMS. The damage to brain function is the external reality and the delusion works as the defense against the impairment.

Neuroscientists, as outlined previously, have identified a relationship between focal brain damage and various delusional misidentification syndromes. The abnormal beliefs that people with these syndromes present is typically interpreted using a cognitive psychological framework. While cognitive interpretations can account for the formation of false beliefs, they are not satisfactory for explaining bizarre and persistent delusional states and why these states are resistant to being challenged. The newly emerging field of neuro-psychoanalysis is now attempting to understand why this is so. In many (but not all) cases of delusional misidentification, patients demonstrate some level of pathology in their self-awareness as well as regression to immature styles of thinking and defense mechanisms. It is thought that delusional patients that do not suffer this regression possibly have more cognitive reserves (Venneri & Shanks, 2010).

Brain abnormalities in the right medial-frontal and orbitofrontal regions result in ego-disequilibrium which in turn causes problems with ego boundaries and the inability of the ego to observe its own processes (Feinberg, 2010, 2011). This presents as difficulties in patients not knowing themselves and also, presumably, not knowing where they end, and others begin. Feinberg has proposed a four-tiered hierarchical model of delusional neuropathologies. This model begins with first level cognitive deficits which then lead to second level self-related deficits. The self-related deficits in turn lead to various primitive level defenses which include denial, projection, splitting and dissociation. This third level then results in the fourth level which are the presence of various delusional syndromes including delusional misidentification disorders (Feinberg, 2010). This model fits quite well with DMS, especially Capras syndrome, Cottard's syndrome, and Fregoli delusion where recognition of self and others are problematic. Disorders such as prosopagnosia would seem to spare regions of the brain that are related to ego-function and in disorders such as alien hand syndrome self/no self-confusion is mostly time-limited. In BDD, especially the apotemnophilia variety, sense of self/not self appears to be disrupted. Ego splitting has been also been noted (Thess, 2014). Dissociation of the body-self, as well as the parts of the body, from the ego points to the possibility of object relations pathology (Sarasohn, 2002).

It is not surprising to discover that insight oriented psychodynamic psychotherapy that challenges delusional beliefs systems exacerbates negative transference and emotional withdrawal of the patient. A more relational approach, addressing early object relations, as well as addressing super ego issues related to body hating and how these are enacted in the transference are possible successful psychoanalytic therapeutic approaches (Lemma, 2009; Thess, 2014).

10. Delusional Misidentification and Popular Culture

Appearances of DMS in popular and traditional cultural expressions are extensive. For the sake of brevity only a few are examined here. One of the best examples of a sort of Fregoli delusion which is central to the film *Being John Malkovich* (Jonze, 1999). In this film there is a tunnel in a strange half floor of an office building. Travel through this tunnel allows people to experience 'being' the actor John Malkovich for a short time. Later in the film, John Malkovich himself discovers the existence of the tunnel and goes through it. When he emerges everyone else is a version of Malkovich, with his face and everything they say coming out as the word *Malkovich*.

Science fiction has been an especially fruitful ground for the emergence of modern stories related to imposters masquerading as humans. This can be seen most readily in stories about robots or androids. In many cases these stories revolve around the 'imposters' wanting to become human, or being indistinguishable from humans, as in the Phillip K. Dick story *Do Androids Dream of Electric Sheep?* (1968/1996), which was made into the movie *Blade Runner* (Scott, 1982), or the Isaac Asimov Robot series (1982) which has had a number of film adaptations including most recently the film *I Robot* (Proyas, 2004). In these modern portrayals, humans are generally anxious about the imposter status of the robots and androids as well as being paranoid about their intentions. It is possible that the popularity of the imposters among us theme relates to a subconscious fear of misidentification in general and loss of identity in particular.

An older instance of DMS can be found primarily in the British Isles. In times past British or Celtic babies were sometimes thought to be kidnapped by fairies and replaced by identical looking children. The replacement children, called changelings, were often sickly and exhibited abnormal behavior.

Evans (2000) describes the Irish belief in changelings that is typical of the British Isles;

> *"Mothers and babies were thought to be especially liable to be abducted by the fairies, and protective charms were hidden in a baby's dress or placed in the cradle. When children were taken to be baptized, too, special preparations were made and precautions taken, for example, a County Antrim clergyman reported that his parishioners would place a piece of bread and cheese in the child's clothing.*
> *The old custom of dressing boys in girls' clothes, in long frocks, until they were ten or eleven years of age has been explained as a means of deceiving the fairies, who were always on the lookout for healthy young boys whom they could replace by feeble 'changelings'.*
> *For the same reason it is unwise to praise a child without adding a saving 'God bless him', and young boys are still half jocularly referred to as 'rogues and Tories'.*
> *The belief in 'changelings' may have arisen as an explanation of the high mortality rate among baby boys as compared with girls."* (p. 289)

Indeed, changeling legends may be related to high infant mortality rates in general. When an infant becomes sick and dies for no apparent reason, the human mind will seek an explanation for such a tragic event. If no logical reason can be found the human mind invents a reason that can provide meaning to the tragedy and lessen its sting. There is always a chance the original child can be returned by the fairies, or the thought the original child is being raised by the fairies and has been given special powers can be of comfort to the grieving parents. The death of a child is so difficult to accept that the trauma must be repaired with a delusion. In this case, the imposter delusion keeps the child alive[3].

11. Conclusion

Even though DMS are rare, they present with diverse forms that include delusion, cognitive deficits, and misidentification related to problems confusing and distinguishing between self and other. DMS primarily have an organic basis and therefore the primary modes of treatment for the disorders are medical. Nevertheless, brain abnormalities found in many DMS do give rise to psychological issues. Addressing these psychological issues may help people suffering from DMS better deal with disturbances in brain function. A number of psychological treatment modalities show promise in being able to accomplish this. The many instances of DMS-related cultural phenomena remind us that perhaps some level of delusion and misidentification is part of the human condition, serving to defend us from loss of identity and our mortality.

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[3]Another belief related to infant mortality and the changeling legends is the 'evil eye' which has its origins in the Mediterranean regions. The warding off of the evil eye has a number of forms in different places and can be understood as a delusional belief that prevents infant mortality.

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Nutritional Factors and Academic Performance of Primary School Children in an Urban City in Southern Nigeria

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Abstract
Background: Dietary habits and nutritional status of school children are essential for their growth, cognitive development and subsequent educational achievement. This study assessed the association between nutritional factors and academic performance of primary school children in Benin City. Methods: This cross-sectional study was conducted out among 636 primary school children selected by multistage sampling technique. Pretested, interviewer-administered questionnaire was the data collection tool and anthropometric measurements were taken. Data were analyzed using SPSS statistical package version 22.0 and level of significance was set at $p < 0.05$. Results: Mean age (± SD) was 8.8 (±2.3) years. Only 241 (37.7%) of the respondents ate the three main meals in the last one week preceding the study. Breakfast was skipped by 267 (41.8%) of the respondents. Majority (90.9%) of them had high dietary diversity (consumed > 6 food groups). Prevalence of stunting, underweight, thinness and overweight/obesity was 16.9%, 10.6%, 24.1% and 8.0%, respectively. Those who skipped breakfast (10.9%) had significantly higher proportion of low academic performance compared with those who did not (7.3%), $p<0.001$. Those with low dietary diversity score had significantly higher proportion of low academic performance compared with those who had high dietary diversity score (66.7% versus 7.4%), $p=0.003$. Conclusion: Breakfast skipping and low dietary diversity were significantly associated with poor academic performance of the study population. The government should strengthen its commitment to implementing the school feeding programme in the state and nutrition education of mothers on benefits of not skipping meals especially breakfast should be carried out.

Keywords: Academic Performance, Nutritional Status, Meal Pattern, School Children

INTRODUCTION

Adequate nutrition involves appropriate intake of nutrients which are essential for physical growth, development and good health of children. (Ochola & Masibo, 2014) The adequacy of nutrients in diets eaten is known to be directly related to dietary diversity. (Rathnayake, Madushani & Silva, 2012, Sealey-Potts & Potts, 2014) Dietary diversity which involves eating a variety of foods across and within food groups has long been recognized as a

key element of high-quality diets. (Sealey-Potts & Potts, 2014) Consuming foods from different groups improves nutrient adequacy and reduces the chance of a deficiency or excess of a single nutrient thus promotes good nutritional and health status. (Sealey-Potts & Potts, 2014) Nutrient-rich foods from diverse diets are important elements in child feeding and is essential for promoting their nutritional status. (Alamu, Gondwe, Eyinla & Maziya-Dixon, 2019) In Sub-Saharan African countries including Nigeria, diets of school children are predominantly based on starchy foods with little or no animal products and few fresh fruits and vegetables. (Bello, Ekekezie & Afolabi, 2016, Ndukwu, 2014) Unhealthy eating habits including poor dietary diversity, meal skipping (especially breakfast), poor intake of fruits and vegetables as well as snacking on foods of low nutritive values contribute significantly to malnutrition among primary school children. (Abiba, Naa, Grace & Kubreziga, 2012)

It is estimated that almost one-third of children in developing countries are malnourished. (Food and Agriculture Organization, 2014) In Nigeria, several studies have reported the high burden of malnutrition among primary school children, including undernutrition (underweight, stunting, thinness) (Bello, Ekekezie & Afolabi, 2016, Ndukwu, 2014, Asiegbu et al., 2017, Ene-Obong et al., 2012, Adedeji et al, 2018) and over-nutrition (overweight obesity). (Bello, Ekekezie & Afolabi, 2016, Asiegbu et al., 2017, Ene-Obong et al., 2012, Adedeji et al, 2018) Breakfast plays a critical role in energy balance and dietary regulation and it is important in meeting the day's nutritional needs. (Nicklas et al., 1993) Evidence from systematic reviews from studies among children and adolescents has shown that eating breakfast is associated with a reduced risk of becoming overweight or obese and a reduction in body mass index (BMI). (Szajewska & Ruszczyński, 2010, de la Hunty et al., 2013) Breakfast meals contribute to improving cognition among school age children, (Wesnes, Pincock & Scholey, 2012) in addition to improvements in tasks regarding memory function. (Wesnes, Pincock & Scholey, 2012, Wesnes et al., 2003) Consumption of fruits is associated with better diet quality and decreased risk of obesity in children. (O'Neil1, Nicklas TA & Fulgoni, 2015) A healthy, balanced diet not only determines the health status of a child (Praveen Kulkarni et al., 2014) but can improve brain capacity, maximize cognitive capabilities and improve academic performance in school age children. (Rausch, 2013) Nutritional status of school aged children imparts their health, cognition and subsequently their educational achievement. (Best, 2010)

Though studies have shown that it is more difficult for children to learn without adequate food and nutrition, about 66 million primary school-age children go to school hungry across the developing world, with 23 million in Africa alone. (World Bank, 2012) The nutritional and health benefits of school feeding programmes in terms of improvements in weight, height, school attendance, mathematics performance and improved concentration among school children have been reported. (Yendaw & Dayour, 2015, Jomaa et al., 2011) Consequently, school-feeding programmes have been established and implemented by governments across the globe to address hunger and its negative effect on the nutritional status and learning capacity of school-age children. (Drake et al., 2016) In Nigeria, the National Home Grown School Feeding Programme (NHGSFP) was launched in 2016 by the present (Buhari) administration and it aimed to curb hunger and malnutrition by feeding 5.5 million school pupils one meal a day for all public primary schools annually. (Federal Government of Nigeria, 2017) As at 2017, it was reported that 300 million meals have been served to more than 7.5 million pupils in 46,000 Public Primary Schools in 22 states. (Federal Government of Nigeria, 2017)

There is a dearth of research on the association between nutritional factors and academic performance of school children in the study area. Therefore, this study was carried out to assess the association between nutritional factors (breakfast skipping, dietary diversity and nutritional status) and academic performance of primary school children in Benin City. Findings from this study will provide baseline data with a view to making recommendations to appropriate authorities. Results from this study will also be used to evaluate the impact of the school feeding programme on the nutritional status and academic performance of primary school children in Benin City when fully implemented in the State.

METHODOLOGY

This school-based descriptive cross-sectional study was carried out between February and May 2018 in Benin City, the capital of Edo State, located in the South-South geopolitical zone of Nigeria. Benin City with a total population of 1,309,830 is made up of three (3) Local Government Areas (LGAs) namely, Egor, Oredo, and Ikpoba-Okha. These LGAs are made up of more than 90% urban areas. There are 505 registered primary schools

(262 public and 243 private) in Benin City. The study population included pupils in public and private primary schools in Benin City. All enrolled school aged children between the ages of 6-12 years present on the day of the study were eligible to participate in the study while those who were too ill were excluded. A minimum sample size of 610 was calculated using the Cochrane formula used for descriptive studies, (Cochrane, 1977) assuming a prevalence rate of 72.7% of regular consumption of breakfast among primary school children in a Ghanaian study (Intiful & Lartey, 2014) with a design effect of 2. However, 639 pupils participated in the study.

Multi-stage sampling technique involving four (4) stages was used for selecting participants. In the first stage, simple random sampling technique by balloting was used to select two (Egor and Oredo) out of the three LGAs in Benin City. In the second stage, two wards each were selected from the selected LGAs by simple random sampling technique (balloting). Ugbowo and Uselu-1 were selected from Egor LGA and Iyaro and Ikpema were selected from Oredo LGA. In the third stage, one public and one private primary school were selected from each of the selected wards using simple random sampling technique by computer generated random numbers, giving a total of eight schools (four public and four private). The fourth stage comprised selection of the pupils (participants). The total number of pupils to be selected in each school was determined by proportional to size allocation. Thereafter, in each school, participants were selected from each class arm by simple random sampling using the class attendance register for the day as the sampling frame.

The data collection tool was a structured pretested interviewer-administered questionnaire. Six research assistants who were 500 level medical students of the University of Benin were trained for two days on how to administer the questionnaire. The questionnaire was pretested among primary school pupils in Ovia North-east LGA (another LGA which was not part of the main study) and necessary amendment made before commencement of the actual study. The questionnaire sought information on the sociodemographic characteristics, meal pattern, dietary diversity, anthropometric measurement and academic performance of the participants.

Meal pattern was assessed by asking about frequency of eating breakfast, lunch, dinner as well as consumption of snacks and sugar sweetened beverages in the last one week preceding the study. Dietary diversity was determined by using 24-hour dietary intake recall. The pupils were asked to recall all foods items and beverages consumed both within and outside the home in the previous 24 hours prior to the interview. The ingredients used in preparation of mixed dishes were also noted. The food items were categorized into 12 food groups based on the Food and Agricultural Organization (FAO) guidelines for measuring individual dietary diversity. (Food and Agricultural Organization, 2011) The food groups included: Cereal, Vegetables, White tubers/roots, Fruits, Meat (flesh/organ meat), Eggs, Fish, Legumes/nuts/seeds, Milk/milk products, Oil & fats, Sweets and Beverages. Locally available foods consumed by the pupils were identified and incorporated into the appropriate food groups. Each food group was assigned a score of one and the dietary diversity scores (DDS) for participants were calculated by summing the number of food groups consumed by each respondent over the 24-hour recall period. The scores were then categorized as follows: High ($\geq$ 6 food groups), Medium (4-5 food groups) and Low ($\leq$ 3 food groups). (Food and Agricultural Organization, 2011)

Anthropometric (weight and height) measurements was carried out following the National Health and Nutrition Examination Survey (NHANES) protocol. (Centre for Disease Control and Prevention, 2011) Nutritional status of the children was determined using the World Health Organization (WHO) Anthro-plus® software to compute the anthropometric indices (weight-for-age, height-for-age and BMI-for-age z scores) of the participants. These indices were compared with z-score values of 2007 WHO growth reference standards for children and adolescents 5-19 years. (World Health Organization, 1999, World Health Organization, 2006) For weight-for-age, z-score values of < -2 was regarded as underweight, while values between -2 and +2 was regarded as normal and < -3 indicated severe wasting. For height-for-age, z-score values of < -2 was regarded as stunted, while values between -2 and +2 was regarded as normal and < -3 indicated severe stunting. For BMI-for-age, z-score values < -2 was regarded as thinness while values between -2 and +2 was regarded as normal. Values > +2 was regarded as overweight, and values > +3 was regarded as obese.

Academic performance of the participants was assessed using the last term's examination average score of two core subjects (Mathematics and English Language). These were graded as high (>75%), average (50-74%) and low (< 50%). (Nduagubam et al., 2017) Socioeconomic class for each child was assessed based on the father's

occupation and mother's educational attainment using a model in a previous study. (Olusanya, Okpere & Ezimokhai, 1985)

Approval was sought from the heads of the selected primary schools. Informed consent and assent were obtained from the parents/guardian and pupils, respectively. Names and addresses of respondents were omitted to ensure confidentiality. They were also informed that they had the right to withdraw from the interview at any time and that withdrawal poses no loss or harm. Data was analysed using IBM SPSS version 21.0 software. Univariate analysis was done to assess the distribution of the variables. Bivariate analysis was done to determine nutritional factors associated with academic performance of participants. Tests of association for categorical variables was done using Chi square test and Fisher's exact test. p-value of less than 0.05 was considered statistically significant.

RESULTS

Six hundred and thirty-nine pupils aged between 6 and 12 years participated in the study. Majority of them 439 (68.7%) fell within the age group 8-9 with mean age (± SD) of 8.8 (2.3) years. A higher proportion were males 338 (52.1%), 131 (20.5%) were in primary 5 and 435 (68.1%) were from household sizes ≤6. Three hundred and forty-one (53.4%) of the respondents were in the public schools and 315 (49.3%) of them belonged to low socio-economic class. **(Table 1)**

Table 1: Demographic and socio-economic characteristics of respondents

Variables	Frequency (n=639)	Percent
Age group (years)		
6-7	58	9.1
8-9	439	68.7
10-12	142	22.2
Sex		
Male	338	52.9
Female	301	47.1
School type		
Private	298	46. 6
Public	341	53.4
Class		
Primary 1	129	20.2
Primary 2	128	20.0
Primary 3	85	13,3
Primary 4	74	11.6
Primary 5	131	20.5
Primary 6	92	14.4
Religion		
Christianity	601	94.1
Islam	38	5.9
Mother's level of education		
Primary	181	28.3
Secondary	324	50.7
Tertiary	134	21.0
Household size		
≤ 6	435	68.1
> 6	204	31.9
Socio-economic status		
Upper	195	30.5
Middle	129	20.2
Lower	315	49.3

Mean age (± SD) = 8.8 (2.3) years

Table 2 shows the meal pattern of the respondents in the last one week preceding the study. Only 241 (37.7%) of the respondents ate the three main meals (breakfast, lunch and dinner) in the last one week preceding the study. Three hundred and seventy-two (58.2%), 356 (55.7%) and 424 (66.4%) of the respondents ate breakfast, lunch

and dinner, respectively every day in the last one week preceding the study. Daily intake of snacks and sweetened beverages was reported by 171 (26.8%) and 82 (12.8%) of the respondents, respectively.

Table 2: Meal pattern of respondents in the last one week

Variables	Frequency (n=639)	Percent
Three main meals in the last week		
Yes	241	37.7
No	398	63.3
Breakfast intake/week		
Daily	372	58.2
Sometimes	230	36.0
Never	37	5.8
Lunch intake/week		
Daily	356	55.7
Sometimes	276	43.2
Never	7	1.1
Dinner intake/week		
Daily	424	66.4
Sometimes	208	32.5
Never	7	1.1
Snack intake/week		
Daily	171	26.8
Sometimes	434	67.9
Never	34	5.3
Sweetened beverage intake/week		
Daily	82	12.8
Sometimes	479	75.0
Never	78	12.2

Food groups consumed in the last 24 hours by the respondents included oils and fats 639 (100%), cereals 567 (88.7%), beverages 561 (87.8%), fish 482 (75.4%), milk and milk products 480 (75.1%), and dark green vegetables 480 (75.1%). Majority of the respondents 581 (90.9%) had high dietary diversity (consumed ≥ 6 food groups) while 55 (8.6%) and 3 (0.5%) had medium (consumed 4-5 food groups) and low dietary diversity (consumed ≤ 3 food groups), respectively. **(Table 3)** One hundred and eight (16.9%) of the respondents were stunted, 68 (10.6%) were underweight while 154 (24.1%) and 51 (8.0%) were thin and overweight/obese, respectively. **(Table 4)**

Table 3: Food groups eaten by respondents (24 hours recall)

Variables	Frequency (n=639)	Percent
Food groups*		
Oils and fats	639	100.0
Cereals	567	88.7
Beverages	561	87.8
Fish/other sea foods	482	75.4
Milk and milk products	480	75.1
Vegetables	480	75.1
Sweets	478	74.8
White tubers and root	451	70.6
Fruits (Vitamin A rich fruits/other fruits	450	70.4
Meat (Flesh and organ meat)	411	64.3
Legumes nuts and seeds	379	59.3
Eggs	378	59.2
Dietary Diversity Scoring		
High	581	90.9
Medium	55	8.6
Low	3	0.5

*Multiple responses

Table 4: Nutritional status of respondents

Variables	Frequency (n=639)	Percent
Height-for-age		
Stunted	108	16.9
Normal	531	83.1
Weight-for-age		
Underweight	68	10.6
Normal	571	89.4
BMI-for-age		
Thin	154	24.1
Normal	434	67.9
Overweight/Obese	51	8.0

Those aged 10-12 years 40 (28.2%) had the highest prevalence of thinness compared to those who were 8-9 years 101 (23.0%) and 6-7 years 13 (22.4%) but this was not statistically significant, (p=0.100). Females had the highest proportion of thinness and overweight/obesity compared with the males (26.4% versus 21.3% and 10.3% and 8.6%, respectively) but this was not statistically significant, (p=0.186). Thinness was significantly higher among those in the public schools 98 (28.7%) than private schools 56 (18.8%) while overweight/obesity was higher among those in the private schools 35 (11.7%) than public schools 16 (4.7%), p<0.001. Thinness was higher among those in the primary 4-6, 75 (25.3%) than those in primary 1-3 79 (23.1%) while overweight/obesity was higher among those in primary 1-3, 28 (8.2%) than those in primary 4-6, 23 (7.7%), but association was not statistically significant, p=0.813. Thinness was significantly highest among those whose mothers had primary education 66 (36.5%) while overweight/obesity was highest among those whose mothers had tertiary education 16 (11.9%), p<0.001. Overweight/Obesity was highest among those from household size ≤ 6 than those from household size > 6, (9.0% versus 5.9%) but the association was not statistically significantly, p=0.406. Those in the lower socio-economic class had a significantly higher proportion of thinness than those in the upper socio-economic class (28.9 versus 14.4%), p<0.001. Conversely, those in the upper socio-economic class had a significantly higher proportion of overweight/obesity than those in the lower socio-economic class (9.2% versus 4.1%), p<0.001. **(Table 5)**

For Mathematic, 302 (47.3%) of the respondents had high scores while 246 (38.5%) and 91 (14.2%) had average and low scores, respectively. For English language, 296 (46.3%) of the respondents had high score while 299 (46.8%) and 44 (6.9%) had average and low scores, respectively. Overall, 276 (43.2%) of the respondents had high academic performance while 307 (48.0%) and 56 (8.8%) had average and low academic performance, respectively. **(Table 6)** The association between selected nutritional factors and overall academic performance of the participants is shown in **Table 7**. Those who did not skip breakfast 234 (62.9%) had a significantly higher proportion of high academic performance compared to those who skipped breakfast 42 (15.7%) daily in the last one week preceding the study, p<0.001. Conversely, those who skipped breakfast 29 (10.9%) had a significantly higher proportion of low academic performance compared with those who did not skip breakfast 27 (7.3%) daily in the last one week preceding the study, p<0.001. Those with high dietary diversity score 255 (43.9%) had the highest proportion of overall high academic performance while those with low dietary diversity score 2 (66.7%) had the highest proportion of overall low academic performance, p=0.003. Those who were thin had a higher proportion of low academic performance compared with those who were overweight/obese (7.8% versus 2.0%), but the association was not statistically significant, p=0.422

DISCUSSION

The study described the meal pattern, dietary diversity and nutritional status of primary school children in Benin City and their association with the academic performance of the study population. Only a little over one-third of the study population ate all three main meals (breakfast, lunch and dinner) in the last one week preceding the study indicating that meal skipping is prevalent among them. This is worrisome more so that about two-fifth of the study population reported skipping breakfast which is considered the most important meal of the day. [27] This is similar to what has been reported in other studies. (Ndukwu, 2014, Olusanya, 2010, Amini et al., 2014) Adequate breakfast consumption by school children ensures they meet their daily nutrient and energy intakes. A study in Ghana reported that breakfast meal contributed between 32-41% of the day's energy intake and 30-47% of micronutrient intake. (Intiful & Lartey, 2014)

Table 5: Sociodemographic characteristics and nutritional status (BMI-for-age) of respondents

Variables	Nutritional Status (BMI-for-age)			Test statistics	p-value
	Thin (n=154) n (%)	Normal (n=434) n (%)	Overweight (n=51) n (%)		
Age group (years)					
6-7	13 (22.4)	45 (77.6)	0 (0.0)		
8-9	101 (23.0)	300 (68.3)	38 (11.7)		
10-12	40 (28.2)	89 (62.7)	13 (9.1)	χ^2=7.770	0.100
Sex					
Male	72 (21.3)	237 (70.1)	29 (8.6)		
Female	82 (26.4)	197 (63.3)	32 (10.3)	χ^2=3.366	0.186
School type					
Private	56 (18.8)	207 (69.5)	35 (11.7)		
Public	98 (28.7)	227 (66.6)	16 (4.7)	χ^2=16.636	<0.001*
Class					
Primary 1-3	79 (23.1)	235 (68.7)	28 (8.2)		
Primary 4-6	75 (25.3)	199 (67.0)	23 (7.7)	χ^2=0.413	0.813*
Mother's education					
Primary	66 (36.5)	99 (54.7)	16 (8.8)		
Secondary	67 (20.7)	238(73.4)	19 (5.9)		
Tertiary	21 (15.7)	97 (72.4)	16 (11.9)	χ^2=33.362	<0.001*
Household size					
≤ 6	104 (23.9)	292 (67.1)	39 (9.0)		
> 6	50 (24.5)	142 (69.6)	12 (5.9)	χ^2=1.801	0.406
Socio-economic class					
Upper	28 (14.4)	149 (76.4)	18 (9.2)		
Middle	35 (27.1)	74 (57.4)	20 (15.5)		
Lower	91 (28.9)	211 (67.0)	13 (4.1)	χ^2=30.785	<0.001*

***Statistically Significant**

Table 6: Academic performance of respondents

Variables	Frequency (n=639)	Percent
Mathematic score		
High	302	47.3
Average	246	38.5
Low	91	14.2
English Language score		
High	296	46.3
Average	299	46.8
Low	44	6.9
Overall academic performance		
High	276	43.2
Average	307	48.0
Low	56	8.8

Table 7: Association between nutritional factors and overall academic performance of respondents

Variables	Overall academic performance			Test statistics	p-value
	High (n=276) n (%)	Average (n=307) n (%)	Low (n=56) n (%)		
Breakfast Skipping					
Yes	42 (15.7)	196 (73.4)	29 (10.9)		
No	234 (62.9)	111 (29.8)	27 (7.3)	χ^2=143.8	<0.001*
Dietary Diversity Scoring					
Low	0 (0.0)	1 (33.3)	2 (66.7)		
Medium	21 (38.2)	23 (41.8)	11 (20.0)		
High	255 (43.9)	283 (48.7)	43 (7.4)	χ^2=22.945	0.003*^
BMI-for-age					
Thin	68 (44.2)	74 (48.0)	12 (7.8)		
Normal	184 (42.4)	207 (47.7)	43 (9.9)		
Overweight/Obese	24 (47.0)	26 (51.0)	1 (2.0)	χ^2=3.883	0.422

***Statistically Significant ^Fishers**

Breakfast skipping could be attributed to mothers' inability to prepare meals before their children go to school, usually because they work outside the home and have to leave for work very early Skipping breakfast affects subsequent meal intakes and overall nutritional and health status of children. (Ndukwu, 2014) Breakfast skipping may interfere with the child's level of attention in class and may have negative implications for the achievement of educational objectives and interfere with school enrolment, attendance and performance. (Ochola & Masibo, 2014, Wesnes et al., 2012) Furthermore, skipping breakfast is associated with risk of becoming overweight or obese (Szajewska & Ruszczyński, 2010, de la Hunty et al., 2013 as well as hypertension, diabetes mellitus and cardio-metabolic diseases. (Monzani et al., 2019, Smith et al., 2010) Majority of the respondents had high dietary diversity scoring with a higher proportion of them consuming more of fats/oils and plant-based diets of cereal, roots and tubers with limited foods of animal source. The high consumption of cereal-based foods is in agreement with similar studies in Nigeria (Alamu et al., 2019, Bello et al., 2016, Ndukwu, 2014, Nnebue et al., 2016, Okafor, Odo & Onodigbo, 2020) and other African countries (Abdul-Razak & Zakari, 2019, Alamgea et al., 2018, Nyathela & Oldewage-Theron, 2017, Grobbelaar, Napier & Oldwage-Theron, 2013) which is a reflection of foods that constitute the major staples in the study area. The implication of this is that these dietary pattern may not meet the up the nutritional needs of these children.

It is worth noting that more than one-third of them did not consume eggs, flesh and organ meat as reported in other studies. (Bello et al., 2016, Ndukwu, 2014, Okafor, Odo & Onodigbo, 2020) A possible explanation could be the cultural belief that foods such as eggs, flesh and organ meat are not meant for children but for the adult members of the households or inability to afford these animal sources of protein which are usually more expensive. Adequate protein of animal sources in the diet of growing children is essential for achieving optimal growth and development. We found the full spectrum of malnutrition (stunting, underweight, thinness and overweight/obesity) in our study which adds to the existing evidence of a coexistence of undernutrition and over-nutrition in school age children in developing countries including Nigeria. (Bello et al., 2016, Asiegbu et al., 2017, Ene-Obong et al., 2012, Nyathela & Oldewage-Theron, 2017) This double burden of malnutrition has been attributed to increasing globalization and westernization resulting in changes in dietary pattern from the traditional towards a western diet coupled with sedentary lifestyle and technological advancement. Undernutrition can inhibit growth and development in school children (Best et al., 2010) while over-nutrition will predispose to overweight and obesity which have been reported to be risk factors for the development several chronic non-communicable conditions later in adulthood. (Hainer & Aldhoon-Hainerova, 2013, Bloom et al., 2011)

Age group, sex and household size were not significantly associated with the nutritional status of the respondents. Attending public schools was significantly associated with higher proportion of thinness while private school attendance was significantly associated with higher proportion of overweight/obesity. This trend has been reported by other studies. (Asiegbu et al., 2017, Adedeji et al., 2018, Akor, Okolo S & Okolo A, 2010, Agbo, Envuladu & Zoakah, 2012, Opara, Ikpeme & Ekanem, 2010) Possibly, the difference in the socioeconomic class of children

attending public and private schools could have accounted for this. Parents who enroll their children in public schools are usually from low socioeconomic class and are more likely to provide monotonous diets due to their low purchasing power while those from the higher social class can afford more nutritious diets in addition to energy-dense sugar sweetened beverages, sweets, etc.

Maternal educational level was also significantly associated with nutritional status of the children. Similar findings have been reported by several studies. (Ndukwu, 2014, Adedeji et al., 2018, Sufiyan, Bashir & Umar, 2012, Senbanjo et al., 2011, Owoaje et al., 2014) Maternal education has been documented to be a significant determinant of healthy practices including healthier food choices as well as good health seeking behavior for their households. Mothers with low education are more likely to be ignorant about adequate dietary practices and they may also be less economically empowered which prevents them for purchasing nutritious foods for their households. In addition, mothers with higher education are likely to be employed and more economically empowered and able to afford more nutritious foods. This is corroborated by the finding in this study that the prevalence of thinness was highest among those in the lower socio-economic class while overweight/obesity was highest among those in the upper socio-economic class. This has also been reported elsewhere. (Asiegbu et al., 2017) It could also be that children in the upper socioeconomic class are likely to be less physically active, for example, they are more likely to ride in a car to school, be engaged in longer television viewing time and indoor games such as video games since their parents can afford these gadgets.

The highest proportion of the children had average academic performance which is similar to a previous study. (Okafor et al., 2020) Breakfast intake was significantly associated with high academic performance of the respondents. (Doku et al., 2013, Acham et al., 2012) Consumption of breakfast meals improves cognition among school age children with potential positive effects on their school performance. (Wesnes, Pincock & Scholey, 2012) Studies have shown that school children who took breakfast had higher mental arithmetic task performance, showed better creative thinking and improvements in tasks regarding memory function. (Wesnes, Pincock & Scholey, 2012, Wesnes et al., 2003) A low dietary diversity was significantly associated with poor academic performance of the respondents as has been reported in another study. (Okafor et al., 2020) Of note is that none of those who had low dietary diversity had excellent academic performance. Eating variety of foods from different food groups ensures that all the essential nutrients required for optimum physical growth and cognitive development of the child is available. Though our study did not find a significant association between nutritional status and academic performance, it is well documented that adequate nutritional status has a positive and direct impact on academic achievement. When children's basic nutritional and fitness needs are met, they have the cognitive energy to learn and achieve. There is evidence that healthy, well-nourished children are more prepared to learn, more likely to attend school and class, and able to take advantage of educational opportunities. (Ochola & Masibo, 2014) The limitations of our study include the fact that the dietary intake information collected from the respondents may have been subject to recall bias. In addition, the study utilized information based on self-report by the respondents which might be subject to under- or over-reporting. Though the method for assessment of academic performance of the school children in this study has been used previously (Nduagubam et al., 2017) variation between individual teachers may have affected the measure.

CONCLUSION

The study revealed that nutritional factors such as breakfast skipping and low dietary diversity were significantly associated with poor academic performance of primary school children in Benin City. We recommend that the government should remain committed to providing the resources need to scaled up and extend the implementation of the National Home Grown School Meal Program (NHSMP) to the state since at the time of this report, the programme has not commenced in the state. This will help to ensure that every child is sure of a breakfast meal on every school day. Nutrition education of mothers and household members on preparing diverse diet from locally available food and benefits of not skipping meals especially breakfast should be carried out. Continuous nutrition education of primary school children so they are made aware of healthy food choices and practices. Female education and economic empowerment programmes should be strengthened and scaled up by the Edo State government.

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Authors' Contribution:

VOO: Conception/Design of the research; Data interpretation; Drafting the manuscript; Revising the manuscript for intellectual content and Final approval.

EOO: Design of the research; Data collection/analysis, Drafting the manuscript and Final approval

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Approach of Primary Physicians in the Management of Chronic Cough, in Najran City, Saudi Arabia

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Abstract
Background: Chronic cough can impair quality of life, with serious biomedical and psychosocial impacts. This condition should be managed well by physicians at primary health care level. Objective: To evaluate the approach of primary physicians in the management of chronic cough. Materials and Methods: Cross-sectional study was conducted using an interviewer-administered questionnaire from September 2018-March 2019 in Najran City, Saudi Arabia. All primary physicians (n = 134) working at different primary health care facilities during the study period who agreed to participate were included. Results: The prevalence of chronic cough at primary physician's practice was 25%. The study revealed around 61 % of primary physicians (n=134) have good clinical experience of the management of chronic cough despite the widespread of clinical guidelines. They make definitive diagnosis of chronic cough as following; 66% based on history &physical examination,61% based on further tests and 60 % based on response to empiric therapy. They diagnose their cases secondary to allergy (63%), inflammation (60%), infection (59%), medications (42%) and malignancy (33%). The study showed inadequacy of participants in treating the chronic cough; 63% prescribe a decongestant & an antihistamine for upper airway cough syndrome (UACS), 81% prescribe an inhaled bronchodilators or corticosteroids for asthma, 79% prescribe an antacid agent for gastro-esophageal reflux disease (GERD) and 60% refer to specialized clinic. About 46% of participants approach the child with chronic cough as same as adult approach. Conclusion: Chronic cough is high prevalent in practice of primary care physicians. Although the widespread dissemination of management guidelines of chronic cough, the inadequacy in clinical practice of primary physicians still occurs. Design educational programs and increased awareness for patients and their families about chronic cough are responsible solutions.

Keywords: Chronic Cough, Primary Care, Physicians, Approach

BACKGROUND

Primary care physicians offer the ability to manage difficult and complex health problems, such as chronic cough; however, there are many potential etiologies of this condition and wide variation in management approaches. In adults, chronic cough has been defined as lasting for more than 8 weeks, while in children, cough is considered chronic if present for more than 4 weeks (Chang and Glomb,2006; Irwin and Madison,2000). Persistent and excessive coughing is considered a significant problem that can impair quality of life and lead to serious

biomedical and psychosocial effects. It is associated with a high burden of recurrent health facility visits, personal and family stress, and social embarrassment. It is found that >80% of parents had sought five or more medical consultations for their child with chronic cough in in one year (O'Grady et al.,2017). Physical impairment, psychological upset, school or work absenteeism, and a substantial direct and indirect economic burden are bad impacts of chronic cough (Dal Negro et al.,2019). The morbidity of chronic cough is reported at between 3% and 40% of the population and represents a substantial epidemiological burden with a high global prevalence (10%–20% in the general adult population) as well as a major unmet medical need (Mahashur,2015; Morice and Kastelik,2003).

There are many causes for chronic cough. The most cases can be accounted for by upper airway cough syndrome (UACS), gastro-esophageal reflux disease (GERD), asthma, and non-asthmatic eosinophilic bronchitis (NAEB) (Michaudet and Malaty,2017). Ideally, chronic cough is managed as the manifestation of disease rather than by symptomatic therapy. The width and diversity of etiologies from self-limited to lethal diseases, such as like lung cancer, represent a challenge to the clinical practitioner. The medical expert and well-qualified physician represent the cornerstone of good care and best practice either in curing the chronic cough or minimizing its sequelae and recurrence. An estimated 90% of cases of chronic cough can be worked-up efficiently by a primary physician using a standard protocol based on updated evidence that empowers a primary physician in managing the chronic cough effectively (Lawler,1998). Although the systematic clinical reasoning is the ultimate management approach for chronic cough, most of primary care physicians do not adhere to recommended guidelines (Mackley et al.,2013). Misdiagnosis, over-investigation, irrational medication and inappropriate referral are all examples of malpractice in dealing with chronic cough.

In this study, we evaluated the approach of primary physicians in the management of chronic cough in Najran City, Saudi Arabia. This will be beneficial in strengthening the role of primary care services in solving complex health problems such as chronic cough.

MATERIALS AND METHODS:

This study was conducted using a descriptive and analytic cross-sectional survey design from September 2018-March 2019 in Najran City, in southwestern Saudi Arabia. The primary health services in this region are provided by many governmental and private facilities. The study population consisted of all primary physicians practicing in different specialties; general practitioner, emergency medicine, family medicine, general internal medicine and general pediatric medicine. We had included all primary physicians (n = 134) working at different health services facilities (Ministry of Health [MOH], University Health Services, Military Health Services, National Guard Health Services, Interior Ministry Health Services and Private Health Services) during the study period who agreed to participate; those who declined to participate were excluded.

Researchers constructed a three-parts questionnaire to collect the data. Section 1 was designed to collect data for the most relevant sociodemographic variables of participants, including sex, age, nationality, marital status, job title, medical specialty, qualifications, work place, health care facility, and years of experience. Section 2 consisted of a clinical audit of the total number of patients per clinic and the number of patients presenting with chronic cough per clinic. Section 3 has made in form of self-evaluation for participants regarding their practice in management of chronic cough. It consisted of 20 items (Appendix A) designed to collect data about the primary physicians' approach to chronic cough. Three phrases about diagnosis, 5 phrases about etiology,10 phrases about treatment and 2 phrases about consideration of differences between adult and child age groups. A 5-point Likert scale was adopted to qualify answers ranging from (1) for (Strongly Disagree) up to degree (5) for (Strongly Agree).

The questionnaire`s content and relevance have been tested for their appropriateness, reliability. The content validity had evaluated on reviewing all scale items by three experts and any suggested modifications were done. We use the internal consistency with Cronbach's alpha. The calculated Cronbach's Alpha was (0.789.) for the whole questions which had (5-Point Likert scale) of the questionnaire; these results indicate acceptable reliability for the questionnaire.

Data was collected through face-to-face delivery mode. Then fed to The Statistical Package for Social Sciences program (SPSS v.23) after checking and coding. The basic features of the data in the study had analyzed through frequencies, percentages, mean and standard deviation.

RESULTS

The aim of study was to examine the clinical approach of primary physicians in the management of chronic cough. All participants (N=134) had completed the interview administrated questionnaire. The mmajority (97.8%) of them were non-Saudi, of which 51.5% were female, 97.8% were married and 56.7% were in the 30 to 40 years age group. In terms of medical specialty, 44% of the participants practiced general medicine, 44% held a bachelor's degree only, 73.1% work in the MOH and 54.5% were employed at primary health care (PHC) centers. More than half (53%) of the total participants had 5 to 10 years of clinical experience. On average, participants had managed 24 patients per clinic, where six of patients had chronic cough. All details about baseline characteristics of the sample shown in the Table (1).

Table 1: Demographic data of the sample study (N=134)

Demographic Variables		Count	Percent (%)
Gender	Male	65	48.5
	Female	69	51.5
Age	<30 years	6	4.5
	30-40 years	76	56.7
	41-50 years	44	32.8
	> 50 years	8	6.0
Nationality	Saudi	3	2.2
	Non-Saudi	131	97.8
Marital status	Single	3	2.2
	Married	131	97.8
Job Title	General practionair	75	56.0
	Senior registrar	42	31.3
	Consultant	17	12.7
Medical Specialty	General medicine	59	44.0
	Emergency medicine	9	6.7
	Family medicine	29	21.6
	General internal medicine	5	3.7
	General pediatric medicine	32	23.9
Qualification degree	Bachler	59	44.0
	Diploma	8	6.0
	Master	16	11.9
	PhD.	6	4.5
	Board	45	33.6
Work place	MOH	98	73.1
	University health services	10	7.5
	Military health services	9	6.7
	Private health services	17	12.7
Healthcare facility	PHC-center	73	54.5
	Hospital-outpatient clinic	37	27.6
	Hospital -emergency department	20	14.9
	Polyclinic	4	3.0
Experience duration	<5 years	10	7.5
	5-10 years	71	53.0
	11-20 years	45	33.6
	>20 years	8	6.0

Table (2) represents frequencies and percentages, mean and standard deviation of clinical approach of primary physicians in the management of chronic cough. The highest percentage(82%) was awarded to the phrase (If an environmental irritants is suspected; I eliminate the patient's exposure to irritants) with mean score (4.09) out of (5) and Std. Deviation (1.12493), followed by (If ACE inhibitors using is suspected, I shift to another antihypertensive agent) with mean score (4.05), followed by (If bronchial asthma is suspected, I prescribe an inhaled bronchodilators or corticosteroids) with mean score (4.03) while the lowest percentage (33%)was awarded to the phrase (I find the etiology of most of chronic cough cases is malignancy) with mean (1.64) out of (5) and Std. Deviation (0.85065).The following table shows all detailed of these results.

Table 2: Descriptive statistics of clinical approach of primary physicians to chronic cough (N=134)

Domain		Item	Mean	St. D	Percentage
Diagnosis	1	I make definitive diagnosis for patient with chronic cough based on history &physical examination	3.31	1.21767	66%
	2	I make definitive diagnosis for patient with chronic cough based on further tests	3.07	0.95813	61%
	3	I make definitive diagnosis for patient with chronic cough based on response to empiric therapy	2.99	1.04042	60%
Etiology	4	I find the etiology of most of chronic cough cases is infection	2.94	0.72412	59%
	5	I find the etiology of most of chronic cough cases is allergy	3.15	0.71707	63%
	6	I find the etiology of most of chronic cough cases is inflammation	2.99	0.72968	60%
	7	I find the etiology of most of chronic cough cases is medications	2.11	0.88558	42%
	8	I find the etiology of most of chronic cough cases is malignancy	1.64	0.85065	33%
Treatment	9	I don't treat patient with chronic cough unless I make definitive diagnosis	3.40	1.22087	68%
	10	I explain to patient that most of chronic cough are self-limited	2.19	1.28528	44%
	11	I advise patient with chronic cough about nonpharmacological remedies	2.99	1.26531	60%
	12	If upper airway cough syndrome is suspected, I prescribe a decongestant & an antihistamine	3.13	1.24616	63%
	13	If bronchial asthma is suspected, I prescribe an inhaled bronchodilators or corticosteroids	4.03	0.88377	81%
	14	If gastroesophageal reflux disease is suspected, I prescribe an antacid agent	3.97	0.98414	79%
	15	If ACE inhibitors using is suspected, I shift to another antihypertensive agent	4.05	1.17916	81%
	16	If an environmental irritant is suspected; I eliminate the patient's exposure to irritants	4.09	1.12493	82%
	17	Then after, if chronic cough persists; I think about psychogenic cough	2.84	1.38278	57%
	18	I refer patient with chronic cough to specialized physician	3.01	1.36776	60%
Age group	19	I approach the child with chronic cough as same as adult approach	2.32	1.49148	46%
	20	I advise parents against administering cough medications to children younger than 4 years	3.03	1.57967	61%

DISCUSSION

Study showed that primary physicians (*n* = 134) have approached 25% of their patients with chronic cough, which is slightly higher than the prevalence (22%) in the same setting (Park,2011). This finding reflected how common the chronic cough as primary health condition that needs a systematic and integrated approach. A thorough medical history and physical examination are paramount in the diagnosis of chronic cough. Based on that physician can develop a proper diagnosis and treatment and limit unnecessary testing (Lai et al.,2018). We found the primary physicians (n=134) made definitive diagnosis of chronic cough as following; 66% based on history &physical examination,61% based on further tests and 60 % based on response to empiric therapy. This underscores the importance of the primary physician's role in the initial assessment of chronic cough to place a differential diagnosis, select appropriate test, make a provisional diagnosis and empirical therapy.

The most common etiologies to be considered in the management of patients >15 years of age with cough lasting > 8 weeks; (UACS) secondary to rhino sinus diseases, asthma, (NAEB) and (GERD) (Irwin et al.,2018). Other etiologies include angiotensin-converting enzyme inhibitor (ACE-I) use, environmental triggers, tobacco use,

chronic obstructive pulmonary disease, and obstructive sleep apnea. In children, most cases can be accounted for by three conditions: asthma, protracted bacterial bronchitis, and upper airway cough syndrome (Michaudet and Malaty,2017). One study proposed a clinical method to detect the causes of chronic cough in a primary care setting found (35.9%) post-infectious cough while (ACE-I) induced cough (12.0%). There were only (1.7%) cases of possible lung cancer (Nantha,2014). Through the practice of the study sample, it was clear from primary physician's diagnostic performance that most cases are allergy (63%), inflammation (60%) and infection (59%) and these findings are in line with the most common causes, while the accounted case for medications (42%) and malignancy (33%) are not. This requires more care to enable primary care physicians to know the most common causes of chronic cough, taking into account other lesser-known causes, as well as training them to differentiate between them, whether in history, clinical examination or the necessary tests.

Although empirical therapy is useful in confirming or excluding the final diagnosis of chronic cough, those who use this strategy to treat chronic cough represented 68% of study sample. Treatment guidelines for chronic cough recommend to direct appropriate trials for the most common causes of cough (i.e., UACS, asthma, NAEB, and GERD) in systematic manner. Subsequently assessment of response to that (full, partially or not) should be instituted (Irwin et al.,2006).

The study revealed that about 44% of primary care physicians consider chronic cough to be a temporary problem, and thus violated the definition of chronic cough, which provides for the continuity of cough for more than 8 weeks. This reflects the confusing between acute and chronic cough in terms of definition and etiology as well as the nature of treatment. Sixty percent of them advised their patients with chronic cough about nonpharmacological remedies, ignoring the patient's growing suffering in many domains; physical, psychological, and social. Patients with chronic cough frequently report musculoskeletal chest pains, sleep disturbance, vomiting, and stress incontinence. The psychosocial impact of cough includes a high prevalence of depressive symptoms and worry about serious underlying diseases, difficulty in social life, and disruption of employment can occur (Morice et al.,2006).

The study showed inadequacy of primary care physicians in treating the most common causes of chronic cough, as follows: 63% prescribe a decongestant & an antihistamine for (UACS), 82% eliminate the patient's exposure to environmental irritants, 81% prescribe an inhaled bronchodilators or corticosteroids for asthma, 79% prescribe an antacid agent for (GERD) and around 81% shift to another antihypertensive agent If ACE inhibitors using is suspected. It was remarkable that about 60% of primary care physicians refer patient with chronic cough to specialized clinic. This is irrational referral unless initial treatment was approached including proper history-taking, physical examination, chest x-ray and empirical therapy. A study conducted in Singapore on such cases showed that 65% of the referred cases were diagnosed at the first visit through the patients' detailed history-taking, physical examination and chest radiography (Poulose et al.,2016).

While, the habit cough or psychogenic cough is rare cause and its diagnoses can be made only after an extensive evaluation is performed to rule out uncommon causes of chronic cough, and when cough improves with behavior modification (Irwin et al.,2006). Study showed 57% of primary care physicians think about psychogenic cough if chronic cough persists; and this is not logical thinking.

Despite cough in children is labeled as chronic if present for more than 4 weeks instead of 8 weeks. The approach for chronic cough should be different to those in adults as the etiological factors and some medications used for cough in adults have little role in children and might lead to adverse reactions and toxicity (Chang,2005). Study results revealed 46% of participants approach the child with chronic cough as same as adult approach while only 61% of participants advise parents against cough medications for children.

Taking into account the design of study and sample size, the study reveals that around 61 % of primary physicians have good clinical experience of the management of chronic cough despite the widespread release of simplified clinical practice guidelines. Designing and implementing education programs about the best approach of chronic cough could help physicians in primary care for better management.

CONCLUSION

It is noticeable how common chronic cough is in the practice field of primary care physicians. Although the widespread dissemination of management guidelines of chronic cough, there is variations in approach to chronic cough among primary care physicians. So, design educational programs about chronic cough management is a responsible solution for inadequacy in the clinical practice of primary physicians. Furthermore, the increased awareness of patients and their families about chronic cough is an achievable objective that could improve care and limit financial and social burden. Finally, more and more investigation is required by scholars and leaders in the medical field to resolve a disconnect between the recommended scientific guidelines and the practice of clinicians at primary care level.

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Effect of a Foot Arch Exercise Program for High School Runners

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Abstract
The short-foot exercise (SFE) has been used as a training method for the intrinsic muscles of the foot. The effectiveness of SFE is mostly reported in short-term interventions, with only a few reports of its sustained effects. The purpose of this study was to verify the effect of SFE training for 31 high school runners. All subjects were measured 3 times for 8 months, and underwent ankle stabilization training during the study period. During the first 3 months of the study period, one randomly selected group of subjects underwent SFE, and another group did not, the non-SFE group. Measurement items were pain, navicular drop (ND), modified star excursion balance test (mSEBT), ankle dorsiflexion angle and toe gripping force. A one-way analysis of variance with post-hoc Tukey's test was performed to evaluate differences between groups with multiple comparison analysis for each measurement. The number of physical problems in the SFE group was lower at the time of the second measurement (M2) but increased at the third measurement (M3). In the SFE group, the ND value was significantly decreased at the time of the M2 but was significantly increased at the M3. Toe gripping force showed a significantly larger value in the SFE group at the M3. It was suggested that the SFE was effective for ND and decreasing some pains. There are no studies referring to the sustainability of the effects of the SFE, so these results can be a reference for future investigation of this exercise.

Keywords: Short Foot Exercise, Medial Longitudinal Arch, Sports Injuries, Intrinsic Foot Muscles, Flat Foot, Modified Star Excursion Balance Test, Navicular Drop

1. Introduction

1.Background

The arch of the foot is important when considering foot function. In addition to the mechanical support by bones, joint capsules, and ligaments in the medial longitudinal arch (MLA), the functional support of muscles is very important in absorbing load shock (Hicks, 1954). In order to maintain MLA, the functions of the external foot muscles such as the tibialis posterior muscle and flexor pollicis longus muscle and the intrinsic muscles of the foot such as abductor pollicis longus are important (Pohl, Rabbito & Ferber, 2010). In order to maintain the MLA, the functions of both the extrinsic and intrinsic foot muscles are important (Pohl, Rabbito & Ferber, 2010). In particular, the intrinsic muscles play a critical role in the regulation of absorption and propulsion during dynamic activities (McKeon & Fourchet, 2015). Flatfoot is a common phenomenon caused by a decrease in the arch and excessive pronation of the foot, and is reported to cause overuse injuries and syndromes including plantar fasciitis, achilles tendonitis, hallux valgus, posterior tibialis tendon dysfunction, and patellofemoral pain syndrome (Pohl, Hamill & Davis, 2009, Ryan et al., 2009, Sherman, 1999, Tome, Nawoczenski, Flemister, & Houck, 2006). In terms of maintaining the MLA, when the function of the intrinsic muscles deteriorates, the extrinsic muscles may contract excessively to compensate, thereby increasing traction stress and causing impairments.

Running motion is one of many basic movements used when playing sports. Because running is not only for training athletes but also an easily engageable exercise for ordinary individuals, it has become very popular. Although running promotes positive psychological and physical effects, repetitive motions and other factors are often involved in the activity, frequently causing musculoskeletal disorders. These disorders are more pronounced among track and field athletes who are forced to run at higher levels. Indeed, reports have shown that chronic disorders were strongly associated with the motions involved in running (Zemper, 2005, Lysholm & Wiklander, 1987). Long-distance runners in particular often suffer from chronic pain in the lower limbs and other areas (Tschopp & Brunner, 2017, Dimeo, Peters & Guderian, 2004). Focusing on the arch of the foot, there are several studies of different aspects of the motions involved, such as an excessive ankle/foot pronation in the stance phase of running (Jam, 2006), the lowering of the MLA with navicular drop (ND) (Headlee, Leonard, Hart, Ingersoll, and Hertel, 2008), changes in rigidity of the plantar arches (Miller, Whitcome, Lieberman, Norton & Dyer, 2014), and the increase in impact and acceleration on the tibia during running (Crowell & Davis, 2011). Impaired function of the arch is also reported to be involved in shin splints (medial tibial stress syndrome), posterior tibial tendonitis and flatfoot, all of which can trouble track and field athletes (Pohl, Hamill & Davis, 2009, Newman, Witchalls, Waddington & Adams, 2013).

Because track and field athletes continuously apply load to their feet during running, exercises for training the intrinsic muscles may reduce the load on the extrinsic muscles, which in turn can then better maintain arch function (Sulowska, Oleksy, Mika, Bylina & Sołtan, 2016). Gooding et al. compared four exercises (the short-foot exercise, toes-spread-out exercise, first-toe-extension exercise, and second- to fifth-toe-extension exercise) for training the intrinsic muscles of the foot, and reported on the effectiveness of each exercise (Gooding, Feger, Hart & Hertel, 2016). One of the four exercises studied, the short-foot exercise (SFE), has been used in many studies as a training method for the intrinsic muscles of the foot (Jung, Koh & Kwon, 2011, Okamura, Knai, Hasegawa, Otsuka & Oki, 2019, Namsawang, Eungpinichpong, Vichiansiri & Rattanathongkom, 2019). The SFE selectively trains the abductor hallucis muscle, which is the largest of the intrinsic muscles and is highly active during loading. It holds the arch by contracting the abductor hallucis muscle during loading. It was reported that the SFE appeared to train the intrinsic muscles more effectively than the towel-curl exercise (Lynn, Padilla & Tsang, 2012), and there was preliminary evidence suggesting that SFE training may have value in statically and dynamically supporting the MLA (Mulligan & Cook, 2013). There are also reports that it contributes to reducing flatfeet (Okamura et al., 2020, Kim EK & Kim JS, 2016), varus sprains or foot instability (Lee E., Cho, Lee S., 2019), and knee problems such as patellofemoral pain syndrome (Lee, Yoon & Cynn, 2017). Although there are some negative reports about its effects (Haun, Brown, Hannigan & Johnson, 2020), it seems to be considered a general training method for the intrinsic muscles.

1.2 Purpose

The effectiveness of SFE is mostly reported in short-term interventions, with only a few reports of its sustained effects. This study provided an opportunity to give training to high school track and field athletes on ankle joints and foot arches with a focus on maintaining and improving arch function. The purpose of this study was to verify the effect of SFE training on the intrinsic muscles of the foot.

2. Method

2.1 Subjectss

An initial group of 49 high school runners were recruited, and then people who were unable to participate in all 3 measurements or be followed during the intervention period were excluded from the study. A total of 31 people (20 men and 11 women; mean age ± standard deviation: 15.6 ± 0.7 years; height: 164.9 ± 8.0 cm; weight: 52.5 ± 6.9 kg) were selected as subjects for this study. All subjects were informed about the purpose and procedures of the study and they provided written informed consent prior to participation. This study was approved by the Takasaki Health and Welfare University Ethics Review Committee (No. 2966).

2.2 Study Design

All subjects were measured 3 times for 8 months, the period between the first measurement (M1) and the second measurement (M2) were 3 months, and the period between M2 and the third measurement (M3) were 5 months. All subjects underwent ankle stabilization training during the study period. During the first 3 months of the study period, one randomly selected group of subjects underwent SFE for the purpose of activating the intrinsic muscles of the foot, and another group did not, the non-SFE group. The results of the 3 measurements in both groups were compared

2.3 Measurements

2.3.1 Pain

At the time of the M1, subjects were asked about any pain occurring during normal running movements in the last half year. In this study, pain was defined as that which caused the individual to miss practice or running for at least 1 day. At the time of the M2 and M3, the subjects were asked similarly about any pain they experienced.

2.3.2 Physical assessment items

2.3.2.1 Navicular drop (ND)
The height from the floor to the lower end of the navicular tuberosity (hereinafter referred to as the arch height) and the foot length from the posterior surface of the calcaneus to the tip of the toe were measured in the unloaded position and the loaded position. The non-loaded position was a sitting position with the hip and knee joints at 90° and no weight applied, and the loaded position was a forward squat with the measured limb forward and the lower leg advanced forward. The value obtained by subtracting the arch height at the load position from the arch height at the non-load position was calculated as ND.

2.3.2.2 Modified Star Excursion Balance Test (mSEBT)
As an evaluation of dynamic balance, the mSEBT was administered (van Lieshout et al., 2016). The maximum reach distance was measured by placing both hands on the lumbar region and performing a reach on one leg in three directions: front, inner back, and outer back. The measurement was performed three times in each direction, and the maximum value was divided by the leg length (distance from the most anterior end of the superior anterior iliac spine to the distal end of the malleolus) to calculate the reach rate. The average value of the measured values in each direction was extracted as data for analysis.

(3) Ankle dorsiflexion angle

Following the method of Bennell et al., a measurement of dorsiflexion was calculated from the inclination angle of the lower leg with respect to the horizontal line of the floor (Bennell et al., 1998). With the subjects' hip and knee joints flexed and loaded on the front leg, we placed the tilt angle meter on the front of the lower leg and measured the angle in the maximum dorsiflexion position. The measurement was performed twice in units of 1° and the average value was calculated.

(4) Toe gripping force

As in another study, toe grip was measured with subjects sitting barefoot with their knee position at 90° flexion and the ankle plantar dorsiflexion at 0° (Nakae, Murata, Kai, Soma & Satou, 2013). The measurement was made using a toe muscle-strength measuring device T.K.K. II 3364 (Takei Koki Co., Ltd.). We fixed the position of the foot by placing the toe on the bar and measured the toe grip force used to pull the bar. The measurement was performed three times on each side and the maximum value was used. The average value of the left and right measurement values was extracted as the data to be used in the analysis in this study.

2.4 Training routine

The ankle stabilization training carried out with both groups consisted of 8 types of training on an unstable plate. These exercises stabilize the ankle joint by stimulating the foot's extrinsic muscles and improve windlass function by stabilizing the hip joint. They consisted of ① heel raise on two legs (10 times), ② one-leg standing with the other leg backward (both sides, 10 seconds each), ③ one-leg standing with the other leg forward (both sides, 10 seconds each), ④ leg swing with one-leg standing (both sides, 10 seconds each), ⑤ one-leg heel raise with knee in an extended position (both sides, 10 times), ⑥ one-leg heel raise with knee in a flexed position (both sides, 10 times), ⑦ two-leg squats (10 times), and ⑧ one-leg squats (both sides, 10 times). Subjects chose between two types of unstable plates that had different levels of difficulty. Both groups conducted these exercises twice a week during the study period.

The SFE was performed only by the SFE group. With reference to the method of Jung et al., the subjects sat in a chair with hip and knee joints at 90° (Jung et al., 2011). They were guided to bring the first metatarsal head close to the heel without bending their toes and to hold this position for 5 seconds, then relax for 3 seconds. This was repeated for 5 minutes on each side (totally 10 minutes on both sides), and the effect was judged by the examiner palpating the abductor malleus of the toe during each exercise. When it was judged that sufficient contraction of the first toe abductor muscles was obtained without the toe flexor and tibialis posterior muscles contracting to compensate, the difficulty was adjusted by performing the same exercise in the standing position. The training was conducted 3 times a week for 3 months.

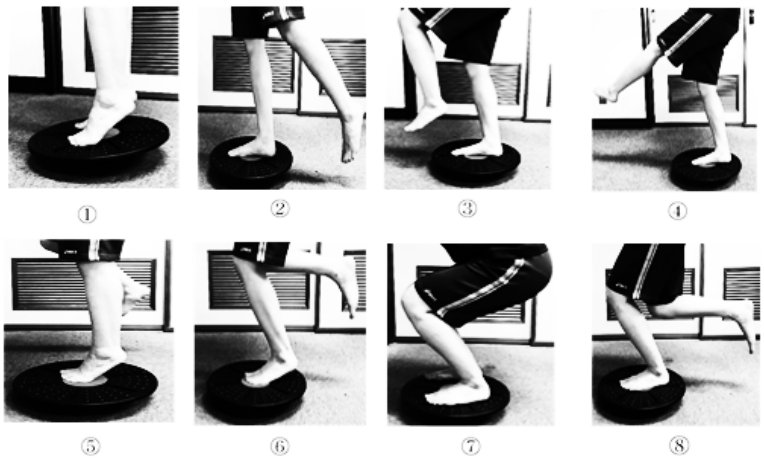

Figure-1 Ankle stabilization training program

① heel raise 1, ② one-leg standing 1, ③ one-leg standing 2, ④ leg swing
⑤ heel raise 1, ⑥ heel raise 2, ⑦ two-leg squat, ⑧ one-leg squat

2.5 Analysis

All measurement results were confirmed to be normally distributed, so a one-way analysis of variance (ANOVA) with post-hoc Tukey's test was performed to evaluate differences between groups with multiple comparison analysis for each measurement. All statistical analyses were conducted using SPSS 24.0J for Windows, with the significance level set at 5%.

3. Results

3.1 Pain

The number of incidents of pain at each measurement time is presented in Table 1. The number of physical problems in the SFE group was lower at the time of M2 but increased at the M3.

Table-1 The number of pains (physical problems)

		SFE Group (n=13)			Non-SFE Group (n=18)		
		1st	2nd	3rd	1st	2nd	3rd
Number		6	3	8	7	10	5
Contents	Upper thigh	0	0	1	1	2	1
	Knee joint	1	0	2	2	1	0
	Lower thigh	3	1	3	2	3	1
	Ankle joint	0	1	1	1	2	1
	Foot/Finger	2	1	1	1	2	2

SFE=Short Foot Exercise

3.2 Physical Assessment

Table 2 shows the results of the measurement and one-way ANOVA, and Table 3 shows the results of the post-hoc test. In the SFE group, the ND value was significantly decreased at the time of the M2 but was significantly increased at the M3, returning to the same level as the initial results. The mSEBT was significantly higher in the non-SFE group at the M2 but no other significant differences were observed. The ankle dorsiflexion angle was

significantly larger in both groups at the time of the M2. Toe gripping force showed a significantly larger value in the SFE group at the M3.

Table-2 The results of the physical assessment values and the one-way ANOVA in each group

	SFE Group (n=13)				Non-SFE Group (n=18)			
	1st	2nd	3rd	p value*	1st	2nd	3rd	p
ND (cm)	0.83±0.52	0.57±0.41	0.73±0.38	0.029	1.12±0.72	0.80±0.38	0.90±0.44	0.185
mSEBT (%)	0.91±0.11	0.98±0.09	0.93±0.10	0.163	0.89±0.16	1.01±0.08	0.96±0.08	0.001
ADROM (deg)	40.2±3.5	50.7±4.4	46.5±3.4	0.004	42.9±3.1	53.4±3.2	47.6±3.2	0.002
TGF (kgf)	10.1±5.3	10.7±4.9	14.9±5.6	0.048	9.7±4.2	10.6±5.3	12.8±4.7	0.129

SFE=Short Foot Exercise, ND=Navicular Drop, mSEBT=modified Star Excursion Balance Test
ADROM=Ankle Dorsiflexion Range of Motion, TGF=Toe Gripping Force
Value: average±SD(standard deviation), * = one-way analysis of variance (one-way ANOVA)

Table 3 The results of post-hoc test in each group

	SFE Group (n=13)			Non-SFE Group (n=18)		
	1st-2nd	1st-3rd	2nd-3rd	1st-2nd	1st-3rd	2nd-3rd
ND	0.046 (0.11 - 0.65)	0.771 (-0.27 - 0.48)	0.039 (0.03 - 0.21)			
mSEBT (%)				0.001 (-0.14 - -0.04)	0.173 (-0.09 – 0.01)	0.078 (-0.004 - 0.10)
ADROM (deg)	0.003 (3.4 - 18.1)	0.092 (-0.8 - 13.5)	0.314 (-11.7 - 2.9)	0.001 (3.2 - 14.9)	0.363 (-2.5 - 9.1)	0.050 (-11.6 - 0.01)
TGF (kgf)	0.945 (-5.8 - 4.6)	0047 (-9.9 - -0.03)	0.034 (-9.3 – -0.99)			

SFE=Short Foot Exercise, ND=Navicular Drop, mSEBT=modified Star Excursion Balance Test
ADROM=Ankle Dorsiflexion Range of Motion, TGF=Toe Grip force
Value: p value (95% Confidence Interval)

4. Discussion

In this study, high school track and field athletes were selected as subjects for the purpose of validating SFE training. Benett et al. reported that ND in cross-country athletes in unloaded and standing positions were 3.6 ± 3.3 mm in healthy runners and 6.8 ± 3.7 mm in runners with injuries (Bennett et al., 2001). Since the arch height measurement in this study measures the ND in a state close to motion, the ND was calculated from the difference in arch height between the unloaded position and the loaded position in the knee flexion position, which tended to have a relatively large value. Pes planus was defined as ND exceeding 13 mm (Cote, Brunet, Gansneder & Shultz, 2005), so the subjects in this study were considered appropriate as an intervention target.

In the SFE group, the ND value significantly decreased three months after SFE was performed, indicating effectiveness from the viewpoint of reinforcement in the longitudinal arch of the foot. Uncer et al. reported that short-term intervention was effective for ND (Unver, Erdem & Akbas, 2019), and another study showed that the muscle activity of the abductor hallucis dorsi muscle was significantly increased during SFE training (Jung et al., 2011). In other studies, it has been suggested that the improvement of the arch through use of the SFE was effective for avoiding various injuries (Okamura et al., 2020, Lee, Yoon & Cynn, 2017, Kim EK & Kim JS, 2016). It was possible that the SFE intervention makes it possible to maintain the arch even under load. Although the generalization of the training effects in this study is speculative, the number of pain incidents increased in the non-SFE group at the time of M2 while the number of pain incidents in the SFE group decreased, suggesting the SFE was effective.

Of note, in the SFE group the value of ND at the M3 increased significantly compared with the M2, almost reaching the same level as the M1 and indicating the importance of continuing intervention to maintain improvements. Because the number of pain incidents reported at the time of the M3 was also increased, it is possible the pain was

caused by the decline in arch function that earlier showed improvement. There are no studies referring to the sustainability of the effects of the SFE, so these results can be a reference for future investigation of this exercise. The ankle stabilization training carried out in both groups was also expected to effect improvement in the arch by improving the windlass function and strengthening the extrinsic foot muscles. In the non-SFE group, ND tended to decrease but no significant change was observed. Therefore, it is suggested that the combination of this training with the SFE focusing on the intrinsic muscles was more effective in improving the arch of the foot. The ankle dorsiflexion angle was significantly larger in both groups at the time of the M2, suggesting the mobility of the foot was improved by conducting the unstable-plate training.

Although previous studies reported changes in arch function leading to some balancing improvement (Birinci & Demirbas, 2017), no significant change was observed in mSEBT in the SFE group in this study. A significant improvement was observed in the non-SFE group, possibly because the training with the unstable plate improved the nerve-muscle coordination and postural control in the one-leg standing position. In this study, the value of mSEBT was calculated by taking the average value of all directions, but the characteristics in each direction could be measured in future studies.

The toe gripping force of the SFE group increased significantly at the time of the M3. It was reported that strengthening the toe flexor muscle group resulted in decreased ND, and as a result was effective in preventing hallux valgus (Yokozuka, Okazaki, Sakamoto & Takahashi, 2019). In this study, toe gripping force in the SFE group increased during the period when SFE was not performed, resulting in increased ND and increased pain. It was undeniable that extrinsic muscles were activated rather than intrinsic muscles, which might have been counterproductive from the perspective of injury prevention. In athletes performing repeated running movements, increased muscle output of the toes might cause a decrease in the rocker function of the foot and a decrease in shock absorbing function, resulting in an excessive load on the foot and lower limbs. It is expected that further verification will be needed in the future, including exploring the detailed mechanism of the toe and arch functions. There was also a report that the SFE consisted of movements that were difficult for subjects to picture, and that learning it was therefore difficult. Also worth considering is that the SFE in this study repeated movements for 5 minutes that did not involve any joint movements, so it could cause fatigue and poor concentration in long-term implementation. There are many reports that the training's positive effect was increased by performing it in combination with other methods (Kim & Lee, 2020, Namsawang, Eungpinichpong, Vichiansiri & Rattanathongkom, 2019, Okamura, Kanai, Hasegawa, Otsuka & Oki, 2019, Jung, Koh & Kwon, 2011). It is necessary to devise training with regular measurements of effects and share that feedback. Beyond the exercises, there are many other factors that also affect foot problems, so it is necessary to consider not only physical functions, but also shoes, insoles and environmental factors (Miller et al., 2014). Furthermore, in athletics, running and practice routines differ between long-distance athletes and short-distance athletes, so there might be differences in intervention effects. However, the subjects of this study were both short- and long-distance athletes so no comparison could be made, and the group was too small for differences between men and women to be explored. In the future, it would be necessary to increase the number of subjects and examine the characteristics of each group in more depth.

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Case Report: Management of Respiratory Failure Following Snake Bite

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Abstract
Venomous snakebite cases are life-threatening medical emergencies. Most deaths were caused by respiratory failure due to acute neuromuscular paralysis. In this case, a man, 17 years old, was treated for snakebite on his upper arm one-hour prior hospital admission. Snakes was identified as cobras. Patient experienced symptoms of vomiting, seizures, headaches, weakness in the extremities and decreased consciousness. Local examination revealed two deep teeth marks. No hemorrhagic and myotonic manifestations were found. He then experienced respiratory failure, intubated and treated in the intensive care unit. Management of respiratory failure due to neurotoxic snake bites, namely administration of snake antivenom to bind poison, anti-cholinesterase and atrophine sulfate to release toxins from neuromuscular. Supportive therapy included ventilators, fluids, nutrition, tetanus toxoid, antibiotics. Fasciotomy was done on the bite wound because compartement syndrome was found. This patient did not show other abnormal manifestations because patient was promptly taken to the hospital. On day 3 hospital stay, he showed improvement, on day 6, he was moved to the ward. To achieve optimal results in cases of venomous snake bites, early diagnosis, early transportation to hospital and adequate management of snakebite were needed.

Keywords: Anti Snake Venom, Neurotoxic, Respiratory Failure, Snake Bite

INTRODUCTION

Snake bites were classified by WHO as neglected tropical disease. Kasturiratne et. Al (2008) estimated 1.2 million snake bites occurred annually, 421,000 venomous snake bites and mortality rate up to 20,000 snake bites worldwide. Most deaths were due to respiratory failure following the bite of neurotoxic snakes. Neurotoxicity were caused by snake species of Elapidae (family elapidae) such as Kraits (Bungarus spp), Cobras (Naja spp), Taipan (Oxyuranus spp), and Tiger Snake (Notechis spp). Snake venom had different enzymatic and non-enzymatic components. Snakes were classified based on their toxicity; hematotoxic, myotoxic and neurotoxic. In the neurotoxic type, manifestations of respiratory failure caused by acute neuromuscular paralysis were the main

causes of morbidity and mortality (Kasturirane, et al., 2008; Ranakawa, Lalloo, & de Silva, 2013).

Respiratory failure, a syndrome where the respiratory system cannot perform the function of gas exchange, both oxygenation and or elimination of carbon dioxide (CO_2). There were two types of respiratory failure, namely type I respiratory failure (hypoxemia), in which oxygenation disturbance occurred and type II respiratory failure (hypercapni) where ventilation was disrupted to eliminate CO_2. In the case of this neurotoxic snake bite, hyperpapni breath failure occurred. This was due to the effect of the snake's toxin that attacked neuromuscular junction, triggering acute neuromuscular paralysis and difficult ventilation (Kasturirane, et al., 2008; Ranakawa, Lalloo, & de Silva, 2013)

Management of acute respiratory failure in patients with snake bites required multidisciplinary involvement. Causative therapy aimed to eliminate the effects of snake venom from neuromuscular junction. This type of therapy used snake antivenom (SAV) based on its type. Supportive therapy was given to promote the primary life functions by providing mechanical ventilation to support adequate respiration, nutrition and fluids. Additional therapy was done by treating wound area with wound care, antibiotics for the prevention of infection and fasciotomy if needed (Ranakawa, Lalloo, & de Silva, 2013; Warrell, 2010; Kakaria, Narkhede, Agrawal, Bhavsar, & Nukte, 2014).

CASE REPORT

Patient's identity

Name	: An. S
Age	: 17 years
Ethnicity	: Sundanese
Occupation	: Student
Medical record	: 688368
Hospital admission	: 23/01/2020
ICU admission	: 23/01/2020
ICU discharge	: 28/01/2020

Subjective

Chief complain: Bitten by cobra snake

A-17-year man weighed 60 kg came to Emergency Department in Soreang District Hospital with decreased consciousness following snake bite one hour prior hospital admission. He was alert at first but on the way to the hospital, his consciousness was declining. He also experienced two times of vomiting, headache and difficulties in moving both upper and lower extremities. After arrival, he showed three times seizure with five minutes duration each. He was known to pet a Cobra snake since one month ago.

Objective

General condition: severely ill
- Consciousness : Comatus E1M1V1
- Vital signs :
  BP : 100/70 mmHg HR :109x/'
  RR : 30x/mnt T : 36,8 °C
- BW: 60 kg BH: 170 cm BMI: 21
- Predicted Body Weight (male) : 50+[2,3x(67-60)] = 66,1 kg

Primary survey :
- A: clear airway
- B: Retraction +/+ nasal flares + RR: 35 x/min, ronchi +/+, slem +/+
  Wheezing -/- SpO2: 92% with SMNR 10 liter/min

- C: BP 100/70 mmHg; regular adequate pulse 100-120 x/m, murmur -.
- D: comatus, GCS 3 (E1M1V1), motoric 0/0/0/0 ptosis eyelids, pupil isocor
- E: venomous snake bite trauma at right forearm

Secondary survey :
- Head: ptosis right and left eyelids, red eyes (-)
- Neck: JVP does not increase
- Thorax: basic vesicular sounds, ronchi +/ + slem ++ / +
- Abdomen: flat, not distended, bowel sound (+) N, melena (-), hematuria (-), brownish urine (-)
- Extremities: petechie (-), ecchymosis (-)
- Local status: visible snake bite marks on the right forearm, edema, erythema, bull and necrotic tissue was found.

ECG result: sinus tachycardia

Emergency Department laboratory results:
- Routine blood count: Hb : 17,4 gr/dl Ht: 51% Leuko: 29.400 /uL Trombo: 381.000 /uL
- Coagulation function : PT 15,6s aPTT: 38,3s INR: 1,57
- GDP: 196,1 mg/dl Ureum: 12,0 Creatinine: 0,88 mg/dl
- Electrolyte: Natrium: 136 meq/L Kalium: 4,10 meq/L Calcium: 8,42 mg/dL Magnesium: 1.35 mg/dl
- Xray was not done

Assessment : Decreased consciousness and acute respiratory failure due to neurotoxic snake bite grade IV

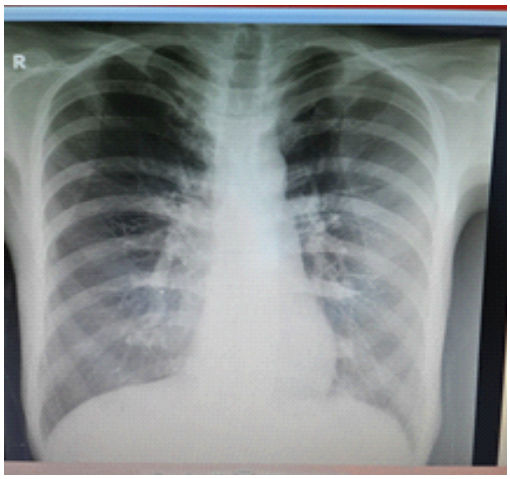
Therapy plan:
- ICU care with ventilator
- Injection five vials of serum antivenin (SAV) in D5% 500 cc for 30-60 minutes
- Cetriaxon 1x2 gram iv injection
- ATS 1500 iv
- Wound toilet with chlorhexidine and wound immobilization with elastic bandage
- Dexametason 3x5 mg iv injection
- Intubation
- Consult to Surgery Department

ICU CARE

Day 1: 23 January 2020

Subjective : -
Objective :
On 16.00, arrival at ICU, patient was intubated with ETT no.7
- GCS 3 (E1M1Vt)
- APACHE score: 23
- Airway was installed ETT no 7 depth of 22 cm
- Breathing : on ventilator
  Mode SIMV RR: 12 x/' TV: 400 ml PEEP: 5 FiO2: 50% gradually reduced until 45% SpO2 92-98%
- Circulation :
  - NIBP : 110/80 mmHg without vasopressor
  - HR : sinus tachycardia, 120 x/'
  - Temperature : 36,5-37,5 °C
- Pain : CPOT 0
- Laboratory result :
  - Albumin : 3,6 Lactate 1,2 SGOT: 27 SGPT: 25
  - BGA : pH: 7,34 pCO2: 37,4 pO2: 158 HCO3: 19,5 BE: -5 SpO2 99% Pf 264,5

- Fluid balance :
  - Intake : 1466 cc
  - Output : 1627 cc
  - Cummulative balance : -161 cc, clear urine
- Thorax x-ray : Bronchopneumonia bilateral



Assessment : Decreased consciousness and acute respiratory failure due to neurotoxic snake bite grade IV

Therapy plan:
- Fasciotomy by surgical department
- Injection five SAV vials in D5% 500 cc within 6 hours
- Ceftriaxon 1x2 gram iv (D1) injection
- Dexamethason 3x5 mg iv injection
- Prostigmin: SA = 10 ampul: 5 ampul iv continue in 24 hour
- Blood glucose test every one hour.
- Feeding (F) : fasting
- Analgetic (A) : fentanyl 25 mcgr/hour
- Sedation (S) : -
- Tromboprophylaxis (T) : -
- Head of bed elevation ((H); +
- Ulcer gastric prevention (U): Omeprazol 2x40 mg iv
- Glucose control (G) : -

Day-2: 24 January 2020

Subjective : -
Objective :
- Consciousness E1M1Vt
- Breathing : on ventilator
  Mode Ventilator SIMV PS RR: 12-15 x/' TV: 375-420 ml PEEP: 5 PS 6-8 FiO2: 45% SpO2 97-99%
- Circulation :
  - BP : 118/75 mmHg without vasopresor
  - HR : sinus tachycardia, 109-110 x/'
  - Temperature : 36,4-36,8 °C
- Abdomen : bowel sound+, NGT murky 50 cc
- Pain : CPOT 1
- Laboratory result :
  - BGA : pH: 7,48 pCO2: 30,5 pO2: 109,4 HCO3: 23,6 BE: -3 SpO2 98,1% Pf 260,5

  - Hb: 12,8 Ht: 37,1 Leu: 15.080 Trombo: 205.000 Na: 135 K: 4,0 Cl: 98 Ca: 4,49 Mg: 2,5
- Fluid balance :
  - Intake : 2040 cc
  - Output : 2248 cc
  - Cummulative balance : +208 cc

Assesment : Decreased consciousness and acute respiratory failure due to neurotoxic snake bite grade IV

Therapy plan:

- Ceftriaxon 1 x 2 gram iv (D2) injection
- Dexamethasone 3 x 5 mg iv injection
- Prostigmin: SA = 10 ampul: 5 ampul iv continue in 24 hours
- Ca gluconas 2 gr
- Feeding (F) : formula RS 1000 kcal diet
- Analgetics (A) : fentanyl 25 mcg/hour iv continue
- Sedation (S) : midazolam 3 mg/hour iv continue
- Tromboprophylaxis (T) : -
- Head of bed elevation ((H); +
- Ulcer gastric prevention (U): Omeprazol 2x40 mg iv
- Glucose control (G) : blood glucose test within normal limit

During the patient's treatment, an muscle strength with hand grasping, ability to open eyes, moving limbs were evaluated.

Fasciotomy was done, wound care was done every day.

Day 2 : 24 January 2020

The patient condition hasn't changed. Hemodynamics and therapy in intensive care remain the same

Day-3: 25 January 2020

Subjective : -

Objective : began to open the eyes slowly, fingers and toes can be moved

- Consciousness: E2M2Vt
- Breathing : on ventilator
  Mode SIMV PS RR: 14-20 x/' TV: 360-425 ml PS: 6-8 PEEP: 5 FiO2: 45% SpO2 98-100%
- Circulation:
  - BP : 128/70 mmHg
  - HR : sinus tachycardia, 100-109 x/'
  - Temperature: 36,4-36,8 °C
- Pain : CPOT 2
- Laboratory result :
  AGD : pH: 7,49 pCO2: 29,3 pO2: 116,2 HCO3: 22,7 BE: 0,9 SpO2 98,2% Pf 258,2
- Fluid balance :
  - Intake : 2040 cc
  - Output : 2248 cc
  - Cummulative balance : +208 cc

Assessment : Decreased consciousness and acute respiratory failure due to neurotoxic snake bite grade IV

Therapy plan:

- Ceftriaxon 1 x 2 gram iv (D3) injection
- Dexamethasone 3 x 5 mg iv injection
- Prostigmin: SA = 10 ampul: 5 ampul iv continue in 24 hours
- Feeding (F) : liquid diet 500 kcal
- Analgetics (A) : fentanyl 25 mcgr iv

- Sedation (S) : midazolam 3 mg/hour iv continue
- Tromboprophylaxis (T) : -
- Head of bed elevation ((H); +
- Ulcer gastric prevention (U): Omeprazol 2x40 mg iv
- Glucose control (G) : blood glucose test within normal limit

Day-4: 26 January 2020

Subjective :gaining muscle strength, dyspnea improved
Objective : begin to open eyes, able to grasp hands, increase strength of limbs
- Consciousness E3M5Vt
- Breathing : on ventilator
  Spontaneous mode RR: 18-22 x/' TV: 360-420 ml PEEP: 5 PS 6 FiO2: 45% SpO2 98-100%
- Circulation :
  - BP : 130/85 mmHg
  - HR : sinus rhythm, 84 x/'
  - Temperature : 36,5-37,5 ℃
- Pain : CPOT 2
- Laboratory result:
  - Hb: 12,0 Ht: 35,5 Leu: 6.090 Trombo: 204.000
  - BGA: pH: 7,514 pCO2: 28 pO2:191 HCO3:23,4 BE: 0,3 SpO2 99,1% Pf 424,4
- Fluid balance :
  - Intake : 2699 cc
  - Output : 2461 cc
  - Cummulative balance : +238 cc

Assessment : Decrease consciousness and type II respiratory failure (hypercapnia) due to neurotoxic snake bite grade IV

Therapy plan:
- Ceftriaxon 1 x 2 gram iv (D4) injection
- Mestinon 4x1
- Dexamethasone 3x5 mg iv injection
- Feeding (F) : liquid diet 1500 kcal
- Analgetics (A) : paracetamol 4x1 gr iv
- Sedation (S) : midazolam 3 mg/hour iv continue
- Tromboprophylaxis (T) : -
- Head of bed elevation ((H); +
- Ulcer gastric prevention (U): Omeprazol 2x40 mg iv
- Glucose control (G) : blood glucose test within normal limmit

Day-5: 27 January 2020

Subjective: muscle strength gaining, decreasing dyspneu
Objective : ptosis (-), hand grip (+)
- Consciousness E4M6Vt
- Breathing : on ventilator
  Spontaneous mode RR: 18-20 x/' TV: 350-430 ml PEEP: 4 PS: 4 FiO2: 40% SpO2 98-100%
- Circulation :
  - NIBP : 130/85 mmHg
  - HR : sinus rhythm, 84 x/'
  - Temperature: 36,5-37,5 ℃
- Pain : CPOT 2
- Laboratory result :
  - Hb: 12,1 Ht: 36,5 Leu: 8.230 Trombo: 287.000

- Na: 136 K: 4,2 Cl: 100 Ca: 4,37 Mg: 2,2
- BGA : pH: 7,415 pCO2: 34 pO2:148,8 HCO3:23 BE:-1,3 SpO2 99% Pf 328

- Fluid balance :
  - Intake : 2322 cc
  - Output : 2650 cc
  - Cummulative balance : -320 cc

Assesmen : Type II respiratory failure (hypercapnia) due to neurotoxic snake bite grade IV

Plan therapy:
- Ceftriaxon 1 x 2 gram iv (D6) injection
- Mestinon 4x1
- Feeding (F) : liquid diet 1500 kcal
- Analgetics (A) : paracetamol 4x1 gr iv
- Sedation (S) :
- Tromboprophylaxis (T) : -
- Head of bed elevation ((H); +
- Ulcer gastric prevention (U): -
- Glucose control (G) : blood glucose test within normal limit
- Plan: extubation

Day-6: 28 January2020

Subjective : dyspnea (-)
Objective : ptosis (-), hand grip (+), extremity muscle strength (+)

- Breathing : binasal canul 3l/' satuaration 98-100% RR 15-18x/'
- Circulation:
  - NIBP : 120/75 mmHg
  - HR : sinus rhythm, 80 x/'
  - Temperature : 36,5-37,2 ℃
- Pain : NRS 2

- Fluid balance :
  - Intake : 1745 cc
  - Output : 2470 cc
  - Cummulative balance : -725 cc

Assesmen : Type II respiratory failure (hypercapnia) due to neurotoxic snake bite grade IV (improved)

Therapy plan:
- Mestinon 4x1 tablet per oral
- Feeding (F) : formula RS 1500 kcal
- Move to ward

Tabel 1. Ventilator mode per day

Date	**23/1/20**	**24/1/20**	**25/1/20**	**26/1/20**	**27/1/20**	**28/1/20**
	D1	**D2**	**D3**	**D4**	**D5**	**D6**
Mode	SIMV	SIMV PS	SIMV PS	Spontaneous	Spontaneous	NC
RR	12	12-15	14-20	18-20	18-20	15
PS	-	8	6	6	4	-
PEEP	5	5	5	5	4	-
VT	400	375-420	360-425	360-420	350-430	-

FiO2	50%	45%	45%	45%	40%	-
SaO2	98%	99%	98%	100%	98%	99%
P/F ratio	264	260	258	424	328	-

DISCUSSION

In many countries in the Southeast Asian region, snakebite was classified as a notable medical emergency and accounted hospital admission. This condition resulted in death or chronic disability in patients of childbearing age (Kasturirane, et al., 2008; Ranakawa, Lalloo, & de Silva, 2013). The characteristics of snake species in each country differed depending on the local geographical conditions. This made each country develop snake antivenom (SAV) in accordance with the type of poisonous snake in that country. For example, the type found in England was viper, so British government made a monovalent SAV (one type) for viper snakes venom. There were numerous and variant type of snakes. Indonesian government combined for 3 types of SAV in 1 (polyvalent) for the snake species Bungarus spp, Naja spp, Ankilostrodon spp (Warrell, 2010; Kakaria, Narkhede, Agrawal, Bhavsar, & Nukte, 2014). Patients suffering from snake bites should be taken to the hospital immediately to get primary clinical assessment and rapid resuscitation. Cardiopulmonary resuscitation might be needed, including oxygenation and intravenous access (Kasturirane, et al., 2008; Warrell, 2010). In emergency settings, patients were assessed from airway (airway patency), breathing (breathing movement), circulation, disability (disability of the nervous system), and exposure.

Differential diagnosis

In the case of snake bites, consider the possibility of cardiotoxic, renotoxic, myotoxic, neurotoxic and hematotoxic snakebites. Careful history taking, physical examination and complete supporting examination is needed to rule out other toxic diagnoses (Ranakawa, Lalloo, & de Silva, 2013; Kakaria, Narkhede, Agrawal, Bhavsar, & Nukte, 2014). Examination of hemostasis profile, ECG, urinalysis, and neurological status were needed. In general assessment, detection of hypovolemia and shock must be carried out with its bleeding signs (petechiae, purpura, ecchymosis and conjunctival bleeding), or bleeding in the gums and nose. Abdominal pain might indicate gastrointestinal bleeding. Lower back pain and tenderness might refer to acute renal ischemia. Intracranial bleeding was characterized by lateralization of neurological signs, seizures or disturbance of consciousness (in the absence of respiratory or circulatory failure). Rhabdomyolisis, myoglobinuria can be found clearly three hours after the bite (Ranakawa, Lalloo, & de Silva, 2013; Warrell, 2010; Kakaria, Narkhede, Agrawal, Bhavsar, & Nukte, 2014). In this case, no myoglobinuria was detected and no signs of bleeding were found. This could be due to the varied signs and symptoms of bleeding based snake species. In this case neurotoxic manifestations such as dizziness, nausea, vomiting, ptosis, headaches, convulsions and acute respiratory failure were found. Pysical examination revealed that snake venom was neurotoxic, but not hematotoxic, cardiotoxic, myotoxic or renotoxic. Therefore, it is important to identify the type of snake for diagnostic and therapeutic purposes.

Pathophysiology of Respiratory Failure

Decreased consciousness, seizures with history of vomiting in this patient was due to neurotoxic manifestation of cobra (Naja spp) venom which attacked the neuromuscular junction (Ranakawa, Lalloo, & de Silva, 2013; Warrell, 2010; Kakaria, Narkhede, Agrawal, Bhavsar, & Nukte, 2014). Immediate management in this patient was possible because he was directly sent to the hospital. Cobra toxin effects could be irreversible if patient's arrival was delayed. The results of blood gas analysis shortly after the patient was intubated didn't show a significant increase in their CO_2 pressure. Respiratory failure in snake bite cases occurs because neurotoxins of snakes spread to neuromuscular junction and damage the nerves both in pre-synapses, post synapses and in the central. This resulted in paralysis of the skeletal muscles including respiratory muscles, palate, palpebral and extremities.

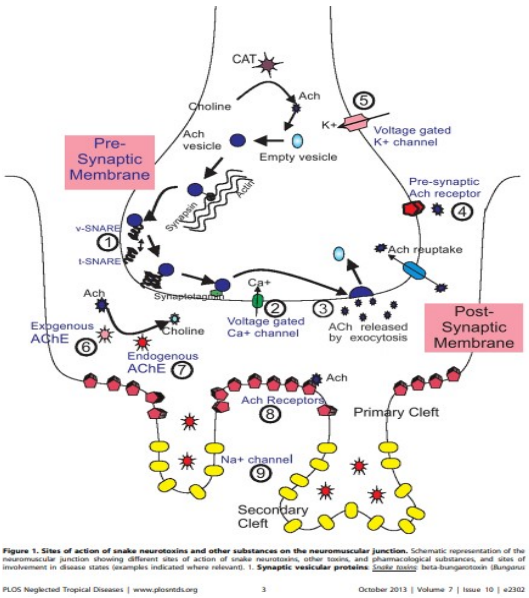


Figure 1. Neurotoxic mechanism in snakebite

Under certain conditions, snake bites might cause hypotension leading to severe shock due to cardiovascular effect from poisons or secondary effects such as hypovolemia, release of inflammatory vasoactive mediators, hemorrhagic shock, or rarely primary anaphylaxis induced by the poison itself (Ranakawa, Lalloo, & de Silva, 2013). In this case, the patient didn't experience shock, his vital signs were normal. This might be caused by the neurotoxic type of Naja spp poison while shock cases mostly found in cardiotoxic snake bites (Hifumi, et al., 2015; Djunaedi, 2009; Anil, et al., 2010). Snake bites might lead to cardiac arrest following hyperkalemia due to rhabdomyolysis after bites of certain krait, and Russell vipers. In this case, the patient did not experience cardiac arrest. But it was necessary to monitor electrolytes, especially hyperkalemia and kidney function. Another emergency clinical situation was the possibility of kidney failure and septicemia, which was triggered by necrosis of bite wound. This might happen if hospital admission was delayed. In this case, fortunately, the patient was taken to hospital one hour after being bitten. Kidney function was found normal, shown by ureum and creatinine within normal limits.

Management of Respiratory Failure due to Snake Bite

Respiratory failure was a complication of acute neuromuscular paralysis due to inhibition of snake toxins in the neuromuscular junction. This inhibition can occur in pre-synapses, post synapses or autonomic ganglia. Patient in this case experienced a type II (hypercapni) respiratory failure (Sanmuganathan, 1998; WHO, 2010; Agrawal, et al., 2001). In general, lungs was in good condition, without infection and no other abnormalities found in its parenchyma. Management of respiratory failure by intubation and ventilators was needed to support ventilation functions while protecting the lungs from pneumonia aspiration. Meanwhile, to restore respiratory function and other organs due to paralysis, it was necessary to do causative treatment (Anil, et al., 2010).

Causative therapy

Antivenin therapy were first described by Albert Calmette in the Institute of Pasteur, Saigon in 1890. Antivenin was an immunoglobulin purified from horse plasma, donkeys or sheep that were immune with one or more species of snake toxin. Monovalent antivenin (monospecific) neutralized toxins from one snake species. Polyvalent antivenin neutralized toxins from several species of different snakes, usually the main ones that had adverse medical effect, in certain geographical area. Antibodies that were raised against poisons from one species may have cross neutralization activity against other poisons, usually from closely related species. This is known as paraspecific activity. Antivenin is indicated when there is one or more of the following: hemostatic abnormalities, neurotoxic signs, cardiovascular abnormalities, acute kidney injury, hemoglobinuria and rapid expansion of

swelling. In Indonesia, government supplied polyvalent antivenin and it was derived from antibodies against the poison Ankystrodon, Bungarus, and Naja sputarix (Warrell, 2010) (Kakaria, Narkhede, Agrawal, Bhavsar, & Nukte, 2014) (Hifumi, et al., 2015).

Table 2. Guideline for antivenin therapy according to Luck (Djunaedi, 2009).

Grade	Envenom severity	Teeth	Edema/ erythema (cm)	Systemic symptoms	Number of vial
0	none	+	<2	-	0
I	Minimal	+	2-15	-	5
II	Moderat	+	15-20	+	10
III	Severe	+	>30	++	15
IV	Severe	+	<2	+++	15

In this case, patient received 15 vials of SAV in total administered in Dextrose 5% infusion. He experienced severe systemic symptoms including respiratory failure and classified as Grade IV.

Classification

Grading of snakebite severity cases were divided into four grades, generally symptoms appear in 2-6 hours after the bite (Niasari & Latief, 2003).

Table 3 Classification of venomous snakebite (Niasari & Latief, 2003).

***Crotalidae* famili**			***Elapidae* famili**		
Grading	**Severity**	**Signs and symptoms**	**Grading**	**Severity**	**Signs and symptoms**
1	Minor	Bite marks, no edema, no pain, no systemic symptoms, no coagulopathy	0	None	History of snakebite, local edema with strokes, no neurological disorder
2	Moderate	Bite marks, local edema, no systemic symptoms, no coagulopathy	1	Moderate	Grade 0 with neurological signs or with euphoria, vomiting, nausea, paresthesia, ptosis, paralysis, dyspnea
3	Severe	Bite marks, regional edema (2 segments from extremity), pain not resolved with analgetics, no systemic symptoms, with coagulopathy	2	Severe	Grade 1 symptoms with repiratory muscle paralysis in the first 36 hours
4	Major	Bite marks, extensive edema, systemic symptoms (vomiting, headache, abdominal and chest pain, shock), systemic trombosis			

Anti-cholinesterase

Snake venom contains complex enzymes, polypeptides, non-enzymatic proteins, nucleotides and other substances. Cobra snake poison (Naja spp) as in this case, neurotoxins that act on post synapses (α-neurotoxin) were bound to nicotinic type acetylcholine receptors in the muscles, also called thee-finger toxin (Agrawal, et al., 2001) (Niasari & Latief, 2003). Provision of anti-cholinesterase must be accompanied with administration of atropine sulfas.

Atropine was given to prevent undesirable muscarinic side effects of anti-cholinesterase, such as bradycardia, hypersalivation and sweating. This snake poison was nerve-damaging and could be irreversible if it is delayed. Research showed time over 210 minutes since snakebite as an irreversible time limit of damage (Anil, et al., 2010). Administration of anti-cholinesterase in patients with neurotoxics might overcome post synapse neurotoxic blocks, but did not play a role in overcoming pre-synapse or central blocks. The types of drugs used include neostigmine and prostigmine, which were given together with atropine sulfate, to avoid respiratory muscle paralysis, respiratory failure, and death. Neostigmine dose given 0.01-0.04 mg / kg every 1-3 hours or continuous intravenous with a maximum dose of 10 mg / 24 hours. An anticholinesterase trial: atrophine sulfate 0.6 mg followed by prostigmine 0.02 mg / kg im or endrophonium 10 mg iv for cobra bite were recommended by WHO (Anil, et al., 2010) (Sanmuganathan, 1998). Patient was given 10: 5 ampoules of athropine sulphate and neostigmine within 24 hours (Sanmuganathan, 1998). Substitution of intravenous preparations for oral mestinon was carried out on day 5.

Supportive therapy

Tabel 4. Indications of Mechanical Ventilators in Breath Failure due to Snake Bites (Agrawal, et al., 2001).

Respiratory rate	Apneu, no breath in 10 seconds, or RR>25-30/’
Respiratory pattern	Apneu, irregular respiration, agonal, gasping
Clinical signs and symptoms	Cough reflex (-), gag reflex (-), RR <10x/’, salivary retention, broken neck sign
Blood Gas Analysis result	pH <7,30, paCO2 >50 mmHg, severe hypoxemia, PaO2 <60 mmHg in FiO2>50% or PaO2 <40 mmHg in any FiO2
Ventilatory Support Profilaxis	To reduce pulmonary complication Severe cyanosis Coma

In this case the patient had not shown signs of severe acute hypercapni, PH was still 7.34 with PaCO2 37.4 and PO2 158, blood gas analysis was done after the patient was intubated, and may interfere with the results. In addition the patient was also immediately resuscitated, hindering severe acidosis. Ventilator support was given according to the patient's respiratory conditions, while administering causative therapy in the form of snake antivenin and anti-cholin esterase. Patients remained in comatus state, could breathe spontaneously, but clinical signs of muscle paralysis was found such as ptosis, limb weakness and shortness of breath. Extubation was carried out on the fifth day after clinical improvement of ptosis, limb muscle strength, respiratory muscle strength, based on improvement criteria for blood gas analysis. The FASTHUG bundle was undertaken, but preventative thromboprophylaxis was not performed. This patient should still be given thromboprophylaxis considering the risk of thrombus. Giving 2x5000 heparin subcutan units could be an option.

Additional therapy

Additional therapy included management of bite site from infection, including the use of broad-spectrum antibiotics immediately (amoxicillin, cephalosporin, gentamicin plus metronidazole) and tetanus prophylaxis (Sanmuganathan, 1998). In this patient, an increase in the number of leukocytes at entry (29,400) was found and might be due to the inflammatory reaction caused by snake venom that the body responded. According to WHO guidelines, it was necessary to administer broadspectrum antibiotics, as an option one of which was Ceftriaxone 1x2 gram iv. Ceftriaxone administration showed a good response, with a significant decrease in the number of leukocytes the following day. Ceftriaxon was given until signs of infection improve. In addition, monitoring of vigilance against the occurrence of compartement syndrome in the bite area was needed. Fasciotomy was performed because there was a clear tension (intra-compartment pressure> 40 mmHg in adults), weakness, hypoaesthesia, pain in passive stretching of compartments on palpation (WHO, 2010). However, before fasciotomy, normal hemostatic function must be confirmed. In this case, fasciotomy was done because the bitten limb showed compartment syndrome.

CONCLUSION

Management of snake bites is very dependent on the type of snake venom. Snake venom can be neurotoxic, cardiotoxic, myotoxic, renotoxic or hematotoxic. Careful history, physical and laboratory examination are needed to determine the type of snake venom. Respiratory failure in cases of neurotoxic snake bites in this case was diagnosed based on clinical symptoms of acute neuromuscular paralysis and laboratory results.

Gold standards of treatment given to patients include antivenom and anti-acetylcholine esterase (causative therapy), ventilator support (supportive therapy) and prophylactic infections of the bitten limb (additional therapy). Early diagnosis, early transportation to the hospital and also adequate management of neurotoxin snake bites are very important to achieve optimal results

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Efficacy of Homeopathy in Children with Retinoblastoma (RB): A Review

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Abstract
Retinoblastoma (RB) is a rapidly developing cancer that develops from the immature cells of a retina, the light-detecting tissue of the eye and is the most common malignant tumor of the eye in children. There are very few known risk factors for retinoblastoma, but the main gene changes inside cells that can lead to retinoblastoma are now fairly well known. Early in fetal development, well before birth, cells in the retina of the eye divide to make new cells to fill the retina. At a certain point, these cells normally stop dividing and become mature retinal cells. But sometimes something goes wrong with this process. Instead of maturing, some retinal cells continue to grow out of control, which can lead to retinoblastoma. The article aims in describing the role of homeopathy in managing RB. The use of homeopathic remedies is raising in the modern area especially in chronic disease as well as DNA mutations like RB and is proved effective in clinical practice. Managing cases of RB in homeopathy is an art. However, more scientific research studies are needed to be done to validate the effectiveness, and explain the safety profile of homeopathic remedies for their anti-retinoblastoma potential. Because, homoeopathy system of medicine is stand on law of similia i.e. Similia Similibus Curenture.

Keywords: Homoeopathy, Retinoblastoma, RB1, Similia, DNA

Introduction

Retinoblastomais a cancer thatstarts in the retina, the very back part of the eye. It is the most common type of eye cancer in children. Retinoblastomais a rare form of cancer, affecting 1 in 15,000 to 1 in 30,000 live births. Retinoblastoma is considered a childhood cancer since 95% of cases occur in children less than 5 years of age. There seems to bean equal chance of the condition occurring in either eye, in either boys or girls, and regardless of race. About 75% of cases occur in one eye, and about 25% of cases occur in both eyes (Medbroadcast.com, 2020). Retinoblastomais a complicated subject that can be challenging for both medical professionals and affected families to fully understand. Imprecise terminology compound confusion.To avoid unnecessary complexity, it is important to use precise terminology when thinking or talking about retinoblastoma (Lee & Murphree, 2013). Retinoblastomais a malignant tumor of the embryonic neural retina. It affects young children under the age of 5 years. Tumours may be unilateral or bilateral,unifocal or multifocal.There are hereditary and non hereditary forms of the disease and the disease can be sporadic or familial. Intraocular growth occurs first, prior to invasion of structures within the globe or spread to metastatic sites. In developed nations, presentation with metastatic disease is unusual. However, metastatic disease not uncommon in developing nations, where it is a significant cause of morbidity and mortality (Lanzkowsky, 2010).

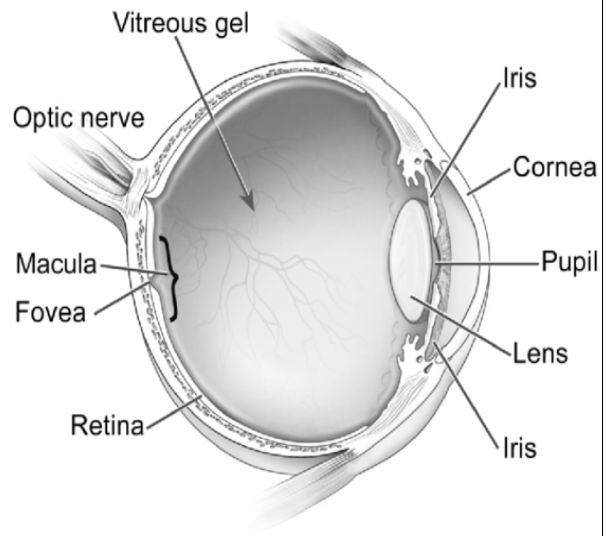

Figure 1: Normal anatomy of eye

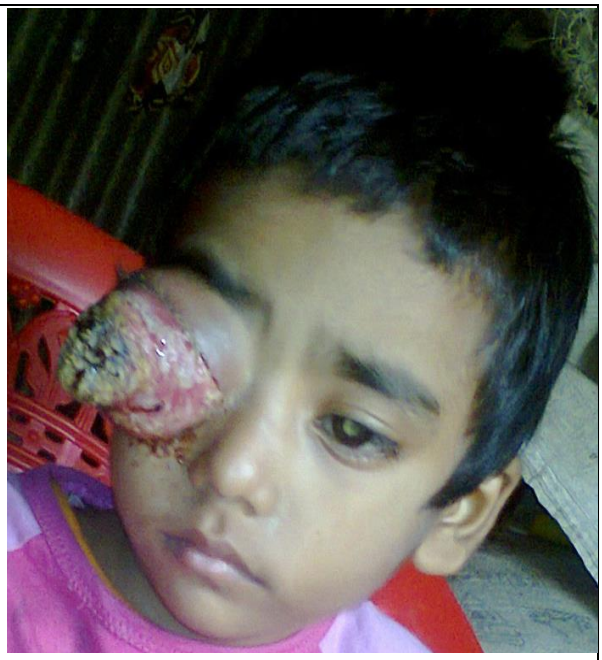

Figure2 : Retinoblastoma of eye

There are several Homoeopathic medicines to control RB, However, these medicines are used in accordance of symptoms similarity, family history and based on others predisposing factors, cause of genetic and chronic miasmatic background. So there is a need of alternative treatment to control and manage RB. This review aims to describe role of homeopathy in managing RB. The expression of this child disorder is manifested at multiple levels, thus affecting the quality of life of the child and the parents. Even with advancement in medical treatment, there are few hopes for such patient and at times not available for all. This study attempts to understand the scope of homoeopathy for such a challenging condition and to explore the concept of RB through the dynamicity of homoeopathic medicines.

Material and methods

This study is conductive with descriptive method and section is divided by subheadings, sub-sub headings. Methods that are already summarized, and indicated by a reference. All modifications to existing methods are described.

Literature Review of Retinoblastoma

Definition

Retinoblastoma is a rare type of eye cancer that usually develops in early childhood, typically before the age of 5. This form of cancer develops in the retina, which is the specialized light-sensitive tissue at the back of the eye that detects light and color (Reference, G., 2020). Retina is made up of nerve tissue thats enses light as it comes through the front of eye. The retina sends signals through optic nerve to brain, wherethesesignals are interpreted as images. A rare form of eye cancer retinoblastomais the most common form of cancer affecting the eye in children. Retinoblastoma may occur in one or both eyes (Mayo Clinic. 2020).

Classification and Staging

Classifying and staging retinoblastomais an essential first stepwhen planning how to manage a Childwith the condition; it also gives important information about prognosis. Classification schemes in cancer are mainly used to compare the results of different treatments and to enable a prognosis to be given (D., A., & S. (2018).

Table 1:Classification Systems forIntraocularRetinoblastoma

Group	International Intraocular Retinoblastoma Classification (IIRC)	Intraocular Classification of Retinoblastoma(ICRB)
Group A (very low risk)	All tumours are 3 mm or smaller, confined to the retina and at least 3 mm from the foveola and 1.5 mm from the optic nerve. No vitreous or subretinal seeding is allowed.	Retinoblastoma ≤ 3 mm (in basal dimension or thickness).
Group B (low risk)	Eyes with no vitreous or subretinal seeding and discrete retinal tumour of any size or location. Retinal tumours may be of any size or location not in group A. Small cuff of subretinal fluid extending ≤5 mm from the base of the tumour is allowed.	Retinoblastoma> 3 mm (in basal dimension or thickness) or • Macular location (≤3 mm to foveola) • Juxtapapillary location (≤1.5 mm to disc) • Additional subretinal fluid (≤3 mm from margin).
Group C (moderat e risk)	Eyes with focal vitreous or subretinal seeding and discrete retinal tumours of any size and location. Any seeding must be local, fine, and limited so as to be theoretically treatable with a radioactive plaque. Up to one quadrant of sub retinal fluid may be present.	Retinoblastoma with: • Subretinal seeds ≤ 3 mm from tumour • Vitreous seeds ≤ 3 mm from tumour • Both subretinal and vitreous seeds ≤ 3 mm from tumour
Group D (high risk)	Eyes with diffuse vitreous or subretinal seeding and/or massive, non-discrete endophytic or exophytic disease. Eyes with more extensive seeding than Group C. Massive and/or diffuse intraocular Disseminated disease including exophytic disease and >1 quadrant of retinal detachment. May consist of ‘greasy’ vitreous seeding or a vascular masses. Subretinal seeding may be plaque-like.	Retinoblastoma with: • Subretinal seeds> 3 mm from tumour • Vitreous seeds> 3 mm from tumour • Both subretinal and vitreous seeds> 3 mm From retinoblastoma

Group E (very high risk)	Eyesthathavebeendestroyedanatomicallyorfunctionallywithoneormoreof thefollowing: Irreversible neovascular glaucoma, massive intraocular haemorrhage, aseptic orbital cellulitis, tumour anterior to anterior vitreous face, tumour touching the lens, diffuse infiltrating retinoblastoma and phthisis or pre-phthisis.	• Extensive retinoblastoma occupying>50% globe or with • Neovascular glaucoma • Opaque media from haemorrhage in anterior chamber, vitreous or subretinal space. • Invasion of post laminar optic nerve, • choroid (>2 mm), sclera, orbit, anterior Chamber

Table 2: International Retinoblastoma Staging System (IRSS)

Stage	Clinical Description
0	Patient treated conservatively
I	Eye enucleated, completely resected histologically
II	Eye enucleated, microscopic residual tumour
III	Regional extension
A	Overt orbital disease
B	Preauricular or cervical lymphnode extension
IV	Metastatic disease
A	Heamatogenous metastasis (without central nervous system involvement) 1 Single lesion 2 Multiple lesions
B	Central nervous system extension (with or without any other site of regional or metastatic disease. 1. Prechiasmatic lesion. 2. Central nervous system mass. 3. Leptomeningeal and cerebrospinal fluid disease.

Causes

Retinoblastoma is caused by a mutation in the *RB1* gene on chromosome 13. This gene is responsible for producing a protein that functions as a tumor suppressor, and every cell in the body has 2 copies of the gene. When both copies are mutated, the cell divides uncontrollably, leading to tumor formation. About 60% of retinoblastomas are due to spontaneous (de novo) mutations that are nonhereditary. The remaining cases are due to a hereditary mutation that is passed down from one (or both) parents.

A mutation in the second copy of the gene then leads to tumor formation. Inherited retinoblastoma cases are more likely to involve both eyes with multiple tumours in each eye, and tend to develop before the first birthday, and may be associated with a separate tumor in the brain, called *trilateral retinoblastoma* in about 1 in 20 children with bilateral retinoblastoma (Specialists, T., 2020).

Every cell in the body contains a gene called RB1, which provides instructions for making a protein called pRB. This protein acts as a tumor suppressor, which means that it regulates cell growth and keeps cells from dividing too quickly or in an uncontrolled way. Children who develop retinoblastoma have one or more mutations in the RB1 gene in cells in the retina. Cells that contain a mutated gene are unable to produce functional pRB protein, and they therefore divide in an unregulated manner, forming a tumor. In a small percentage of children with retinoblastoma a larger section of genetic material is missing, and the chromosomal changes involve several genes in addition to RB1. Affected children usually also have intellectual disability, slow growth, and distinctive facial features (such as prominent eyebrows, a short nose with a broad nasal bridge, and ear abnormalities) (Columbiaeye.org. 2020).

Sign and symptoms of RB

Retinoblastoma is hard to diagnose early because the symptoms are not obvious. At first to notice a white reflection in child's pupil called the cat's-eye reflex. This is when you can actually see the tumor as the eye moves and light reflects off the tumor. Sometimes photographs are useful in picking up this abnormal light reflex. The child may have been squinting or having difficulty focusing both eyes on the same object. This is called strabismus and usually occurs if the tumor is located in or very near the visually most sensitive part of the eye. Symptoms occurring in later stages of the disease include a painful red eye and loss or decrease of vision in the affected eye (Cincinnatichildrens.org. 2020). Most often, however, parents notice following symptoms or signs such as:

- A pupil that looks white or red, instead of the normal black
- A crossed eye, which is an eye looking either toward the ear or toward the nose
- Poor vision
- A red, painful-looking eye
- An enlarged pupil
- Different-colour irises

Diagnosis of RB

Many tests are used to find, or diagnose, cancer. Also tests are done to learn if cancer has spread to another part of the body from where it started. It is called metastasis. For example, imaging tests can show if the cancer has spread. Imaging tests show pictures of the inside of the body. Doctors may also do tests to learn which treatments could work best.

For most types of cancer, a biopsy is the only sure way for the doctor to know if an area of the body has cancer. In a biopsy, the doctor takes a small sample of tissue for testing in a laboratory. If a biopsy is not possible, the doctor may suggest other tests that will help make a diagnosis.

Following these options are considered for diagnosing this type of cancer. Not all tests listed below will be used for every person.

- The type of cancer suspected.
- Child's signs and symptoms.
- Child's age and general health.
- The results of earlier medical tests.

The next step after observing any symptom is to have the child examined by a specialist, who will do a thorough ophthalmic examination to check the retina for a tumor. Depending on the child's age, either a local or general anesthetic is used during the eye examination. Anesthetic is a medication that blocks the awareness of pain. The specialist will make a drawing or take a photograph of the tumor in the eye to provide a record for future examinations and treatment. Additional tests may also be done to locate or confirm the presence of a tumor. In addition to a physical examination, the following tests may be used to diagnose retinoblastoma.

- Ultrasound.
- Computed tomography (CT or CAT) scan.

- Magnetic resonance imaging (MRI).
- MRI or CT scan of the brain.Blood tests.
- Lumbar puncture (spinal tap).
- Bone marrow aspiration and biopsy.
- Hearing test.

After diagnostic tests are done, doctor will review all of the results of RB patient. If the diagnosis is cancer, these results also help the doctor describe the cancer. This is called staging (Cancer.Net. 2020).

Homoeopathic concept for treatment of RB

RB is the most common primary tumor of the eye in infants and young children. This form of eye cancer is caused by uncontrolled division of the cells that make up the retina in the back of the eye, and requires prompt evaluation and treatment by a team of specialists. Though homeopathy is based on totality of symptoms similarity especially such kind of cancerous disorders like RB has a great scope treatment and management in it. At first has to sort out which symptoms are more important to tackle the spread of RB. Therefore we have to conscious to administer homeopathic remedy RB patients. This cancer begins with a change in the structure and function of a cell that causes the cell to divide and multiply out of control. The cells can subsequently invade and damage surroundings tissues, and cells can break away and spread to other areas in the body. Childhood cancer like RB can occur in the same part of the body as adults, but there are differences. Childhood cancer can occur suddenly, without early symptoms and have a high rate of cure. There are Different types of childhood cancer such as Leukemia, Hodgkin lymphoma, on Hodgkin lymphoma, Brain tumor, Spinal cord tumor, Osteosarcoma,Wilms tumor, Neuroblastoma, Rhabdomyosarcoma, Ewing Family tumours etc. With the main signs of RB like a pupil that looks white or red, instead of the normal black, a crossed eye, which is an eye looking either toward the ear or toward the nose, poor vision, a red, painful-looking eye, an enlarged pupil, different-colored irises etc. Others characteristic symptoms may arise along with childhood cancer mainly depends upon the type of cancer, some common findings are; weight loss, rashes, bleeding or excessive bruising, tiredness or excessive fatigue, recurrent infection, early morning headache often associated with vomiting, nausea with or without vomiting, persistent and recurrent pyrexia or fever of unknown origin, mass or lump in the region of neck, abdomen, pelvis, chest, or armpit etc. After doing repertorization homoeopathically, if we can deal with RB patients, hope cure would be possible like others cancerous disorders.

Homeopathic medicines for Retinoblastoma

Homeopathy is one of the most popular holistic systems of medicine. The selection of remedy is based upon the theory of individualization and symptoms similarity by using holistic approach. This is the only way through which a state of complete health can be regained by removing all the sign and symptoms from which the patient is suffering. The aim of homeopathy is not only to treat symptoms of childhood cancer like RB but to address its underlying cause and individual susceptibility. As far as therapeutic medication is concerned, several remedies are available to treat RB symptoms that can be selected on the basis of cause, sensations and modalities of the complaints. For individualized remedy selection and treatment, the patient should consult a qualified homeopathic doctor in person. There are following remedies which are helpful in the treatment of childhood cancer (RB) symptoms: Arsenic album, Bromium, Cadmium Sulph, Carbo Animalis , Carcinosin, Conium, Hydrastis, Lycopodium, Nitric Acid, Phosphorous, Phytolacca, Silicea, Antim Crude, Apis Mel, Arsenic Iod, Aurum Mur, Baptesia, Bellis P, Cadmium Sulph, Calcaria Carb, Carbo Veg, Graphites, Iodium, Kali Bi, Kali Iod, Kali Phos, Kali Sulph, Kreosote, Lachesis, Mercurius, Opium, SecaleCor, Sulphur, Thuja, and many other medicines.

Discussion

As homoeopathy is the method of scientific treatment with various kinds of medicines, can produce symptoms similarity,so it only can cure the diseases totally. Homeopathic medicines are selected after a full individualizing examination and case-analysis, which includes the medical history of the patient, physical and mental

constitution, family history, presenting symptoms, underlying pathology, possible causative factors etc. A miasmatic tendency (predisposition/susceptibility) is also often taken into account for the treatment of chronic conditions. We have studied and applied different remedies from Materia Medica is indicated case and thenfollow up satisfactory withour confidence leveland in the treatment of RB has become stronger. Most of the cases of RBs have constitutional etiology, and genetic matter but the exact cause is unknown. Causes of RB often found due to some precipitating factors; Physical or emotional stress, overall male or female children are more affected. Almost RB cases belonging to either fundamentally sycosis or dominantly tubercular miasm.

Results

The priority of Rb treatment by homeopathic symptomatic remedy is to preserve the life of the child, then to preserve vision, and then to minimize complications or side effects of treatment. The exact course of treatment will depend on the individual case and will be decided by the expert homeopathic partitionner with more precautions.

Conclusion

Homeopathy treats the person as a whole. It means that homeopathic treatment focuses on the patient as a person, as well as his pathological condition. The homeopathic medicines are selected after a full individualizing examination and case-analysis, which includes the medical history of the patient, physical and mental constitution, family history, presenting symptoms, underlying pathology, possible causative factors etc. A miasmatic tendency (predisposition/susceptibility) is also often taken into account for the treatment of chronic conditions. A homeopathy doctor tries to treat more than just the presenting symptoms. The disease diagnosis is important but in homeopathy, the cause of disease is not justified. Other factors like mental, emotional and physical stress that could predispose a person to illness are also looked for. Now a day, even modern medicine also considers a large number of diseases as psychosomatic. The correct homeopathy remedy tries to correct this disease predisposition. The focus is not on curing the disease but to cure the person who is sick, to restore the health. If disease pathology is not very advanced, homeopathy remedies do give a hope for cure but even in incurable cases, the quality of life can be greatly improved with homeopathic medicines.

Homeopathy is a holistic system of medicine. This means that homeopathy treats the human being as a whole. Detailed mental and physical symptoms of the whole being are taken into consideration while prescribing. This form of homeopathic treatment is called as constitutional treatment. In cases where the RBs are due to deep seated chronic disorders like others cancerous illness, this constitutional treatment is usually taken up by homeopathic physicians.

In the Allopathic mode of treatment, the treatment comprises of chemotherapy radiotherapy and combines therapy try to control the metastasis of RB. Unfortunately, these are not curative, but only control the situation. Timely administered homeopathic medicines help avoid surgery for RB and its inherent complications. In short, homeopathic treatment is targeted towards the root cause of the illness and hence the disease is treated from the core. Homeopathy believes in treating the patient and not just the disease. Though the exact cause is unknown of RB but gene (DNA) may be an important cause. Homeopathy is strongly recommended for management of RB, especially when they are small in size. Homeopathy has an exceptional proven safety record with the FDA with 200 years of clinical effectiveness. Since it treats in totality, it leads to a permanent long-lasting cure, rather than a temporary suppression of symptoms. Homeopathy has a very significant role to play in cases of RB.

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Conflicts of interest
Declare if any conflict of interest exists.

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Therapeutic Effects of Ketogenic Diet in the Treatment of Epilepsy

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Abstract
Epilepsy is characterized by seizures due to abnormal discharge of nerve impulses from the brain. Antiepileptic drugs are used to counter these seizures. However, in some types and severities in epilepsy where seizures are resistant to drugs, ketogenic diet (high in fat and low in carbohydrates) is used. In this review beneficial effects of ketogenic diet have been explored in treating epilepsy. It is used as a standard treatment for refractory epilepsy and has showed positive effects in treating all types of epilepsy, in all ages, especially in children. These findings were supported by previous studies which proved that ketogenic diet optimized the therapeutic effects against epilepsy by decreasing the oxidative stress, neuronal damage and enhancing the function of mitochondria. However, the exact mechanism of ketogenic diet in the treatment of epilepsy is still unknown but it can be used as potential therapy for children. More researches are needed to conclude the same for adults.

Objective: The purpose of the study is to investigate the mechanism and action of the ketogenic diet in the treatment of epilepsy along with the side effects. Through this review, the reader can get a full understanding on how efficient the therapy is practically, the diet's tolerable levels and effectiveness.

Keywords: Ketogenic Diet, Ketogenic Diet Therapy, Epilepsy, Seizures, Ketone Bodies, Amino Acids

1. Introduction

Ketogenic Diet (KD) is referred to as high fat and a very low carbohydrate diet that shares many similarities with the low-carbs diet. Over a century, it is used as a beneficial treatment for epileptic individual (Rho, 2017). Faith Healer introduced a KD diet in 1920's in Greece to help epileptic children (Walczyk & Wick, 2017). KD may increase the effects of fasting leading to the formation of ketones in the liver, the main ones being, Beta-hydroxybutyrate, acetones and acetoacetates (J. M. Freeman & Kossoff, 2010). In the 1940's, the initiation of anti-epileptic drugs started to replace the ketogenic diet, but overtime, the ketogenic therapies got higher consideration in the 1990's. It has now become a standard treatment for epileptic patients along with its uses in many other neurological disorders such as Alzheimer disease, Parkinson's disease, and amyotrophic lateral sclerosis, cerebral injury and also ischemia (Barañano & Hartman, 2008) (Guelpa, 1911; Prins & Matsumoto, 2014; Tefera & Borges, 2017; Zhao et al., 2006).

The efficacy of the KD diet is not linked to the type of seizures/epilepsy, age, sex and etiology (Coppola et al., 2002). Numerous studies have revealed positive results of KD on adolescents, adults and children. KD showed more significant result for the improvement of cognition and social behavior among children 3-8 years of age than gluten and casein free diets (El-Rashidy et al., 2017). Thiele EA observed that children may also take the vitamin and mineral supplements along with Ca supplements when they are on KD diet. Moreover, in ketogenic diet fat necessities are encountered by heavy cream, dietary fats and oils. Children may also encourage consuming specific fruits, vegetables and proteins. In addition, fruits and vegetables which contain starch, simple sugars, pasta and grains should be avoided (Thiele, 2003). Ketogenic diet has exhibited promising results in generalized and partial epilepsy in adults. The diet has manifest to be bearable in the majority of patients (Sirven et al., 1999).

The high fat low carb diet prevents starvation and provides necessary calories to the body by oxidation of fats which surpass the TCA cycle. By the oxidation of fats, production of ketone bodies increased which are used by cells for energy creation including the brain, when glucose is absent. The ketone bodies further undergo oxidation and acetyl-CoA is released which then goes into the TCA cycle as summarized in Fig.1 (Gasior, Rogawski, & Hartman, 2006). The micronutrients present in the KD are in the ratio 4:1 (4 gram of fat for 0.5g proteins and 0.5g carbs – 8% proteins, 2% carbohydrates and 90% fats (McDonald & Cervenka, 2018) (Allen et al., 2014).

An epileptic seizure can be physiologically defined as "a state produced by an abnormal excessive neuronal discharge within the central nervous system" (Penfield & Erickson, 1941). In Europe, the estimated figure of children and adolescents having active epilepsy is 0.9 million. Moreover, an estimated percentage of 20-30% of epileptic populace have >1 seizure/month (Forsgren, Beghi, Oun, & Sillanpää, 2005). According to previous epidemiological studies showed that there was a reduction in 50% seizures in adults who were given 22-25% classic KD treatment (12). In addition, a number of other evidence based studies showed that ketogenic diet is more effective in refractory epilepsy than anticonvulsant medications among children (Acharya, Hattiangady, & Shetty, 2008).

The efficacy of KD has been seen across a diversity of age, types of seizures and the severity of seizures. The role of KD in epilepsy is very evident among a diverse group of studies. Various studies documented that the effectiveness of KD in intractable epilepsy among adults was 13-70%. Previous clinical researches indicated that KD contains some potential procedural limitations, such as improper study designs and sub optimal categorized patients and populace (Neal et al., 2008) . Furthermore, 38% children receiving KDT had a greater than 50% decrease in seizures, 7% had greater than 90% reduction in the amount of seizures (Sampaio, 2016). Clinical researches done till now do contain potential procedural limitations, such as improper study designs and sub optimal categorized patients and populace. To counteract these limitations, a no. of creative, prospective randomized controlled trials (RCT's) have been planned, and executed. The outcomes of these studies will expectantly offer important information to better understand the role of KDT in the treatment procedures in various types of epilepsy (J. Freeman, Veggiotti, Lanzi, Tagliabue, & Perucca, 2006).

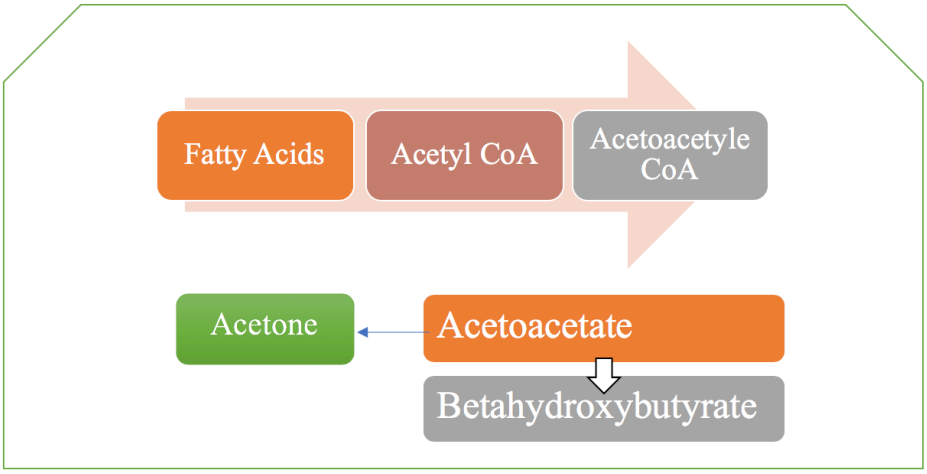

Fig 1. Production of ketone bodies by oxidation of fats

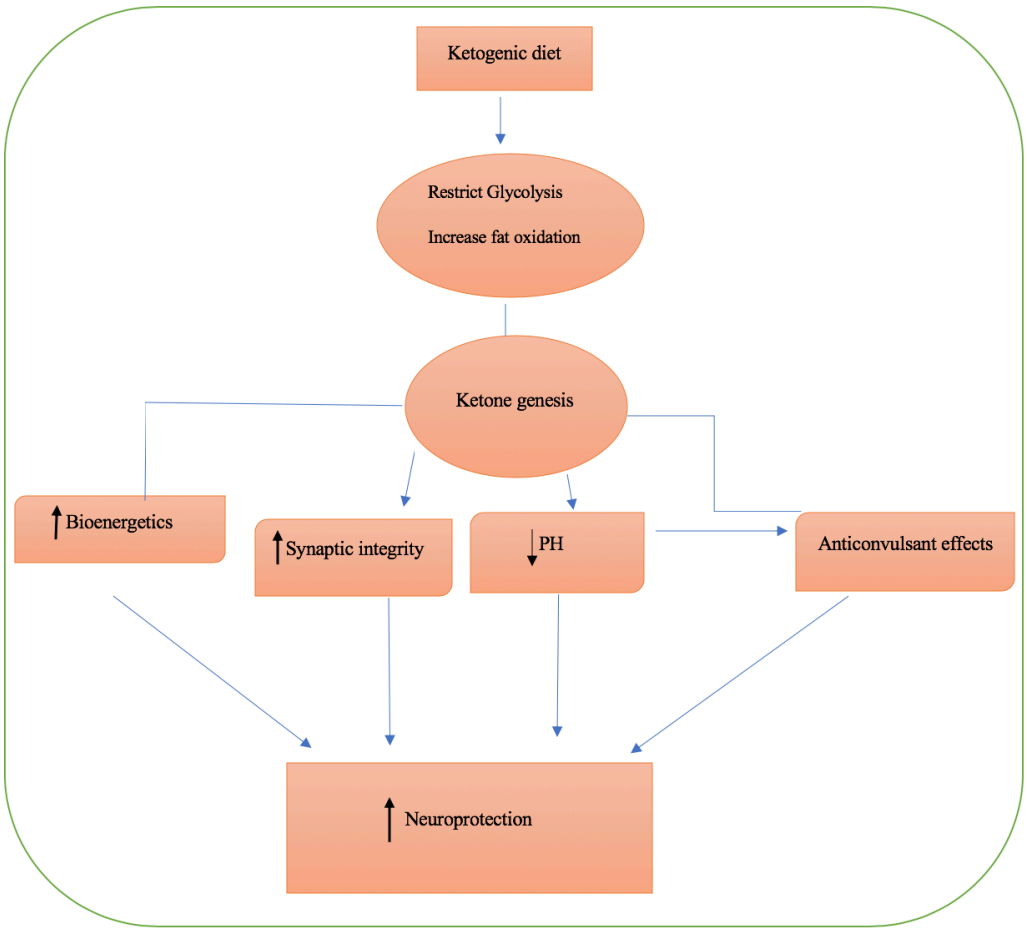

Fig 2. Basic mechanism of the role of KD in decreasing convulsions in epilepsy

2. Literature Review

KD is the oldest and the most effective therapy used for treating epilepsy. It is shown to be most beneficial in treating interactable epilepsy in children (Thiele, 2003). In 1921, Wilder initiated ketogenic diet comprised of high fat and low carbohydrates for the treatment of epilepsy and its effectiveness was analyzed by clinical trial performed by Peterman, Helmholtz, Keith and Livingston (MILLICHAP, JONES, & RUDIS, 1964). During KDT, the consumption of carbs is decreased to almost 50g/day or 10% of total calories. Consumption of protein increases to 1.2-1.5g/kg/day and the remaining ingestion of energy is from fats (60-80%)(Aragon et al., 2017).

Epilepsy is considered as the most common disorder of the brain, can befall at any age and is diagnosed through clinical and neurophysiological investigations (Duncan, Sander, Sisodiya, & Walker, 2006). It is too multifaceted to be considered a disease. In fact, it can better be called as a syndrome categorized by seizures that can occur due to a variety of conditions. Different types of epilepsy occur due to dysfunctions in potentially different biological pathways. Drugs used to target one pathway will only treat a specific no. of epileptic patients because the mechanism of the medication is specific to specific type of epilepsy. Potential pathways which are responsible for causing seizures include: glucose/amino acid transport, mitochondrial dysfunction and neuronal myelination. Present studies do not have the ability to test every person to detect the actual etiology of epilepsy which leads to an increased number of misdiagnosis. So the usage of ketogenic diet is suggested as a primary long term treatment in terms of effectiveness and efficiency (Clanton, Wu, Akabani, & Aramayo, 2017).

2.1 Mechanism

The 2 circumstances should be considered when KDT is to be used before the failure of 2-3 anti-convulsant medications. The first one is the glucose transporter deficiency syndrome, when transportation of glucose to the BBB (blood brain barrier) is weakened. The second is the loss of pyruvate dehydrogenase when pyruvate isn't metabolized to acetyl co-A (Kossoff et al., 2009). Researches also suggest that many other causes may benefit from KDT. For example, epilepsies caused by genes (ex: juvenile myoclonic and absence epilepsy) and epilepsies caused by catastrophes such as those due to deformities (ex: lissencephaly, hypoxic-ischemic injury, migrating focal seizures of infancy, and febrile infection-related epilepsy syndrome) (Thammongkol et al., 2012).

Various studies demonstrated that KD as an adjunct treatment in children and adults with refractory epilepsy, is considered as a first-choice treatment in some explicit metabolic disorders. For example, in glucose transporter type 1 and pyruvate dehydrogenase deficiencies, and mitochondrial complex I defects. Papers also suggest that KDT is significantly effective in West syndrome, severe myoclonic epilepsy of infancy, myoclonic-astatic epilepsy, febrile infection related epileptic syndrome, and drug-resistant idiopathic generalized epilepsies or refractory status epilepticus (Elia, Klepper, Leiendecker, & Hartmann, 2017; McDonald & Cervenka, 2017).

Epilepsy is brought by phenotypic alterations in endothelium of brain which bring seizure reactions due to changes in blood brain barrier and they have abnormal expression of glucose transporter molecule (GLUT1).I t is also characterized by hypo metabolism in seizure foci and altered properties of non-excitable CNS cells which lead to decreased uptake of ions from channels. Glucose uptake is hindered but ketone bodies generated by ketogenic diet can be used as an alternative to glucose and can cross Blood Brain Barrier easily as depicted by the flow diagram Fig.3 (Janigro, 1999).

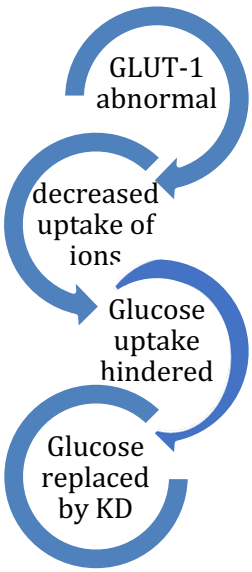

Fig 3. Glucose uptake hindered by brain cells

Many researches have been focused on how the ketone bodies show anti-convulsant effects. There have been discrepancies in researches trying to associate guarding against seizures with the amount of ketone bodies. This proposes the fact that some other processes can be involved in KDT's positive outcomes on seizures. Many mechanisms have been suggested (Fig 4) such as; the production of ATP's causing the neurons to become resistant when the demand of metabolism is high during seizures; changes in the pH of the brain altering the excitation of neurons; the inhibition of fatty acid/ion channels by ketone bodies (KB); and changes in the metabolism of AA (amino acids) that lead to the production of Gamma aminobutyric acid (GABA), a neurotransmitter of the brain (Barañano & Hartman, 2008).

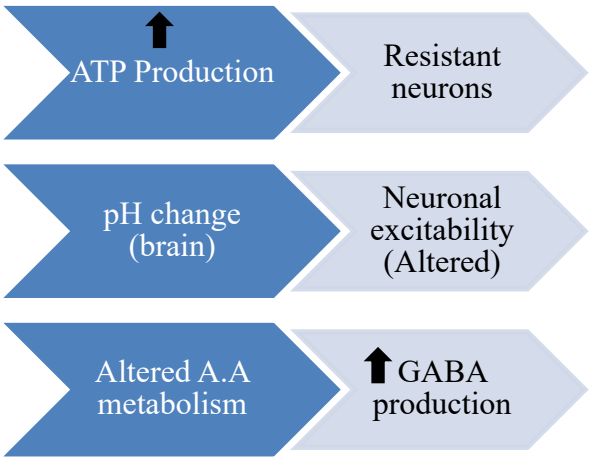

Fig 4. Positive Effects of KD on seizure reduction

GABA signaling is the best studied goal of study. Epilepsy was induced by GABA antagonists in mice and they were seen to exhibit an extraordinary response to KD (Bough, Gudi, Han, Rathod, & Eagles, 2002). Aspartate is an amino acid. The role of aspartate is to stop the action of glutamate decarboxylase. Glutamate decarboxylase catalyzes alpha-ketoglutarate to GABA. If the level of aspartate is decreased by KD, it would indorse the production of GABA. The excitatory neurotransmitter glutamate would then be converted to glutamine in astrocytes (the glial cells of the nervous system). Neurons take up glutamine which is converted to GABA, which hinders neuron action (Fig 5) (Zhang, Xu, Zhang, Yang, & Li, 2018).

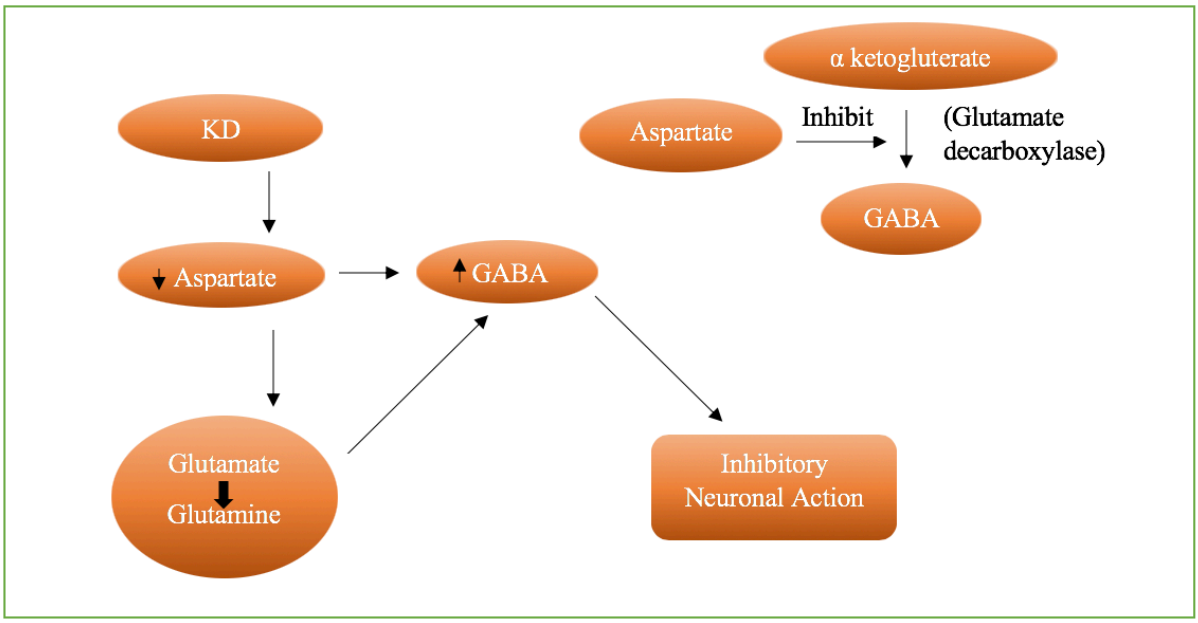

Fig 5. Role of KD in inhibition of neuron action

Levels of Poly unsaturated fatty acids are also increased along with ketone bodies in epileptic individuals who were given KD. Studies show that both ketones and PUFA show neuroprotective action in neurodegenerative disorders which are related to improper functioning of the mitochondria. Mechanisms of neuroprotective actions include decreased free radicals in the mitochondria. This would lead to decreased oxidative stress and reduced neuron damage (Fig 6). It is still not clear as to how KD specifically causes an anti-convulsant reaction. But the positive effects of KD do propose the fact that if synthesis of ATP is heightened and reactive oxygen species are suppressed, it can cause a remarkable decrease in epileptic seizures (Masino & Rho, 2012).

2.2 Previous Studies

To validate the effect of KD on refractive epilepsy, another study was done, in which diet, seizure and adverse effects history were taken during a 36-month period. Out of the 29 children who were given KD, 75.8% showed less seizure after 4 weeks and 48.3% of children showed a 90% reduction in the frequency of seizures. At 1 year, 8 epileptic patients continuously presented constructive results. No effective changes were seen in levels of triglycerides, albumin, total protein, creatinine, glycemia, AST's and ALT's. Levels of serum cholesterol were shown to increase in the first 4 weeks, reduced in the next 6 months and had come to normal after that. The overall results concluded that almost $1/3^{rd}$ patients had accomplished a potential decrease in the frequency of seizures, and a few of them were totally cured with no seizures at all (Martins et al., 2012).

The effectiveness and tolerable levels of KD were further proved when a study on 48 children and adults with refractory epilepsy was conducted. Patients were randomly selected in the KD group and the care as usual (CAU) group. The results indicated that mean frequency of seizures was potentially lower in the KD group than in the CAU group and a two-fold decrease was seen in the score of the severity of seizures in the KD group. Gastrointestinal side effects were also higher in the KD group. The results concluded that this RCT trial was a Class 1 proof that KD diet was effective in the treatment of refractory epilepsy in children and adolescents but patients frequently reported gastrointestinal symptoms (Lambrechts et al., 2017).

Another type of epilepsy, Lafora Body Disease (worsened myoclonus epilepsy) was studied in 2006. This type of epilepsy cannot be treated by a specific therapy. In LBD patients the accumulation of polyglucan occurs due to the mutation in the protein that is involved in glycogen metabolism. This study provided KD to such patients and assessed its effectiveness on them. The study involved 5 LBD patients who remained under observation for 10-30 months. The KD brought effective changes in the first 16 months and the nutritional and clinical findings of the patients remained stable during this period. KD therapy was not able to stop the disease progression instead it slowed down the progression rate. However further investigations should be done on a larger case series (Cardinali et al., 2006).

Additional study was conducted in 2014 by Maromi Nei on ketogenic diet as an alternative treatment for epilepsy. Sample size of 29 including adults and adolescents with the mean age of 32 years and range of 11-51 years was collected and were initiated keto-diet for 9 months. Results showed that 52% of them demonstrated improvements by a reduction of 50% of seizure frequencies. 31% showed no improvement, 7% were not able to follow up and frequency of seizures increases in 10% of patients. The study concluded that the diet could be used for the treatment in adults and adolescents with epilepsy, and patients who had a generalized epilepsy who show symptoms can be good choice of applicants for KDT (Nei, Ngo, Sirven, & Sperling, 2014).

An experimental study conducted on mice showed that KD can decrease the episodes of seizures in mice by increasing activation of adenosine A_1 receptors (A_1Rs). KD reduced adenosine kinase, the major adenosine-metabolizing enzyme. Importantly, hippocampal tissue resected from patients with medically intractable epilepsy demonstrated increased adenosine kinase concluding that can reduce seizures by increasing A_1R-mediated inhibition (Masino et al., 2011).

A study conducted on 168 epileptic patients aged ≥ 18 years showed that the effectiveness of KDT varied from 13-70% with the total effectivity rate of 52% for the classic ketogenic diet (Ye, Li, Jiang, Sun, & Liu, 2015). A study on 27 subjects given KD for a duration of 2-118 months showed an 33% complaint rate ≥ 90% seizure reduction in 52% patients and ≥ 50% reduction in 70% patients (Cervenka & Kossoff, 2013). To offer additional

proof for the tolerable levels of KD in adults, another study was conducted. 23 subjects given KD in the ratio of 2-2.5:1 for a duration of 1 year showed a 39% complaint rate ≥ 90% seizure reduction in 8% patients and ≥ 50% reduction in 39% patients. These results concluded that epileptic adults can tolerate KD in the long-term reducing frequency of seizures (Schoeler et al., 2014).

To evaluate the limitations of KD is equally important as its benefits. A study was conducted to calculate the management and prevention of KDT. 129 epileptic patients on 129 on KDT were assessed to review the early and late onset complications. Results exhibited complications of dehydration, nausea, vomiting, diarrhea, constipation, gastritis and fat intolerance. Hypertriglyceridemia, transient hyperuricemia, Increased cholesterol levels, numerous infectious diseases, symptomatic low blood glucose levels, hypoproteinemia, decreased magnesium levels, repetitive decreased sodium levels, low concentrations of high-density lipoprotein, lipoid pneumonia because of aspiration, hepatitis, acute pancreatitis, and persistent metabolic acidosis were also noted. Late-onset complications consisted of osteopenia, renal stones, cardiomyopathy, secondary hypocarnitinemia, and iron-deficiency anemia. Most of these adverse effects were effectively controlled. At the same time 17.1% stopped KDT because of serious side effects, and 3.1% died during KD treatment, 2 deaths were reported due to sepsis, 1 due to cardiomyopathy and 1 due to lipoid pneumonia. The study concluded the basic fact that complications during KD are temporary but should be monitored carefully at the same time (Kang, Chung, Kim, & Kim, 2004). Randomized studies of the ketogenic diet in Cochrane Epilepsy Group's Specialised Register (June 2011), the Cochrane Central Register of Controlled Trials (CENTRAL 2011, Issue 2 of 4), MEDLINE (1948 to May week 4, 2011) and EMBASE (1980 to March 2003) suggest that the KD results in short to medium term benefits in seizure control in children. However, one study of long term outcome report poor tolerance and GIT issues. It was not possible to meta-analyze data from these randomized trials due to heterogeneity. However, all studies showed 30-40% reduction in seizures compared to comparative controls (Levy, Cooper, Giri, & Weston, 2012).

A retrospective case study was reviewed in 29 infants aged two and a half weeks and 23 months given KDT. Results showed that 2 of them showed no signs of seizures after 4 weeks of KDT, 7 showed >50% decrease in seizures and 8 demonstrated a reduction in the severity and frequency of seizures. 45% had no side-effects of the treatment and KDT was stopped in 2 because they could not tolerate the diet. The review came to a conclusion that infants can tolerate KD well even when the intensity of the seizures is high. The results also concluded that 50% reduction is possible with KDT without adverse effects (Ismayilova, Leung, Kumar, Smith, & Williams, 2018).

KD is an effective approach in treating drug-resistant epilepsy in young children. It also provides positive results when given to adults with epilepsy. Researches conducted on KD's effectiveness in adults are few and its treatment usage is limited in adults with intractable epilepsy. A meta-analysis gathered information from a few published researches on treating epilepsy with KD in adults from different sources like PubMed, Embase and Conchrane Library for up to 10th January 2017. The main outcome included a 50% reduction in seizures; the methodology reviewed by the New castle-Ottawa scale. There were 402 articles out of which 16 studies predominantly met the inclusion criteria including 338 patients. The results of the meta-analysis showed the following percentages; 13% adults showed effective symptoms of no seizures, 53% adults had a 50% decrease in seizures and 27% adults with intractable epilepsy decrease in seizure presented seizure drop under 50%. KDT showed less harmful effects like weight loss, high level LDL and raised total cholesterol while on the other hand low glycemic index diet (LGID) and low dose fish oil diet (LFOD) has shown fewer side effects. Thus the meta-analysis concluded that KD is an effective approach to treat intractable epilepsy in adults and also its side effects are well tolerated. Further studies are required to make KD more of an effective treatment approach for intractable epilepsy (Liu et al., 2018).

The acceptance, Tolerance and effectiveness was further evaluated in another study. KDT (formula-based) was given to 10 refractory epileptic children. Results suggested only mild side effects and satisfactory adherence, 50% decrease in seizures were observed in 60% patients and 10% patients became seizure free on KDT (Sampaio, Takakura, & Manreza, 2017), which is also supported by other studies (Martin-McGill, Jenkinson, Smith, & Marson, 2017).

A multi-center research pursued to look into the advantaged of KD in seizure reduction in 50 children with myoclonic-astatic epilepsy (MAE). The reduction in seizures were monitored before during and after treatment.

Results indicated a seizure free outcome in 54% patients and >70% decrease in seizures were seen in 86% patients. 50% children had normal development and cognitive outcomes. Introducing KD earlier did not prove to be effective in a greater decrease in seizures, but potentially lead to remission. The significance of the study was the fact that introducing KDT early in MAE has a robust tenacious anti-convulsant effect with remission in the long term (Stenger et al., 2017).

A study was conducted to govern the effect of KD diet on the action of seizures, anthropometric measurements and biochemical markers, along with GI symptoms. 15-50g CHO modified KD was given for a period of 3 months. Participants included 67.7% white, 50% females 39 years of age, with a BMI of 32.6 kg/m^2. The results again showed a significant effect on seizure reduction. LDL increased from 131 mg/dl to 144 mg/dl and HDL from 57-69 mg/dl. Triglycerides elevated from 96-91mg/dl. GI scores were not affected with modified KD in epileptic adults. Significant reductions in seizure frequency were also noted, concluding the fact that KDT may be a valuable option in the treatment of seizures and weight gain in epileptic adults (Schuchmann et al., 2017).

The total evidence of these studies show that KD and its variants are a good alternative for non-surgical pharmaco-resistant patients with epilepsy of any age, taking into account that the type of diet should be designed individually and that less-restrictive and more-palatable diets are usually better options for adults and adolescents (D'Andrea-Meira et al., 2019).

3. Results

#	Source	Study Design	Condition	Population	Main Outcomes
1.	Martins et al., 2012	Experimental Study	Questionnaire and Diet Evaluation – (CHO-3-5%) Dietary Fat – 70% Protein – Not Restricted	A total of 102 respondents 102 completed the questionnaire 17 commenced the diet	Constipation (n = 6) and loose stools (n = 3), shown as adverse effects. No other complication Increase in seizures (n=1)
2.	Lambrechts et al., 2017	Randomized Clinical Trials	Randomized to KD or Care as Usual	Refractory epilepsy patients of 1-18 years of age.	Primary Results - 50% decrease in seizures after a 4-month period. Mean Seizure frequency in KD (56%) compared to control (99%) The group treated with KD showed a higher rate of GI symptoms.
3.	Cardinali et al., 2006	Pilot Study	LBD patients treated with KD	5-Lafora body Disease patients	KD well tolerable in 1st 16 mos. Didn't stop the progression of the disease in the long term.
4.	Nei, Ngo, Sirven, & Sperling, 2014	Long term results report on epileptic adults treated with KD	Started KD and follow up until discontinuation of the diet	29 adults and adolescents with refractory epilepsy (11-51 years of age) (16 women, 13 men)	52% decrease in the frequency of seizures 45% with greater than 50% decrease in the frequency of seizures, 31% - no improvement 10% with greater than 50% rise in frequency of seizures.
5.	Schoeler et al., 2014	A review on the feasibility of KD	KDT – with follow-ups for 1-10 years	23 epileptic adults	1 – experienced psychosis GI symptoms most common Decrease in the frequency of seizures Increased alertness and concentration
6.	(Kang, Chung, Kim, & Kim, 2004	Review on early and late -onset complications of KD	KDT – followed for greater than a year.	Results of 129 epileptic patients on KD	Early onset complications – dehydration, nausea, vomiting, diarrhea, constipation, fat intolerance and gastritis,

					hypertriglyceridemia, transient hyperuricemia, hypercholesterolemia, symptomatic hypoglycemia, hypoproteinemia, hypomagnesemia, repetitive hyponatremia, low concentrations of high-density lipoprotein, lipoid pneumonia due to aspiration, hepatitis, acute pancreatitis, and persistent metabolic acidosis Late-onset complications - osteopenia, renal stones, cardiomyopathy, secondary hypocarnitinemia, and iron-deficiency anemia.
8.	Ismayilova, Leung, Kumar, Smith, & Williams, 2018	Retrospective case-note review (2006-2016)	KDT for more than 4 weeks.	29 Children <2years	2/29 – seizure free 7 - >50% decrease in seizures 8 – reduction in the frequency of seizures
9.	Liu et al., 2018	Meta-analysis of observational studies	Effect of KDT	402 articles studied, out of which, 16 studies including 338 patients met the inclusion criteria	13% adults showed effective symptoms of no seizures, 53% adults had a 50% decrease in seizures and 27% adults with intractable epilepsy decrease in seizure presented seizure drop under 50%
10.	Sampaio, Takakura, & Manreza, 2017	Experimental Study	KDT; - CHO to Fat ratio for 3 mos. Orally Fed – 2:1 in 1st week 3:1 in 2nd week 4:1 in 3rd week Enterally Fed:-3:1 – at initiation 4:1 after 2 weeks	10 children with refractory epilepsy (9mos-16 yrs of age)	60% patients showed >50% decrease in the frequency of seizures. 10%- eizure-free
11.	Stenger et al., 2017	Retrospective Study	KDT	50 epileptic children treated by KDT	54% seizure free after 6 mos Earlier KDT – better cognitive outcome and significant results in remission
12.	Schuchmann et al., 2017	Experimental Study	15–50 net g of CHO/d for 3 mos.	31 enrolled patients Follow up of 12 patients at 3 mos. 67.7% white, 50.0% female, aged 39	Seizure frequency (n=9) reduced with KDT Two subjects reduction in frequency of seizures by ≥ 50%, 3 participants -decrease in frequency of seizures by < 50% Low-density lipoprotein cholesterol from 131 mg/dL to 144 mg/dL. High-density lipoprotein 57mg/dL to 69mg/dL, Triglycerides down from 96 mg/dL to 91 mg/dL baseline GI scores (n=4) low, did not change with alterations in KDT

4. Conclusion

KD, thus supports seizure control and inhibits progression of epilepsy. The ratio of fats to protein is 4:1 and fats to carbohydrates are 3:1. It shifts the energy metabolism of the body from carbs to fats which is the leading cause of generating ketone bodies. It is used as standard treatment for the patients of epilepsy particularly the refractory

epilepsy where medication is failed to prove positive effects. Positive results were seen in treating generalized and partial epilepsy with ketogenic diet.

KD is rapidly gaining popularity in almost all fields in the health sector. KD can be and is also used in a variety of other neurological disorders, such as Alzheimer's, Parkinson's and brain tumors, along with brain injuries, and weight management. It is being used for many years, and it's benefits in epilepsy outweigh the side effects. It should be kept in mind that both medicines and restricted diets do have some consequences but can be stabilized if given in the right proportions and monitored strictly with proper follow-ups. RD's who prescribe the diet need to be well acquainted on the basics of KD and how to manage the diet according to the patient. Many randomized control trials with an increase in the number of case-studies still need to be done in order to extensively investigate its mechanisms and effects on epileptic patients, and its mechanisms when given with anticonvulsant medications.

5. Recommendations

KD is a recommendable treatment approach towards intractable epilepsy in the children. The drugs that treat epilepsy target only one of its specific kind and therefore isn't functional and desirably beneficial in treating all kinds of epilepsy. KD has helped in reduction of epileptic seizures by 50% in children and adults in most studies conducted till date. It will be beneficial to conduct more class 1 researches to define the role of ketogenic diet in treating epilepsy in children and adults in a better way.

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Case Report: Intensive Care Management of Preeclampsia and HELLP Syndrome

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Abstract
Introduction: Preeclampsia, eclampsia, and HELLP syndrome are life-threatening conditions in 2-8% of pregnant women and result in 70,000 maternal deaths and 50,000 infant deaths worldwide. Preeclampsia, eclampsia, and HELLP syndrome with organ failure are indications for intensive care in pregnant women. The most important goal of management of patients with preeclampsia is to prevent eclampsia and reduce maternal blood pressure. Case: A 35 year old woman with G3P2A0 gravida 29-30 weeks with impending eclampsia who underwent caesarean section. The history revealed complaints of severe headache, blurry vision, heartburn, and a history of high blood pressure during this pregnancy. On the examination of vital signs, the blood pressure was 160/100 mmHg. In laboratory examination, the results of proteinuria (+3) and other results were within normal limits. Preoperative management of intravenous magnesium sulfate, with the oral antihypertensive Methyldopa. Intraoperative general anesthesia was performed, the operation lasted 1 hour, the total bleeding was 250 cc. Postoperatively the patient was transferred to the semi-intensive room (HCU), the patient experienced worsening due to uterine atony. After being resuscitated and intubated, the patient was performed relaparotomy and hysterectomy under general anesthesia. The operation lasts for 2 hours. The patient is then transferred to the intensive care unit (ICU) for close observation. Conclusion: Determination of the basic diagnosis and appropriate initial management and prevention of complications in preeclampsia, eclampsia, and HELLP syndrome can reduce the incidence of morbidity and mortality.

Keywords: Anesthesia Management, Sectio Caesarea, Preeclampsia, Eclampsia

INTRODUCTION

Preeclampsia, eclampsia, and HELLP syndrome are life-threatening conditions for expectant mothers and also unborn baby during pregnancy period. Preeclampsia is referred to as pregnancy-related illness and appears in 2-8% of the expectant mother. Worldwide, its mortality rate is about 70.000 and 50.000 for expectant mothers and unborn babies, respectively. Preeclampsia, eclampsia, and HELLP syndrome, when present, usually are indications for intensive care unit admission, especially if there is more than two organs failure presents and if the patient needs mechanical ventilation support.

There are some diagnostic criteria for preeclampsia as follows: (1) systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥ 90 mmHg occur two times consecutively in between 4 hours of period measurement, (2) proteinuria ≥300 mg/day in ≥ 20 weeks of gestation with unknown history of previous hypertension. In some cases, during the course of preeclampsia, proteinuria may not be found in laboratory examination to establish the diagnosis of preeclampsia. However, preeclampsia still can be diagnosed as hypertension accompanied by thrombocytopenia, liver function disturbance, renal insufficiency, pulmonary edema, and central nervous system dysfunction along with new-onset visual disorder .(Lam & Dierking, 2017 ; Jeyabalan, 2014 ; Robert, et al., 2013)

Eclampsia, defined as episodic convulsive symptoms or decrease of consciousness of patient with preeclampsia where all other possible causes of seizure have been excluded. HELLP syndrome is a life-threatening condition which is accompanied by several symptoms as following: the presence of hemolysis, elevated liver enzyme and decreased of platelet count. (Lam & Dierking, 2017)

The purpose of diagnosis establishment and early rapid management of an expectant mother with preeclampsia, eclampsia, and HELLP syndrome is to reduce morbidity and mortality rate. Therefore, the management requires multivarious disciplines, including obstetricians and intensivists.(Lam & Dierking, 2017) The primary goal for patients with preeclampsia is to lower the blood pressure of expectant mothers below 160/110 mmHg. Magnesium sulfate is a drug of choice to prevent eclampsia episode. However, the mechanism of action is unknown, but it is assumed that Magnesium sulfate has an antagonist effect towards calcium ion therefore depressing neurotransmitter release in the neurons. (Kelsey, 2015)

CASE REPORT

Anamnesis

A 35-year-old housewife referred from maternity clinic came to the emergency department of RSHS on July 17th, 2019, with a chief complaint of severe headache from 3 hours prior to hospital arrival. The patient also complained of heartburn symptoms and blurred vision. This expectant mother was on her third pregnancy of 29-30 gestational weeks. She denied having abdominal contraction or vaginal discharges. The fetal movement was within normal.

She has had history of hypertension during pregnancy (160/100 mmHg) and did not take any regular medication. The history of hypertension from previous pregnancy, DMT2, heart problems, and asthmatic episodes were denied.

The last menstruation period was on December 26th, 2018.

Delivery history:
1. Giving birth assisted by midwife, sponatenous delivery of a fully termed male baby, birth weight was 1500 grams, alive
2. Giving birth assisted by Midwife, spontaneous delivery with a fully termed male baby, birth weight was 2500 grams, deceased when he was 7-year-old
3. G3P2A0

Physical examination

Consciousnes	: Compos mentis
Blood Pressure	: 160/100 mmHg
Heart rate	: 90 x/min
Respiratory	: 20x/min
Temperature	: 36.0^{o} C
Fetal heart beat	: 140-144 x/min
Height	: 152 cm
Weight	: 70 kg
Body Mass Index	: 30,3

Head : pink palpebra conjunctiva, anicteric sclera
Neck : JVP 5 ±2 cmH2O, unpalpable lymph nodes
Chest : fully symmetrical chest expansion,
Vesicular breathing sounds, no ronchi and no rales
Abdomen : Rounded contour, fundal height corresponding to gestational weeks.
Ekstremities : warm extremities, capillary refill time < 2 seconds

Laboratorium examinations

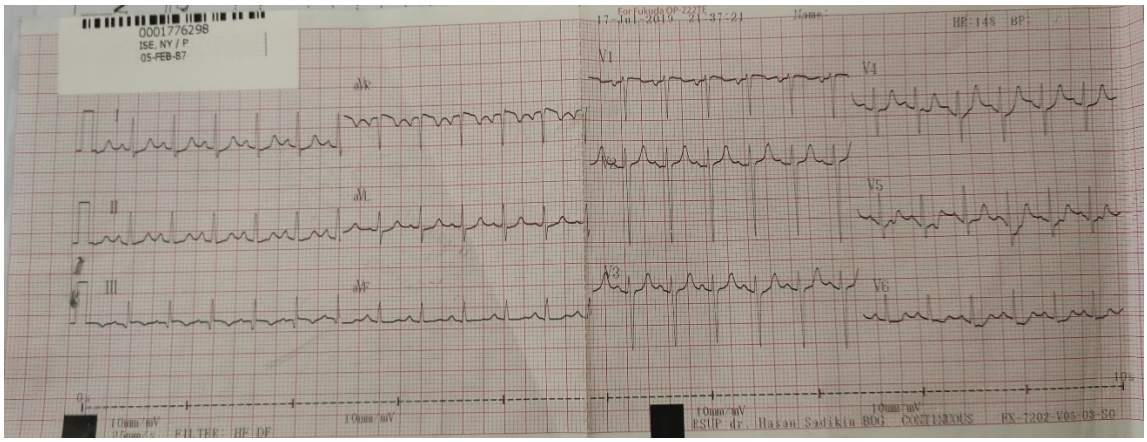
Abdominal Ultrasound (on July 17th, 2019):

Detection of single alive fetal-head with estimation of 29-30 weeks of gestational age, amniotic fluid presents appropriately, SOP 3.3 cm, placenta in the posterior corpus, determined birth weight was 1300 grams.

Laboratory Results

On July 17th, 2019 at 08.01 am							
Hb	**Ht**	**L**	**Tr**	**PT**	**INR**	**APTT**	**Protein Urine**
14	41,4	8,86	111.000	11,0	0,81	25,3	+3

ECG



Diagnosis

G3P2A0 Gravida 29-30 weeks gestational age, with impending eclampsia

Early management in the Emergency department

- A thorough observation of general condition, vital signs, and fetal heartbeat regularly
- O_2 supplementation with nasal cannula 3 liters/min
- Pregnancy termination (Sectio Cesarea) as indicated due to impending eclampsia
- MgSO4 20% 4 grams in 100ml of Ringer Lactate solution dripped intravenously within 10-15 minutes
- MgSO4 20% 10 grams as maintenance dosage in 500ml of Ringer Lactate solution, dripped intravenously 20-30 drops per minutes
- Methyldopa 3x500 mg per-oral
- Informed consent to patient and families

Observation sheet in Emergency department

Time	Contraction	Fetal heartbeat	BP	HR	R	Information
07.10-07.40	-	140-144	160/100	90	20	
07.40-08.10	-	144-148	160/100	90	20	
08.10-09.10	-	148-152	170/100	100	20	
At 9.10 am, the patient was brought to emergency operating theatre						

Morning Shift Emergency Team

Sectio cesarea procedure was delivered with general anesthesia. The surgery went uneventful about an hour, and bleeding volume was about 250ml totally. Postoperative management was in an intermediate observational room.

Patient's condition at Intermediate Observational Recovery Room

The patient was admitted to an intermediate observational recovery room for about 3 hours. Her condition deteriorated due to atonia uteri with massive vaginal bleeding. She was resuscitated and intubated. She was stabilized and brought immediately to operating theatre for emergency re-laparotomy.

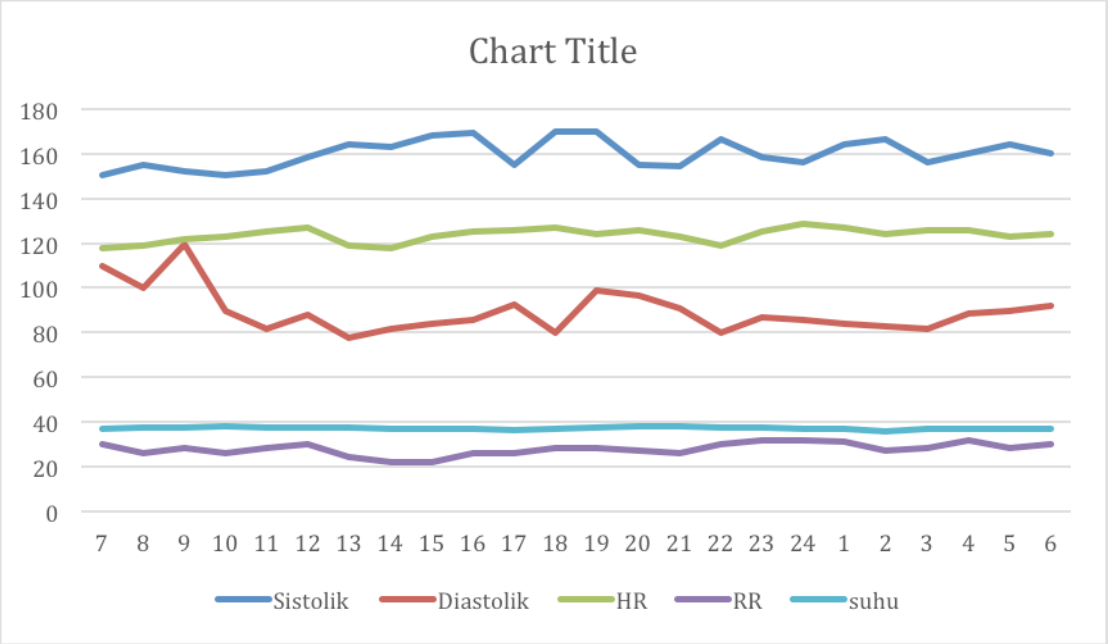
Evening Emergency Shift Team

The patient arrived at the operating theatre at 11.30 pm, then emergency re-laparotomy and hysterectomy were done under general anesthesia. The operation went for about 2 hours and then she was transferred to the intensive care unit postoperatively.

On July 17th, 2019 at 10.36 pm					
Hb	**Ht**	**L**	**Tr**	**Amylase**	**Lipase**
5,9	16,9	15.080	85.000	734	4982
SGOT	**SGPT**	**Bil Total**	**Bil direk**	**Bil Indir**	**Albumin**
2262	1502	7.871	5.121	2.750	1.10
Ureum	**Cr**	**GDS**			
55,3	2,71	127			

Patient monitoring at ICU

Day I (July, 18th 2019)



OBJECTIVE	ASSESSMENT	PLANNING
CNS Consciousness: under the influence of drugs **CVS** BP : 132 / 68 mmHg HR : 140 x/min Temp: 36,8 C **Respiration** RR: 28 x/min CMV/RR 14/TV 400/PEEP 5/FiO2 80% SpO2: 99 % **GIT** soft non distended, bowel sound (+) **GUT** UO : 5-20-0 cc/ hour Balance : + 4640 cc/24jam	Post hemorrhagic shock + Post supravaginal hysterectomy ec atonia uteri in P3A0 premature parturition with cesarean section due to bishop score <6 on impending eclampsia + HELLP syndrome + DIC + acute kidney injury + hypoalbuminemia **Lab result** 18/7/19 Hb 5,6 Ht 16,4 L 6.050 Tr 39.000 PT 13,1 INR 1,18 APTT 36,1 Hb 10,2 Ht 30,3 L 11.570 Tr 113 PT 22,9 INR 2,0 APTT 45,7 SGOT 2040 SGPT 1651 Bil Total 10,391 Bil direct 8,354 Bil indirect 2,037 Albumin 1,92 Ur 64,8 Cr 3,1 Na 139 K 5,1 Cl 107 Ca 4,8 Mg 2,4 pH 7,226 pCO2 46,7 pO2 110,5 HCO3 19,6 BE -6,5 Sat 93,6 Blood culture 18/7/19 Result: not released yet Echohemodynamic : CO 4,8 L/mnt CI 2,82 L/mnt/m2 SV 39 ml/beat IVC max 1,9 IVC min 1.,3 IVC Distensibility 46% VTi max 16,25 VTi min 15,4 SVR 1650 Dyne Result: stable hemodynamic with fluid responsive	F: Fasting→ initiate feeding test A: Fentanyl 30 mcg/hour, Paracetamol 1gr/6 hours S: Midazolam 3mg/hour T : (-) H: Head up 30^0 U: Omeprazole 2x40 mg iv G : (-) Th/ Noradrenaline 0,1 mcg/kgBW/min Rocuronium 20 mg/jam Tranexamic acid 3x500 mg Vitamin K 3x10 mg Ceftriaxone 1x2 gr iv (1) Furosemid drip 30 mg/hour Nebulization with NaCl 0,9% every 6 hours Transfusion of 4 bags of PRC Transfusion of 4 bags of FFP Ca Gluconas 2 gram iv post-transfusion

On July, 18th 2019 at 02.37 am						
Hb	**Ht**	**L**	**Tr**	**PT**	**INR**	**APTT**
5,6	16,4	9.320	31.000	16,1	1,48	49.7

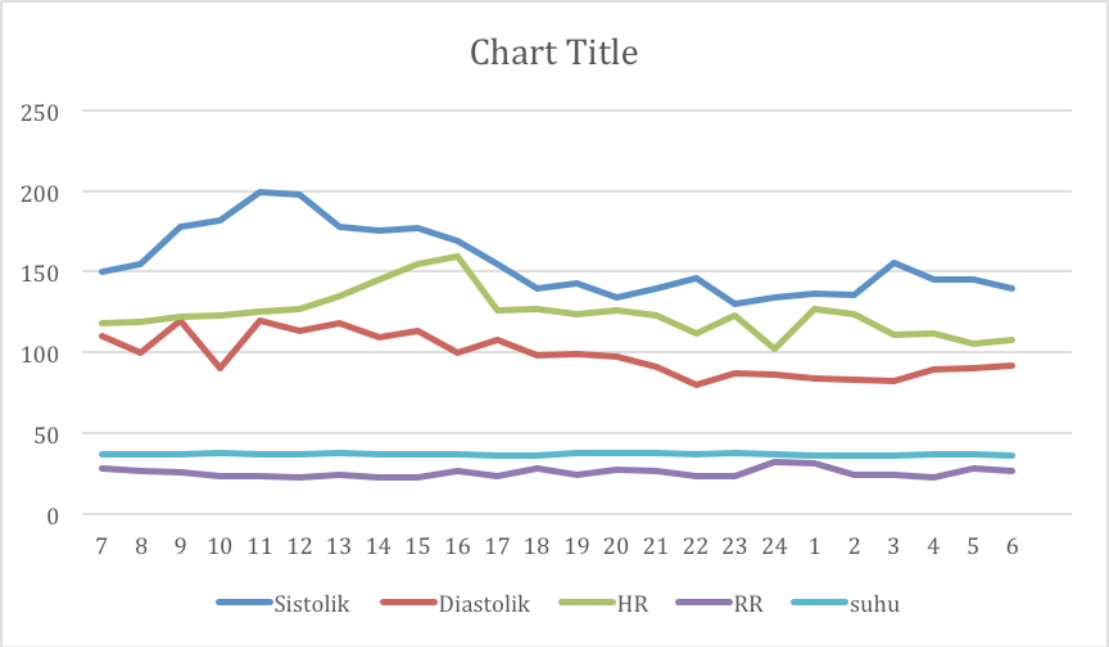
GDS	SGOT	SGPT	Bil Total	Bil Direct	Bil Indirect	Albumin
108	1716	970	6.906	5.532	1.374	1.40
Ur	**Cr**	**Na**	**K**	**Cl**	**Ca**	**Mg**
54	2,77	131	7,7	104	3,75	2,6
Fibrinogen	**D dimer**					
104,4	3,32					

On July, 18th 2019 at 10.08 am						
Hb	**Ht**	**L**	**Tr**	**PT**	**INR**	**APTT**
10,2	30,3	11.570	113.000	22,9	2,00	45.7
SGOT	**SGPT**	**Bil Total**	**Bil Direct**	**Bil Indirect**	**Albumin**	
2040	1651	10.391	8.354	2.037	1.92	
Ur	**Cr**	**Na**	**K**	**Cl**	**Ca**	**Mg**
64,8	3,10	139	5,1	107	4,80	2,4
pH	**pCO2**	**pO2**	**HCO3**	**BE**	**SpO2**	
104,4	3,32	61,3	21,7	-7,8	78,6	

On July, 18th 2019 at 12.21 pm					
pH	**pCO2**	**pO2**	**HCO3**	**BE**	**SpO2**
7,226	46,7	110,5	19,6	-6,5	93,6

On July, 18th 2019 at 10.49 pm						
Hb	**Ht**	**L**	**Tr**	**PT**	**APTT**	**INR**
5,8	16,4	6.050	39.000	13,1	1,18	36,1

Day 2 (July 19th, 2019)

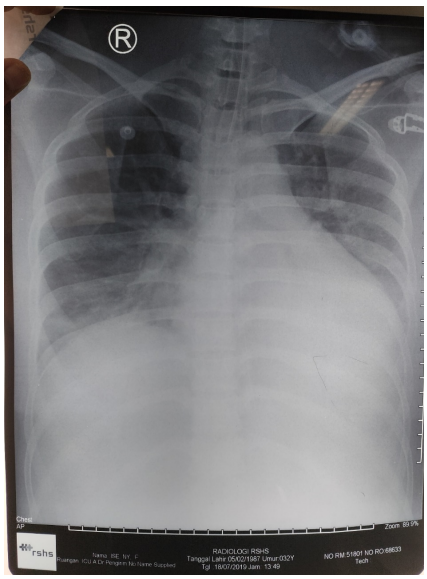


OBJECTIVE	ASSESSMENT	PLANNING
CNS Level of consciousness: E2M3VT **CVS** BP: 161/96 mmHg Hr : 115 x/min Temp: 38 C **Respiration** RR: 20 times/minutes PSIMV/RR 12/PC 16/PS 15/PEEP 5/FiO2 60% (TV 400-550) SpO2: 99 % **GIT** distention (-), bowel sounds (+) **GUT** UO: 0-0-8 cc/ hour Balance : - 2092 cc/24hour	Post hemorrhagic shock + Post supravaginal hysterectomy ec atonia uteri in P3A0 premature parturition with cesarean section due to bishop score <6 on impending eclampsia + HELLP syndrome + DIC + acute kidney injury + electrolyte imbalance **19/7/19** Hb 10,2 Ht 29,5 L 8,33 Tr 56.000 pH 7,279 pCO2 44,0 pO2 54,8 HCO3 20,1 BE -4,8 Sat 74,5 Fibrinogen 232,2 D-dimer 2,53 Laktat 2,3 pH 7,134 pCO2 54,2 pO2 140,3 HCO3 18,4 BE -9,9 Sat 97,6 Blood culture 18/7/19 No results yet	F: Test feeding → gradual liquid diet A: Fentanyl 30 mcg/hour, Paracetamol 1g/6 hour S : - T : - H : Head Up 30 U : Omeprazole 2x40 mg iv G : Th/ Tranexamic acid 3x500 mg Vitamin K 3x10 mg Ceftriaxone 1x2 gr iv (2) Furosemid drip 10 mg/hour Nebu NaCl 0,9% per 6 hour Ca gluconate 2 gram iv The first hemodialysis (UF)

July 19th, 2019 Time: 06.21						
Hb	**Ht**	**L**	**Tr**	**PT**	**INR**	**APTT**
10,2	29,5	8.330	56.000	17,8	1,47	37.5
GDS	**Fibrinogen**	**D dimer**				
77	270	3,89				
Ur	**Cr**	**Na**	**K**	**Cl**	**Ca**	**Mg**
117	5,10	135	6,8	107	3,89	2,1
pH	**pCO2**	**pO2**	**HCO3**	**BE**	**SpO2**	
7,134	54,2	140,3	18,4	-9,9	97,6	

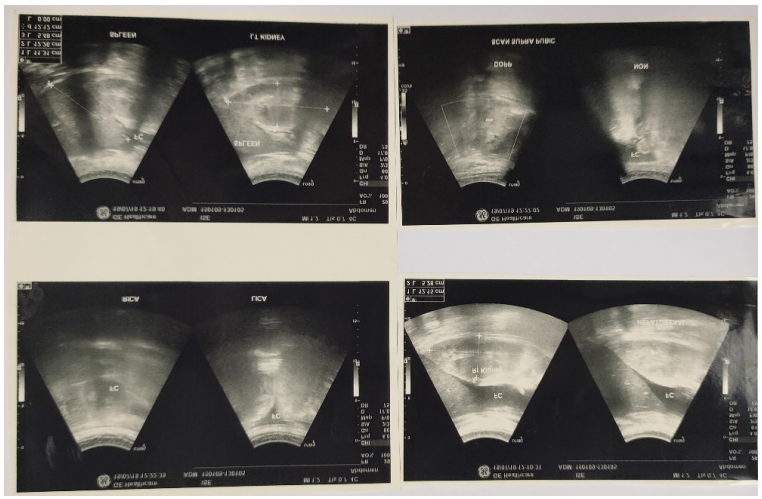
Thorax PA Rongent (July 18th, 2019)

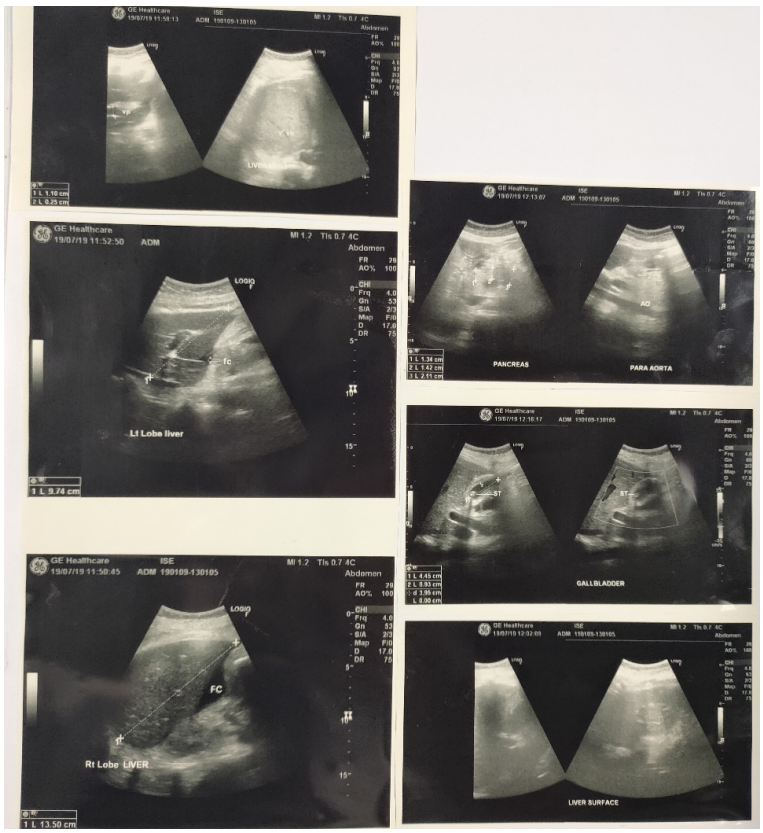
Cardiomegaly without lung congestion, no pneumonia or pulmonary edema



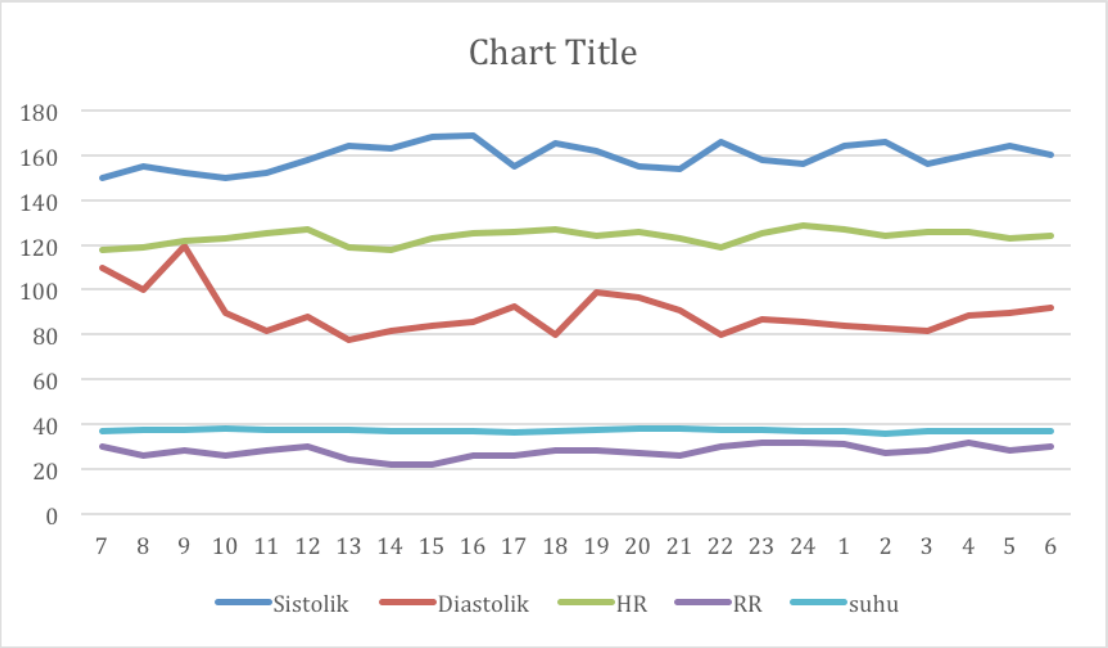
Abdomen Ultrasonography

Impression:
• Isoechoic lesion with indistinctive border, regular in the suprapubic region → suggestive blood clot
• Collection of fluid in hepatorenal, splenorenal and suprapubic areas → ascites
• Multiple cholelithiases, splenomegaly
• No apparent enlargement of the paraaortic / parailiac lymph nodes
• Ultrasonography of the liver, kidneys, and pancreas does not show any abnormality





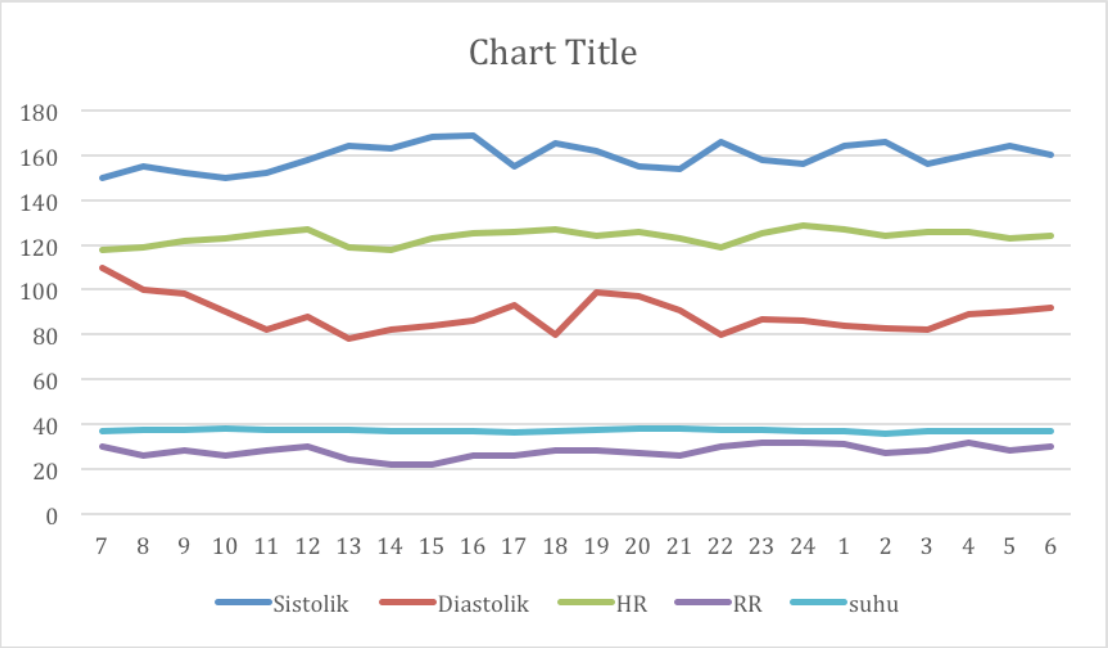
Day 3 (July 20th, 2019)



OBJECTIVE	ASSESSMENT	PLANNING
CNS E2M2Vt **CVS** BP : 157 / 91 mmHg HR : 94 x/min Temp: 37 C **Respiration** RR: 20 x/minute PSIMV/RR 12/PC 15/PEEP 6/FiO2 65% (TV 400-500) SpO2: 99 % **GIT** distension (-) bowel sound (+) **GUT** UO : 0-10-10 cc/ hour Balance : +419,8 cc/24hour	Post hemorrhagic shock + Post supravaginal hysterectomy ec atonia uteri in P3A0 premature parturition with cesarean section due to bishop score <6 on impending eclampsia + HELLP syndrome + DIC + acute kidney injury + anemia + hypoalbuminemia **20/7/19** Hb 8,1 Ht 22 L 7.910 Tr 39.000 PT 10,1 INR 0,9 APTT 28,3 Laktat 1,6 Ur 64 Cr 2,83 Na 134 K 2,83 Cl 100 Ca 4,91 Mg 1,6 pH 7,545 pCO2 25,5 pO2 248,0 HCO3 22,3 BE 0,2 Sat 99,5 Blood culture 18/7/19 No result yet	F: gradual liquid diet A: Fentanyl 30 mcg/hour, Paracetamol 1g/6hour S: - T: - H: Head-Up 30 degree U: Omeprazole 2x40 mg G : Th/ Tranexamic acid 3x500 mg Vitamin K 3x10 mg Ceftriaxone 1x2 gr iv (3) Furosemid drip 30 mg/hour KCl 35 meq/4 hour Nebu NaCl 0,9% per 6 hour

July 20th, 2019 Time: 06.21						
Hb	**Ht**	**L**	**Tr**	**PT**	**INR**	**APTT**
8,1	22	7.910	39.000	10,2	0,90	28,3
Ur	**Cr**	**Na**	**K**	**Cl**	**Ca**	**Mg**
64	2,83	134	4,1	100	4,91	1,6
pH	**pCO2**	**pO2**	**HCO3**	**BE**	**SpO2**	**Laktat**
7,545	25,5	248,0	22,3	0,2	99,5	1,6

Day 4 (July 21st, 2019)



OBJECTIVE	ASSESSMENT	PLANNING
CNS E2M3VT **CVS** BP : 145 / 84 mmHg HR : 111 x/min Temp: 37 C **Respiration** RR: 20 x/ minute PSIMV/RR 12/PC 14/PEEP 8/FiO2 60% (TV 400-500) SpO2: 99 % **GIT** distension (-) bowel sound (+) **GUT** UO : 30-10-10 cc/ hour Balance : - 2530 cc/24hour	Post hemorrhagic shock + Post supravaginal hysterectomy ec atonia uteri in P3A0 premature parturition with cesarean section due to bishop score <6 on impending eclampsia + HELLP syndrome + DIC + acute kidney injury + anemia + electrolyte imbalance + hypoalbuminemia 21/7/19 Hb 7,5 Ht 22,2 L 16.410 Tr 46.000 PT 10,6 INR 0,94 APTT 119,3 GDS 165 Alb 1,7 Lactat 1,6 Ur 131 Cr 5,67 Na 135 K 6,3 Cl 100 Ca 4,29 pH 7,349 pCO2 48,9 pO2 159,8 HCO3 27,2 BE 2,4 Sat 98,4 Blood culture 18/7/19 No result yet Echohemodynamics: CO 6.8 L / min CI 4.16 L / min / m2 SV 52 ml / beat SVI 32 ml / Beat / m2 SVR 871 dyne.sec.atm IVC max 1.66 MIVC Min 1.18 Distesibility index 34% Structural: Normal echo chamber, LVEF eyeballing> 50% Normokinetic Impression: fluid responsive, normal cardiac function	F : :Liquid diet A : Fentanyl 30 mcg/hour, Paracetamol 1g/6hour S : - T : - H : Head Up 30 U : Omeprazole 2x40 mg G : Th/ Tranexamic acid 3x500 mg Vitamin K 3x10 mg Ceftriaxone 1x2 gr iv (4) Furosemid drip 30 mg/hour Nebu NaCl 0,9% per 6 hour Ca gluconate 2 gram Platelet (thrombocyte) transfusion : 7 bags Second haemodialysis Re-evaluate: PT, INR, aPTT

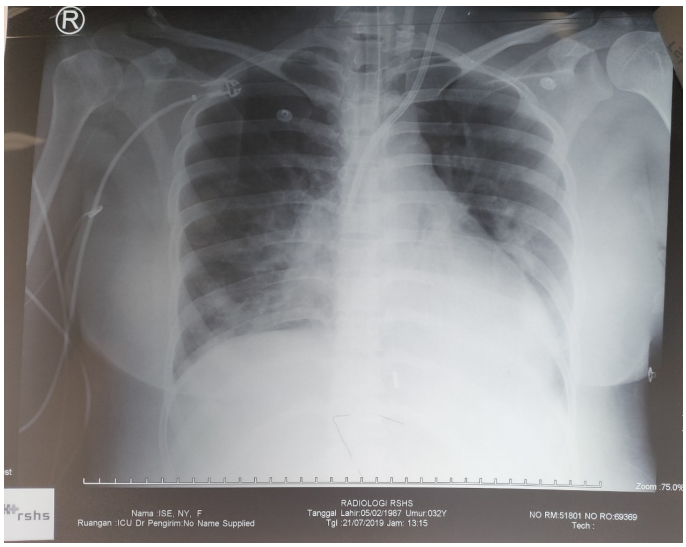
July 21st, 2019 Time: 05.15 am						
Hb	**Ht**	**L**	**Tr**	**PT**	**INR**	**APTT**
7,5	22,2	16.410	46.000	10,0	0,94	119,3
Ur	**Cr**	**Na**	**K**	**Cl**	**Ca**	**Mg**
131	5,67	135	6,3	100	4,29	2,0
pH	**pCO2**	**pO2**	**HCO3**	**BE**	**SpO2**	**Laktat**

7,349	48,9	159,8	27,2	2,3	98,4	1,6

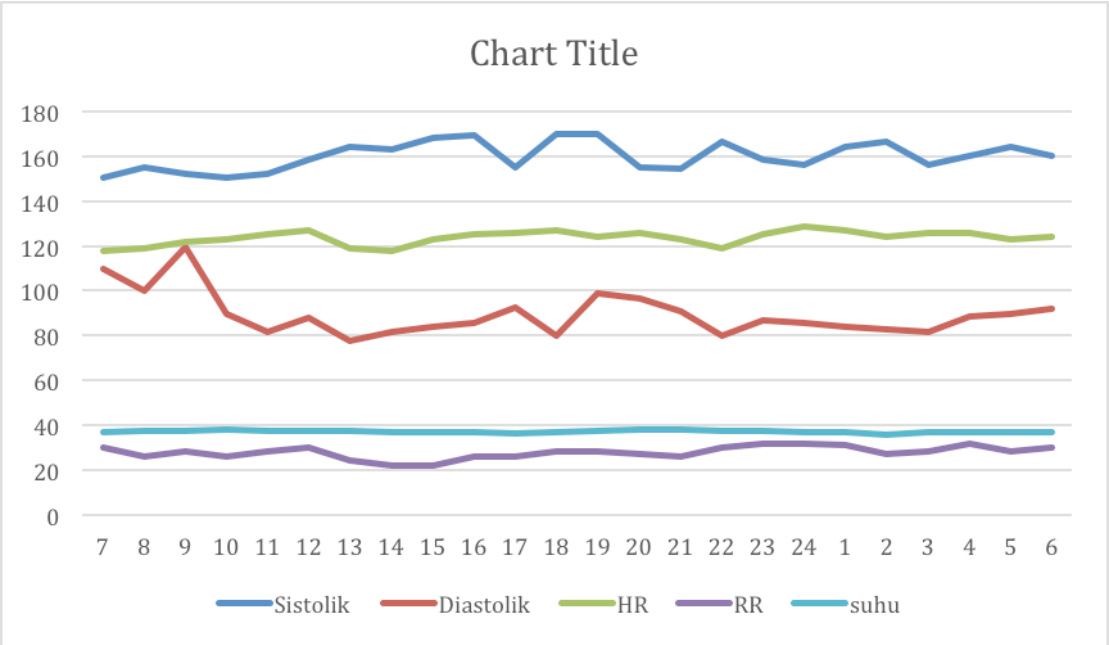
July 21st, 2019 Time: 01. 34 pm						
Hb	**Ht**	**L**	**Tr**	**PT**	**INR**	**APTT**
10,6	21,1	18.430	40.000	9,8	0,87	23,9
Ur	**Cr**	**Na**	**K**	**Cl**	**Ca**	**Mg**
113,9	4,55	145	5,3	99	4,54	2,2
Albumin						
2,2						

Thorax PA X-ray (July 21st, 2019)

Bronchopneumonia, there is no sign of cardiomegaly



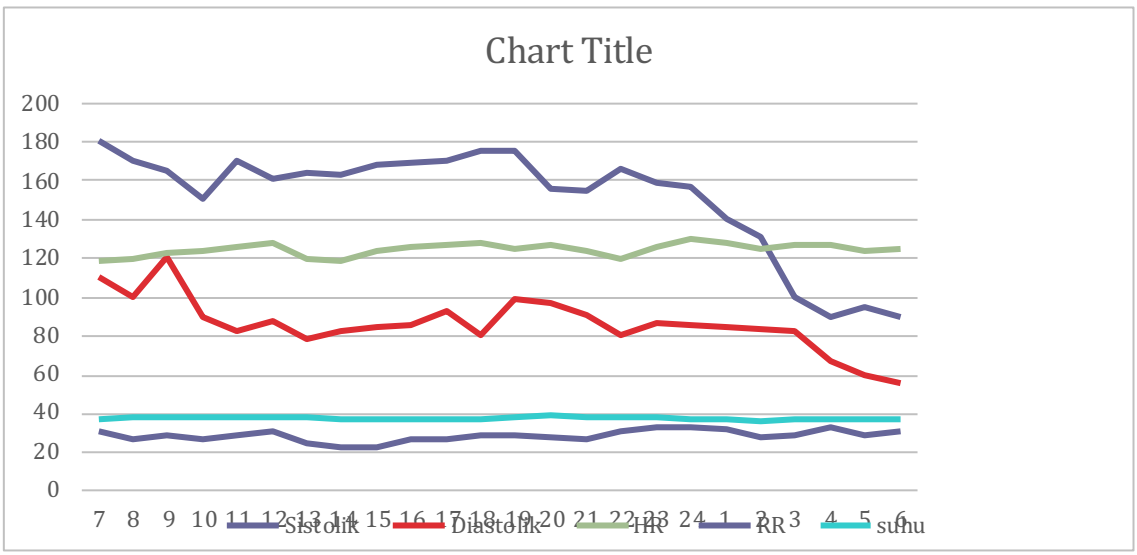
Day 5 (July 22nd, 2019)



OBJECTIVE	ASSESSMENT	PLANNING
CNS E2M3VT **CVS** BP : 161 / 96 mmHg HR : 115 x/menit Temp: 38 C **Respiration** RR : 24 x/ minutes Spontan/PS 15/PEEP 8/FiO2 60% (TV 400-500) SpO2: 99 % **GIT** distension (-) bowel sound (+) **GUT** UO : 0-14-0 cc/ hour Balance : - 24 cc/24hour	Post hemorrhagic shock + Post supravaginal hysterectomy ec atonia uteri in P3A0 premature parturition with cesarean section due to bishop score <6 on impending eclampsia + HELLP syndrome + DIC + acute kidney injury + anemia + electrolyte imbalance + hypoalbuminemia 22/7/19 Hb 8,8, Ht 26,3 L 14.600 Tr 77.000 Ur 143,3 Cr 5,97 Na 134 K 5,8 Cl 98 Ca 4,05 Mg 2,3 pH 7,381 pCO2 48,9 pO2 172,6 HCO3 29,1 BE 4,3 Sat 99,4 Blood culture 18/7/19 No result yet	F: Liquid diet A: Fentanyl 30 mcg/hour, Paracetamol 1g/6hour S: - T: - H: Head-Up 30 degree U: Omeprazole 2x40 mg G : Th/ Tranexamic Acid 3x500 mg Vitamin K 3x10 mg Ceftriaxone 1x2 gr iv (5) Furosemid drip 30 mg/hour Nebu NaCl 0,9% per 6 hour

July 22nd, 2019 Time. 05.41 am						
Hb	**Ht**	**L**	**Tr**	**Ur**	**Cr**	
8,8	26,3	14.660	77.000	143,3	5,97	
Na	**K**	**Cl**	**Ca**	**Mg**		
134	5,8	98	4,05	2,3		
pH	**pCO2**	**pO2**	**HCO3**	**BE**	**SpO2**	
7,381	48,9	172,6	29,1	4,3	99,4	
Ur	**Cr**	**Na**	**K**	**Cl**	**Ca**	**Mg**
168	6,52	136	5,1	95	4;21	2,2

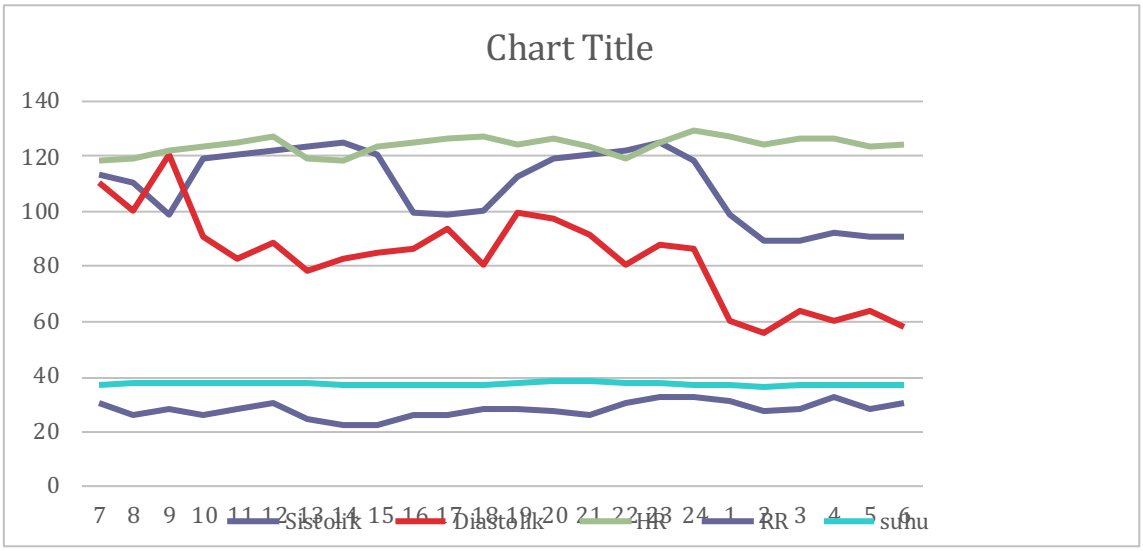
Day 6 (July 23rd, 2019)



OBJECTIVE	ASSESSMENT	PLANNING
CNS $E_1M_2V_t$ **CVS** TD: 180/103 mmHg N:110 x/minute SpO_2: 96% **Respiration** RR : 12 x/minute Spontan/PS 15/PEEP 8/FiO2 60% (TV 400-500) SpO2: 99 % **GIT** distension (-) bowel sound (+) **GUT** UO : 0-14-0 cc/ hour Balance : - 24 cc/24hour	Post hemorrhagic shock + Post supravaginal hysterectomy ec atonia uteri in P3A0 premature parturition with cesarean section due to bishop score <6 on impending eclampsia + HELLP syndrome + DIC + acute kidney injury + anemia + electrolyte imbalance + hypoalbuminemia 22/7/19 Hb 9,2 Ht 26,3 L 23.000 Tr 48.500 Ur 209,1 Cr 7,75 Na 134 K 5,3 Cl 98 Ca 4,03 Mg 2,2 SGOT 193 SGPT 525 Alb 1.80 pH 7.403 pCO2 33,8 pO2 158,9 HCO3 21,3 BE -2,2 Sat 02 98,4 Kultur darah 18/7/19 Tidak terdapat pertumbungan mikroorganisme Culture 7/23/19 1: Escherichia Coli 2: Klebsiella pneumonia Sensitive: Amikacin, Cefepime, Tigecycline, Meropenem	F: Liquid diet A: Fentanyl 30 mcg/hour, Paracetamol 1g/6hour S: Midazolam 5mg/hour T: - H: Head-Up 30 degree U: Omeprazole 2x40 mg G : Th/ Tranexamic Acid 3x500 mg Vitamin K 3x10 mg Ceftriaxone 1x2 gr iv (5) Nebu NaCl 0,9% per 6 hour Dextrose 40% extra 10 units of insulin in D40% 2 extra cycles Ca gluconate in 2 grams of NaCl 0.9% 100 cc drip in 1 hour Midazolam 15mg 5mg / hour NaCL dust 0.9% Perdipin 1mcg / kg / min Furosemide 20mg/hour Hemodialysis

July 23rd, 2019 Time: 05.41						
Hb	**Ht**	**L**	**Tr**	**Ur**	**Cr**	
9,2	26,3	23.000	48.500	209,1	7,75	
Na	**K**	**Cl**	**Ca**	**Mg**		
134	5,3	98	4,03	2,2		
PT	aPTT	INR	SGOT	SGPT	Alb 1,80	
10,6	23,9	0,94	193	525		
pH	**pCO2**	**pO2**	**HCO3**	**BE**	**SpO2**	
7, 403	33,8	158,9	21,3	-2,2	98,4	

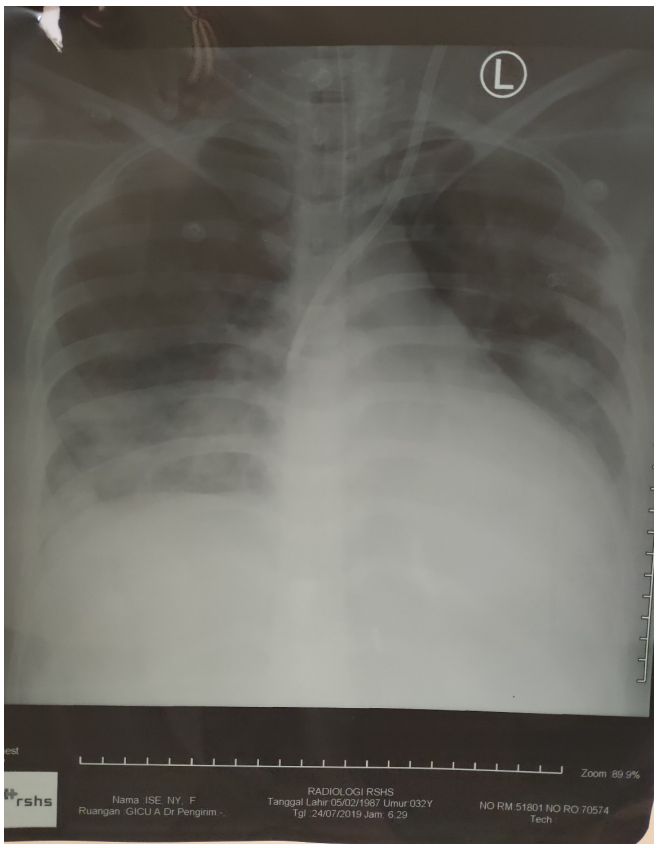
Day 7 (July 24th, 2019)



OBJECTIVE	ASSESSMENT	PLANNING
CNS $E_1M_2V_t$ **CVS** BP: 128/78 mmHg HR:114 x/minute SpO_2: 96% **Respiration** RR : 25 x/minute Spontan/PS 15/PEEP 8/FiO2 60% (TV 400-500) SpO2: 99 % **GIT** distention (-) bowel sound (+) **GUT** UO : 15-34-44 cc/ hours Balance : +594,8 cc/24 hours	Post hemorrhagic shock + Post supravaginal hysterectomy ec atonia uteri in P3A0 premature parturition with cesarean section due to bishop score <6 on impending eclampsia + HELLP syndrome + DIC + acute kidney injury + anemia + electrolyte imbalance + hypoalbuminemia 22/7/19 Hb 10,8 Ht 30,7 L 22.930 Tr 88.000 Ur 116,0 Cr 5,02 Na 137 K 4,3 Cl 98 Ca 4,65 Mg 2,3 Alb 1,8 pH 7,260 pCO2 62,2 pO2 76,1 HCO3 28,2 BE 1,1 Sat 90,6 Total bilirubin 8,789 Bilirubin 7,238 Indirect Bilirubin1.551	F : liquid diet A : Morfin 10mcg/kgbb/hour S : Midazolam 5mg/hour T : - H : Head Up 30 U : Omeprazole 2x40 mg G : Th/ Tranexamic acid 3x500 mg Vitamin K 3x10 mg Ceftriaxone 1x2 gr iv (5) Drip furosemid 30 mg/hours NaCl 0,9% nebulation/ 6 hours Levofloxacin 3x200mg

July 24th, 2019 at 11.13 am

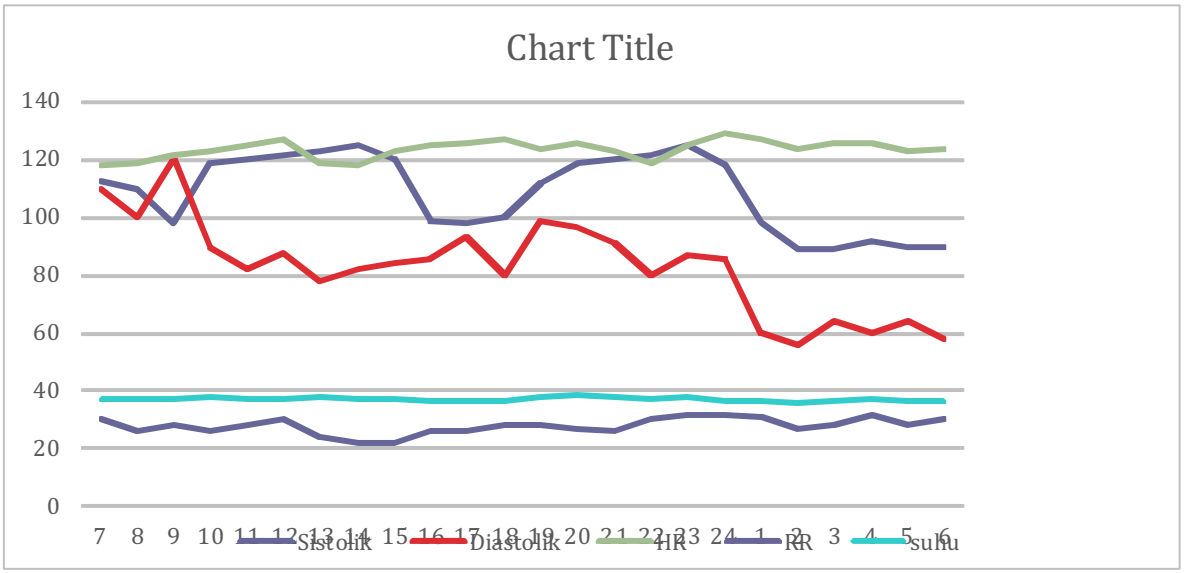
Hb	**Ht**	**L**	**Tr**	**Ur**	**Cr**	
10,8	30,7	22.930	89.000	116.0	5,02	
Na	**K**	**Cl**	**Ca**	**Mg**	**Alb**	
137	4,3	98	4,65	1,8	1,65	
pH	**pCO2**	**pO2**	**HCO3**	**BE**	**SpO2**	
7,260	62,2	76,1	28,2	1,1	90,6	



Description :

- Bilateral pneumonia
- cardiomegaly dd/ position

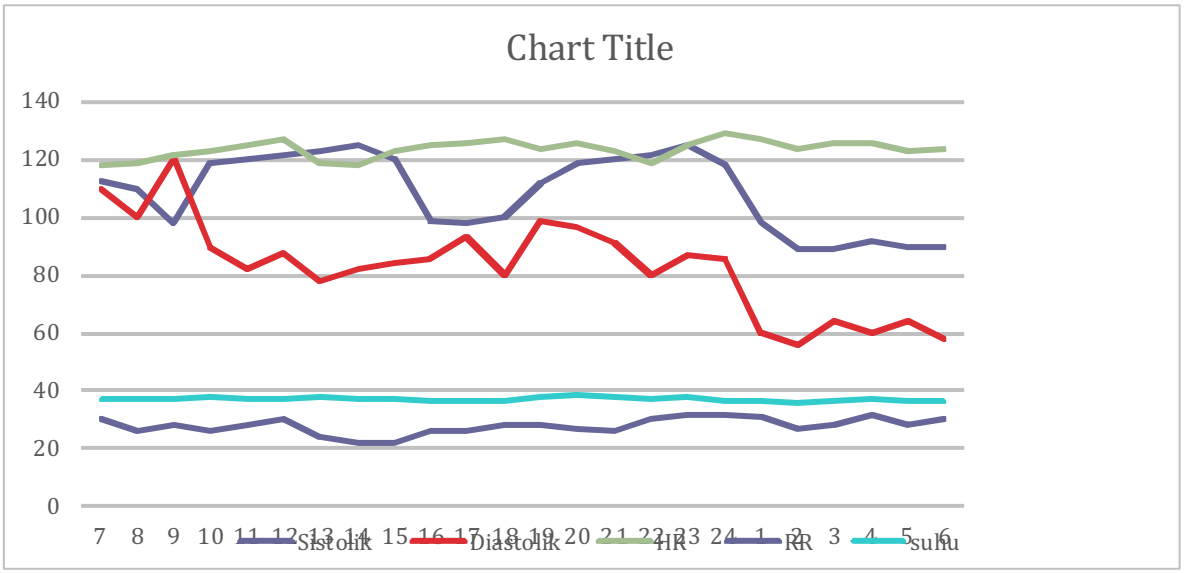
Day 8 (July 25th, 2019)



OBJECTIVE	ASSESSMENT	PLANNING
CNS $E_1M_2V_t$ **CVS** BP: 109/60 mmHg HR:98 x/minute SpO_2: 94% **Respiration** RR : 16 x/minute Spontan/PS 15/PEEP 8/FiO2 60% (TV 400-500) SpO2: 99 % **GIT** distention (-) bowel sound (+) **GUT** UO : 0-14-0 cc/ hour Balance : - 24 cc/24 hours	Post hemorrhagic shock + Post supravaginal hysterectomy ec atonia uteri in P3A0 premature parturition with cesarean section due to bishop score <6 on impending eclampsia + HELLP syndrome + DIC + acute kidney injury + anemia + electrolyte imbalance + hypoalbuminemia 25/7/2019: Hb/ht/L/T: 8,4/25,0/24.230/67.000 Ureum:215,1/Creatinin:7,37/albumin:1,77 Na/K/Cl/Ca/Mg:136/5,0/97/4,33/2,2 pH 7,213 pCO2 56,6 pO2 116,4 HCO3 23,0 BE -4,5 Sat 96,2	F : Liquid diet A : Morfin 10mcg/kg/hour S : Midazolam 5mg/hour T : - H : Head Up 30 U : Omeprazole 2x40 mg G : Th/ Tranexamic acid 3x500 mg Vitamin K 3x10 mg Ceftriaxone 1x2 gr iv (5) Furosemid drip 30 mg/hour NaCl 0,9% nebulation/ 6 hours Cefepime 3x1gr Levofloxcain 3x200mg Norepinephrine 0,5mcg/kg/minute Hemodialysis

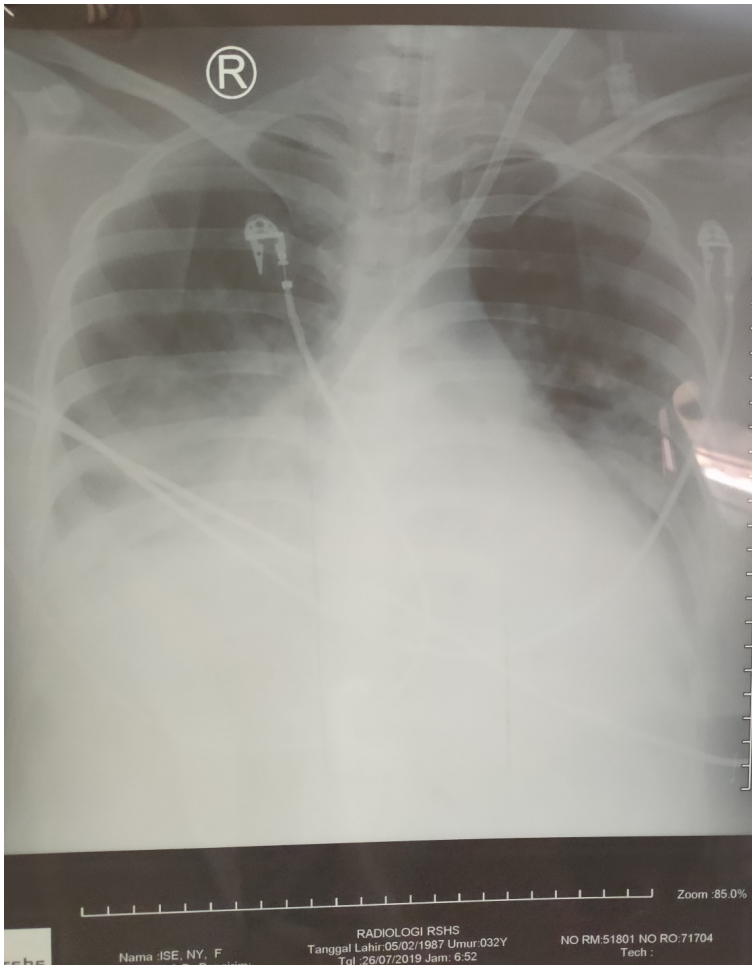
July 25th, 2019 05.41						
Hb	**Ht**	**L**	**Tr**	**Ur**	**Cr**	
8,4	25,0	24,230	67.000	215,1	7,37	
Na	**K**	**Cl**	**Ca**	**Mg**	**Alb**	
136	5,0	97	4,33	2,2	1,77	
pH	**pCO2**	**pO2**	**HCO3**	**BE**	**SpO2**	
7,213	56,6	116,4	23,0	-4,5	96,2	

Day 9 (July 26th, 2019)



OBJECTIVE	ASSESSMENT	PLANNING
CNS $E_1M_1V_t$ **CVS** TD: 97/51 mmHg N:134 x/minute SpO_2: 100% **Respiration** RR : 15 x/minute Spontan/PS 15/PEEP 8/FiO2 60% (TV 400-500) SpO2: 99 % **GIT** distention (-) bowel sound (+) **GUT** UO : 0-14-0 cc/ hour Balance : - 24 cc/24 hours	Post hemorrhagic shock + Post supravaginal hysterectomy ec atonia uteri in P3A0 premature parturition with cesarean section due to bishop score <6 on impending eclampsia + HELLP syndrome + DIC + acute kidney injury + anemia + electrolyte imbalance + hypoalbuminemia 26/7/2019: Hb/ht/L/T: 8,5/26,0/35.700/70.000 PT:10,40 APTT:32,60 INR:0,92 Ureum:77,0 creatinin:3,57 Na/K/Cl/Ca/Mg:145/4,3/104/5,37/1,7	F: liquid diet A: paracetamol 4x1gr S: - T: - H: Head-Up 30 degree U: Omeprazole 2x40 mg G : Th/ Tranexamic acid 3x500 mg Vitamin K 3x10 mg Ceftriaxone 1x2 gr iv (5) Furosemid drip 30 mg/hour NaCl 0,9% nebulation /6 hours Cefepime 3x1gr Levofloxcain 3x200mg Norepinephrine 0,5mcg/kg/minute Dobutamin 5mcg/kg/minute Vasopressin 0,02 unit/hour

July 26th, 2019 05.41						
Hb	**Ht**	**L**	**Tr**	**Ur**	**Cr**	
8,5	26,0	35.700	70.00	77.0	3,75	
Na	**K**	**Cl**	**Ca**	**Mg**		
145	4,3	104	5,3	1,7		
PT	aPTT	INR				
10,4	32,6	0,92				
pH	**pCO2**	**pO2**	**HCO3**	**BE**	**SpO2**	**lactat**
7,196	56,8	100,8	22,2	5,4	94,7	5.0

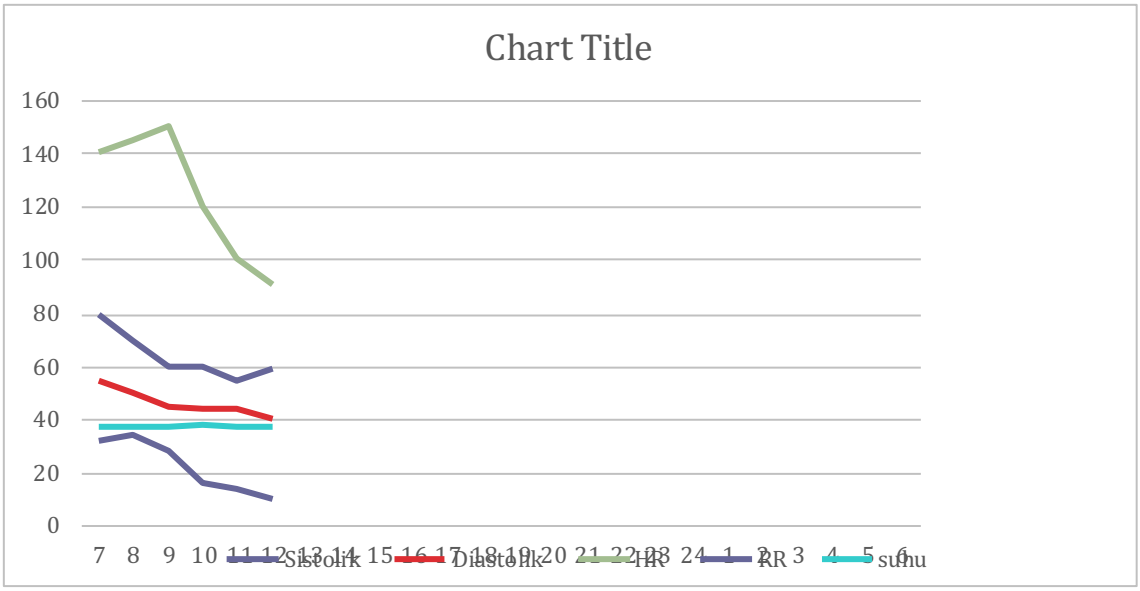


26/7/19

description :

- bilateral pleuropneumonia

Day 10 (July 27th, 2019)



OBJECTIVE	ASSESSMENT	PLANNING
CNS $E_1M_1V_t$ **CVS** BP: 77/53 mmHg HR:130 x/minute SpO_2: 90% **Respiration** RR : 21 x/minute Spontan/PS 15/PEEP 8/FiO2 60% (TV 400-500) SpO2: 99 % **GIT** distention (-) bowel sound (+) **GUT** UO : 0-14-0 cc/ hour Balance : - 24 cc/24 hours	Post hemorrhagic shock + Post supravaginal hysterectomy ec atonia uteri in P3A0 premature parturition with cesarean section due to bishop score <6 on impending eclampsia + HELLP syndrome + DIC + acute kidney injury + anemia + electrolyte imbalance + hypoalbuminemia	F: Nefrisol+Boostpoimun A: paracetamol 4x1gr S: - T: - H: Head-Up 30 degree U: Omeprazole 2x40 mg G : Th/ Tranexamic acid 3x500 mg Vitamin K 3x10 mg Ceftriaxone 1x2 gr iv (5) Furosemide drip 30 mg/hour NaCl 0,9% Nebulation/ 6 hour Cefepime 3x1gr Levofloxcain 3x200mg Norepinephrine 0,5mcg/kg/minute Dobutamin 5mcg/kg/minute
12.34 Asystole		the patient was declared dead

DISCUSSION

Patients are G3P2A0 with 29-30 weeks gestation, during pregnancy known to have a history of uncontrolled hypertension. On physical examination, found blood pressure of 160/100 mmHg and proteinuria 3+. The results of investigations found a decrease in platelet count (Tr 85,000), increased serum transaminase levels (SGOT 2262, SGPT 1502), and increased serum creatinine levels (Cr 2.71). The diagnosis of preeclampsia consists of several criteria, which can be seen in Table 1.

Table 1 Preeclampsia Criteria (Robert, et al., 2013)

Blood Pressure	• Increased systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg at two measurements with a range of at least 4 hours after 20 weeks' gestation in pregnant women not previously known to have hypertension • Increased systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 110 mmHg found in short (minute) intervals that immediately require the administration of antihypertensive drugs
Dan	
Proteinuria	• ≥ 300 mg on urine sample measurements for 24 hours • or • Protein / creatinine ratio ≥ 0.3 • Protein content in dip paper 1+
Or if no proteinuria is found	
Thrombocytopenia	• Platelet count <100,000 / µL
Renal insufficiency	• serum creatinine levels > 1.1 mg / dL or doubling of serum creatinine levels without any other cause of impaired kidney function
Liver disfunction	• Increased serum transaminase levels more than doubled to normal
Pulmonary edema	

Impaired brain function or vision with new-onset	

The patient was later diagnosed with impending eclampsia because, in addition to the signs and symptoms of preeclampsia, the patient complained of severe headaches accompanied by blurred vision and heartburn. In impending eclampsia, there are several clinical symptoms found, such as persistent occipital or frontal headache, blurred vision, photophobia, pain in the epigastric region or the right upper quadrant or both, and changes in consciousness without accompanying seizures. If impending eclampsia is not treated quickly, it can cause seizures or eclampsia.(Robert, et al., 2013)

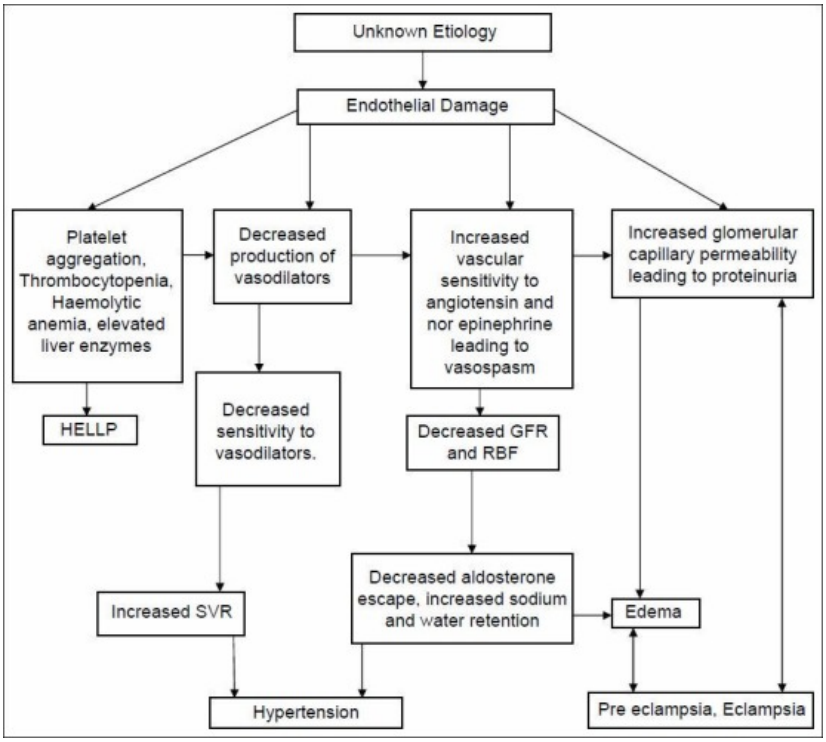
The etiology of preeclampsia is unknown, but there are several risk factors for preeclampsia including primipara, history of preeclampsia in a previous pregnancy, family history of hypertension, multiple or multiple pregnancies, history of thrombophilia, maternal age over 40 years, in vitro fertilization, diabetes, obesity, systemic lupus erythematosus, and a history of chronic hypertension.7 The risk factors for preeclampsia present in these patients are obesity (body mass index 30.3). Obesity increases the risk of preeclampsia by 2-3 times. Some pathophysiology linking obesity with preeclampsia include insulin resistance, inflammatory reaction due to the release of proinflammatory mediators from adipose tissue (CRP, Interleukin-6, TNF-α), reactions due to oxidative stress, adipokine imbalance (leptin and adiponectin), and imbalance angiogenic factors (placental growth factor, vascular endothelial growth factor). (Jeyabalan, 2014)

The pathophysiology underlying preeclampsia is abnormal placental development and an imbalance between angiogenic factors. The pathophysiology of preeclampsia begins with the disturbance of trophoblast invasion of the spiral arteries between 8 and 16 weeks' gestation triggered by immunological disorders. Abnormal invasion results in failure of the process of remodeling of the arteries that function to nourish the placenta, resulting in uteroplacental blood flow fail to meet needs, then the placenta becomes ischemic which triggers the release of proinflammatory mediators. (Lambert, 2014)

Placental growth factor (PlGF) and vascular endothelial growth factor (VEGF) are potent angiogenic factors that function to strengthen the vasodilation effects of prostaglandins (PG) and nitrous oxide (NO) and enhance endothelial function. In preeclampsia occurs the formation of anti-angiogenic mediators such as tyrosine-kinase (sFlt-1), which interferes with vasodilation and results in endothelial dysfunction. An imbalance between pro-angiogenic and anti-angiogenic factors results in extensive endothelial dysfunction, microangiopathy, and vascular vasospasm. This results in impaired perfusion in various organs such as the liver and kidneys.(Lambert, 2014)

The released proinflammatory mediator also triggers the release of pro-coagulation factors so that activation of the coagulation system can then result in disseminated intravascular coagulation. The pathogenesis of disseminated intravascular coagulation is a complex mechanism by which intravascular fibrin deposition occurs and the use of coagulation and platelet factors. This mechanism then causes the formation of thrombus in the microvascular which inhibits perfusion to the tissue resulting in organ failure, in addition to the consumption of many coagulation factors resulting in a deficiency of the coagulation and platelet factors leading in bleeding. (Sahin, 2014)

Figure1 Pathophysiology of preeclampsia



Cited from: Parthasarathy (Parthasarathy, 2013)

The main goal of the management of preeclampsia is to prevent seizures and reduce maternal blood pressure below 160/110 mmHg.(Kelsey, 2015) Management of preeclampsia, eclampsia, and HELLP syndrome consists of:

1. Monitoring the condition of the mother and fetus closely.
2. Giving corticosteroid therapy at 24-34 weeks' gestation to help the fetal lung maturation. The fetus can be born if corticosteroid therapy has been given for 48 hours.
3. Labor is the only definitive therapy in patients with preeclampsia, eclampsia, and HELLP syndrome. At a gestational age of fewer than 24 weeks, pregnancy termination is recommended. In patients with HELLP syndrome and eclampsia who have a gestational age <33-34 weeks, delivery by cesarean section is the first choice.
4. Provision of magnesium sulfate therapy as seizure prophylaxis. The initial dose of magnesium sulfate is given 6 grams intravenously for 20 minutes, followed by a maintenance dose of 2 grams/hour intravenously up to 24 hours postpartum. In the event of a seizure, a bolus of magnesium sulfate can be given 2 grams intravenously for 3-5 minutes. In administering magnesium sulfate periodically, it is necessary to monitor magnesium toxicity by examining serum magnesium levels with a target therapeutic value of magnesium of 5-8 mg / dL.
5. The provision of antihypertensive drugs is recommended if blood pressure ≥ 160/110 mmHg. The purpose of antihypertensive medication is to prevent an increase in intracranial pressure resulting in brain edema and intracranial hemorrhage. Antihypertensive drugs that can be given include hydralazine 5-10 mg intravenously for 2 minutes or labetalol 20-80 mg for 2 minutes or nifedipine 10-20 mg orally with a target blood pressure range of 140-150 / 90-100 mmHg. Other alternative antihypertensive medications include labetalol or nicardipine drip.
6. Platelet transfusion can be given if platelet count <50,000 / µL in patients undergoing cesarean section or platelets ≤ 20,000-50,000 / µL in vaginal delivery or platelets <20,000 / µL accompanied by active bleeding.(Lam & Dierking, 2017; Lambert, et al., 2017; Parthasarathy, 2013)

Early detection and management of preeclampsia, eclampsia, and HELLP syndrome are key ingredients in helping to prevent severe complications. In preeclampsia, complications can arise both short and long term for both mother and baby. Maternal complications include pulmonary edema, myocardial infarction, stroke, acute respiratory distress syndrome, coagulopathy, bleeding, disseminated intravascular coagulation, and injury to the retina. This is related to organ dysfunction caused by the pathophysiological process of preeclampsia. (Robert, et al., 2013)

This patient experienced complications of postpartum hemorrhage due to uterine atony, resulting in hemorrhagic shock (Hb 5,6). The patient is then intubated, fluid resuscitation is performed, then a hysterectomy re-laparotomy is performed. The patient was transferred to the intensive care unit after the operation was completed. In patients with preeclampsia, the incidence of postpartum hemorrhage increases 1.53-fold. The WHO definition of postpartum hemorrhage is a blood loss of ≥ 500 ml within 24 hours. The main causes of postpartum hemorrhage include uterine atony, residual placenta, and coagulopathy.(Altenstadt, 2013)

Predisposing factors for postpartum hemorrhage in these patients are preeclampsia, coagulopathy (INR 1.48, Fibrinogen 104.4, d-dimer 3.22), and thrombocytopenia (Tr 31,000). The patient has a score of The International Society of Thrombosis and Hemostasis (ISTH) with a total of 5 points, which means the patient has disseminated intravascular coagulation. Patients were subsequently given a transfusion of 4 pumpkin PRC, three pints FFP, and seven pints of Thrombocyte concentrate.

The main goal of the management of disseminated intravascular coagulation is to improve the underlying obstetric causes. Besides that, supportive therapy is given to correct coagulation abnormalities. Platelet transfusion can be given if the platelet count is less than 50,000, accompanied by massive bleeding. If there is an extension of the PT, aPTT, and INR values, then a fresh frozen plasma (FFP) of 10-20 ml/kg BW can be given. Non-activated prothrombin complex concentrate (PCC) can be given 25-30 U / kgBB to substitute FFP administration in patients who have experienced excess fluid. If there is only a blood fibrinogen deficiency <1 gram / L, cryoprecipitate transfusion can be given. The administration of a 4 gram cryoprecipitate transfusion can increase serum fibrinogen levels to 1 gram / L. The expected laboratory results are PT, aPTT <1.5 from normal, platelets> 50,000 / µL, and fibrinogen> 1 gram / L. (Sahin, et al., 2014)

On the first day of treatment in the intensive care unit, the patient's hemodynamic status profile was still assisted with noradrenaline administration. Noradrenaline was stopped because the patient's hemodynamic condition stabilized after the administration of the PRC and FFP transfusions aimed at replacing blood loss when the patient was in hemorrhagic shock. During observation in the intensive care unit, the patient was known to have reduced urine production (5-20-0 cc/hour) accompanied by an increase in serum creatinine levels (Cr 3.1). The patient is then given an echo-hemodynamic examination to ensure adequate fluid. Patients are given diuretic therapy (furosemide and hemodialysis are performed to support kidney function because the patient has an acute kidney injury. Acute kidney injury in these patients can be caused by preeclampsia, which is also aggravated by the condition of hemorrhagic shock resulting in decreased perfusion of renal blood flow.

Acute kidney injury occurs in 1-5% of patients with preeclampsia. Preeclampsia results in a decrease in renal blood flow, a reduction in glomerular filtration rate of 30-40%, and renal vasoconstriction, causing kidney damage. Acute kidney injury aggravates conditions arising from complications of preeclampsia for example in placental abruption, disseminated intravascular coagulation, sepsis, postpartum hemorrhage, and intrauterine fetal death..(Prakash & Ganiger, 2017)

Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE) criteria were introduced in 2014 to help determine the requirements and severity of acute kidney injury. RIFLE criteria can be seen in table 2.

Table 2 RIFLE Criteria (Lopes & Jorge, 2013)

Class	Glomerular Filtration Rate (GFR)	Urine Production
Risk	Increased Screat x 1.5 or GFR decrease > 25%	UO < 0.5 ml/jg/h x 6 h
Injury	Increased SCreat x 2 or GFR decrease > 50%	UO < 0.5 ml/kg/h x 12 h
Failure	Increased SCreat x 3 GFR decrease 75% or Screat ≥ 4 mg/dL Acute rise ≥0.5 mg/dL	UO < 0.3 ml/kgH x 24 or anuria x 12 h
Loss of kidney function	Persistent ARF = complete loss of kidney function > 4 weeks	

End-stage kidney disease	End stage kidney disease (>3 months)	

Management of acute kidney injury includes the provision of supportive therapy, dialysis, and treatment of underlying disease. Renal supportive therapy aims to maintain kidney function from further damage, such as avoiding the use of nephrotoxic drugs, overcoming source of infection, maintaining adequate fluid through intravenous infusion, and maintaining sufficient perfusion of renal blood flow. These general steps are also followed by administration of pharmacological therapy to overcome complications due to acute kidney injury such as hypertension, hyperkalemia, metabolic acidosis, and anemia.(Prakash & Ganiger, 2017)

The indications for hemodialysis in acute kidney injury conditions include uremic symptoms (encephalopathy, pericarditis, or neuropathy), fluid overload, hyperkalemia, and metabolic acidosis that have no response to treatment. Hemodialysis is recommended if the glomerular filtration rate drops below 20 ml/min / 1.73 m2.(Prakash & Ganiger, 2017)

CONCLUSION

Preeclampsia, eclampsia, and HELLP syndrome are life-threatening conditions for both mother and fetus during pregnancy that require treatment in Intensive Care Unit. Determining the basis for proper diagnosis and initial management and prevention of complications in preeclampsia, eclampsia, and HELLP syndrome can reduce the incidence of morbidity and mortality.

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Depression: A Major Psychosocial-Lifestyle Sequela of Cardiac Disease Diagnosis

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Abstract

Even the suspicion of cardiac disease diagnosis tends to have significant psychological, physical, and social repercussions for patients. The present study explored the psychosocial and physical lifestyle changes in stable, ambulant patients with suspected or newly diagnosed cardiac disease. This cross-sectional study of cardiac clinic attendees at a public health institution was conducted between July and August 2015. Face-to-face interviews were conducted with eligible patients (aged at least 18 years, not confused, and able to undergo a 20-minute interview) following patient consent. Collected data were analysed using descriptive and analytic methods (chi-squared test and multiple linear regression) using a 5% error and 95% confidence interval. The prevalence of depression increased from 1.7% pre-diagnosis to 36.6% following suspected or confirmed diagnosis. Among demographic variables, only gender was associated with depression, with females being more affected. Diabetes, stress, and eating seafood and sugary foods were associated with increased depression, while exercising at least three times per week was associated with diminished depression. Functional activities (social, communicative, and physical) worsened, with significant differences between pre- and post-diagnosis. Depression was relatively common in the sample, particularly among females. There is a need for increased focus on the development of interventions addressing depression, especially those encouraging physical exercise for optimum management of patients diagnosed with cardiac disease.

Keywords: Depression, Diet, Exercise, Cardiac Patients, Lifestyles

1. Introduction

Cardiovascular disease (coronary artery disease and cerebrovascular disease) is the leading cause of death worldwide (Finegold, Asaria, & Francis, 2012; Mendis, Puska, & Norrving, 2011) owing to an increase in risk factors such as obesity, smoking, sedentary lifestyle, and psychosocial problems (Ministry of Health, Government of Trinidad and Tobago, 2004; World Health Organization (WHO), 2012). Multiple studies have reported the negative social (Havranek et al., 2015), psychosocial (Compare et al., 2013), and emotional (Tennant & McLean, 2001) effects of a cardiovascular disease diagnosis (Bhattacharyya, Stevenson, & Walters, 2016). These, in turn, lead to a further decline in the diagnosed individual's quality of life (Denollet, Vaes, & Brutsaert, 2000; De Smedt, Clays, & De Bacquer, 2016; Hlatky et al., 1997). The accompanying depressive symptoms (Ilić

& Apostolović, 2002; Lesperance, Fraisure-Smith, & Talajic, 1996) and behavioural changes are also associated with negative personal (Habibović et al., 2018) and lifestyle impacts (Brinks, Fowler, Franklin, & Dulai, 2017; Higuera & Holland, 2019).

Major illnesses such as cardiovascular disease have been associated with psychosocial consequences that can affect health (McColl-Kennedy et al., 2017; Turner & Kelly, 2000). Furthermore, understanding the associations and predictors of psychosocial and physical changes in patients with cardiovascular disease can assist healthcare providers in delivering appropriate treatment (Dexter, 2012). In Trinidad and the Caribbean, no studies have explored the psychosocial implications of suspected or confirmed cardiac disease diagnosis. Such evidence may assist healthcare providers in designing more holistic and comprehensive treatment interventions (pharmacological and non-pharmacological). Therefore, this study's aims are:

1) To determine whether there is a change in the prevalence of clinical depression following cardiac disease diagnosis and to ascertain associations and predictors of depression in stable patients with cardiac disease.
2) To determine whether there is a change in physical and social activities following cardiac disease diagnosis and to identify the associations and predictors of such changes.

2. Methods

2.1 Participants

Four hundred participants with cardiac disease were recruited from a government-run general hospital in Trinidad and Tobago. The inclusion criteria were as follows: (1) adults above 18 years of age, (2) clinic attendees for more than one year, (3) referred for the possibility of cardiac disease or diagnosed with a history of ischaemic heart disease (IHD), ST-elevation myocardial infarction, unstable angina, and/or stable angina or IHD complications such as heart failure, and (4) able to communicate for about 20 minutes. Exclusion criteria were confusion or inability to communicate properly.

2.2 Research Design

This study employed a cross-sectional design.

2.3 Sampling Procedure

The sample comprised patients with cardiac disease at the government-run general hospital. A single institution was selected because of cost considerations and similarity in the conditions among hospitalised patients with cardiac disease. Furthermore, we felt that the sample would be representative because there are no differences in patients' age, gender, or ethnicity among the major public health institutes in the region.

The hospital is a public, 745-bed facility that serves about half the population of Trinidad (approximately 600 000 people, South-West Regional Health Authority [SWRHA], 2020). Approximately one-fifth of medical admissions (about 1 400/month) pertain to cardiac disease—mainly IHD, arrhythmias, or valvular heart disease. The calculated sample size was 385 using a margin of error of 5% and a prevalence of 50%. The sample was selected from the hospital clinic using convenience sampling. Individuals being treated for cardiac disease were identified from medical records and through the attending physician. They were briefed on the nature of the study, which was conducted with strict confidentiality. They were informed that participation was voluntary and that they could withdraw at any time without compromising the treatment. Verbal consent was obtained from patients. Ethical approval was granted by the ethics committee of the SWRHA in 2015.

2.4 Measures

Face-to-face interviews were conducted using a 43-item questionnaire after pilot testing for clarity and ease of response. Participants were asked about their present health status and to recall their health status prior to their cardiac disease diagnosis concerning a number of lifestyle and psychosocial issues. Further information was obtained by a review of patient records. The questionnaire included items on the following:

- Sociodemographics (age, gender, ethnicity, marital status, income, employment, height, weight, and waist circumference).
- Medical diagnosis (type of cardiac diagnosis).
- Cardiovascular risk history (smoking, diabetes, hypertension, abdominal obesity, stressful life/depression, daily vegetable and fruit intake, exercise at least three times per week, family history of

IHD, and hypercholesterolemia).
- Lifestyle habits (smoking, alcohol, and diet).
- Activities of daily living.
- Depression (measured using the Patient Health Questionnaire [PHQ-9] with the following items: little interest or pleasure in doing things; feeling down, depressed, or hopeless; trouble falling or staying asleep or sleeping too much; feeling tired or having little energy; poor appetite or overeating; feeling bad about oneself, or feelings of being a failure or having let oneself or family down; trouble concentrating on activities such as reading the newspaper or watching television; moving or speaking so slowly that other people have noticed or the opposite—being so fidgety or restless that movement has been a lot more than usual; and thoughts that one would be better off dead or of hurting oneself in some way).
- Functional status (taking care of oneself, moving in and out of a bed or chair, walking indoors, walking several blocks, walking one block or climbing stairs, doing house work, doing errands, driving a car, and doing vigorous activities such as running).
- Psychological function (feeling nervous, calm, and peaceful; depressed and blue; down in the dumps, etc.).
- Social activity (visiting relatives and friends, participating in community activities , taking care of other people).
- Social function (doing as much work as others in a similar job, taking breaks to complete activities, working a regular number of hours, doing a job as carefully and accurately as others, working as usual, fear of losing a job).
- Interactions (isolating oneself, being affectionate, being irritable towards others).
- General (sexual satisfaction, own health, getting along with friends or family, staying in bed because of illness, cutting down on activities).

Participants' scores on the physical, psychological, and social items were compared before and after diagnosis of cardiac disease. Each question was rated on a five-point scale reflecting varying severity.

Each item on the PHQ-9 (Kroenke, Spitzer, & Williams, 2001) was rated in the following way: not at all=0; several days=1; more than half the days=2; and nearly every day=3. A total score of 0−4, 5−9, 10−14, 15−19, and 20−27 indicated no, mild, moderate, moderately severe, and severe depression, respectively. Scores between 10 and 27 were indicative of clinical depression.

2.5 Data Collection and Analysis

The data were collected during July and August 2015 by a third-year medical student with experience of similar assignments. The collected data were entered into SPSS software version 20 (IBM Corp., Armonk, NY, USA) and securely stored in a computer to which only the researcher and his research assistants had access.

For each item on the psychosocial and physical issues, the difference in score between pre- and post-cardiac disease diagnosis was calculated and the mean difference obtained was used to generate further analyses on depression and functional status. Analyses included descriptive analysis, a chi-squared test of association, and multiple regressions to identify predictors.

3. Results

3.1 Recruitment

Recruitment took place during July and August 2015. A total of 400 individuals diagnosed with cardiac disease participated in a single interview.

3.2 Statistics and Data Analysis

Table 1 shows the participants' characteristics. Participants' mean age was 65.44 (standard deviation [SD]=11.65) years and the duration of their chronic disease was, on average, 6.71 (SD=6.90) years. Patients were mainly females (57.8%), Indo-Trinidadian (79%), and married (49.3%).

Table 1. Participants' Characteristics (Total Sample, Including Patients with Depression; N=400)

		TOTAL		DEPRESSED	
		Number	**Percent**	**Number**	**Percent**
Gender	1 Male	168	42	55	37.7
	2 Female	231	57.8	91	62.3
Ethnicity	1 Afro	67	16.8	18	12.3
	2 Indo	316	79	121	82.9
	3 Chinese	1	0.3	0	0.0
	4 Mixed	16	4	7	4.8
Marital status	1 Married	197	49.3	62	42.5
	2 Single	125	31.3	51	34.9
	3 Divorced/Separated	22	5.5	10	6.8
	4 Common law	6	1.5	1	0.7
	5 Widowed	50	12.5	22	15.1
Employment status	1 Employed	44	11	11	7.5
	2 Unemployed	349	87.3	134	91.8
	3 Self-employed	7	1.8	1	.7
Type of cardiac disease	1 Heart Failure	64	16	22	15.1
	2 Myocardial Infarction	74	18.5	27	18.5
	3 Stable Angina	9	2.3	4	2.7
	4 IHD	251	62.7	93	63.7

Note. IHD: Ischaemic heart disease.

The most common cardiovascular risk was hypertension, followed by diabetes mellitus and a family history of IHD (Figure 1).

3.2.1 Depression Status, Associations, and Predictors

The reliability of the depression scores was acceptable (Cronbach's alpha: 0.689). Patients who suspected a cardiac disease diagnosis had significantly higher depression ($p<.001$), with a mean difference of -5.82 (SD=4.5, standard error of mean=.23). In addition, no significant differences in mean depression scores were found among the different types of patients (heart failure, myocardial infarction, stable angina, and suspected IHD; $p=.4222$). However, the highest average difference in depression was found among patients with myocardial infarction (Table 2). Clinical depression (PHQ score of 10–27) was found in 36.6% (n=146) of the patients, as compared to 1.7% before the suspected cardiac diagnosis (i.e. an increase of 34.9%). Among individuals with clinical depression, the mean age was 65.83 (SD=11.026) years and the majority were females (n= 91, 62.3%).

Table 2. Mean Difference in Depression Scores Before and After Diagnosis by Type of Cardiac Disease

Dependent Variable: Patient Health Questionnaire scores

Type of cardiac disease	Mean	Standard Error	95% Confidence Interval	
			Lower Bound	Upper Bound
1 Heart Failure	-5.203	.564	-6.311	-4.095

2 Myocardial Infarction	-6.162	.524	-7.193	-5.132
3 Stable Angina	-4.333	1.503	-7.288	-1.378
4 IHD	-5.952	.285	-6.512	-5.393

Note. IHD: Ischaemic heart disease.

Among gender, ethnicity, marital status, employment, and type of disease, only gender was significantly associated with overall depression scores: mental health in females was more greatly affected than in males, as evident from the larger decline (0.27 vs -0.44; Table 3).

Table 3. Sociodemographics and Overall Depression

Sociodemographics	F	*P*
Gender	13.205	0.00
Ethnicity	1.385	0.247
Marital status	2.049	0.087
Employment	0.733	0.481
Type of cardiac disease	1.009	0.389

3.2.2 Medical/Lifestyle Factors and Depression

Among the variables evaluated in the questionnaire, diabetes, stress, and eating seafood and sugary foods were positively associated with depression, while exercise was negatively correlated (Table 4) ($p<0.10$).

Table 4. Correlations Between Lifestyle Factors and Depression

Model	Unstandardised Coefficients		Standardised Coefficients	t	*P*
	B	Standard Error	Beta		
(Constant)	4.552	1.957		2.326	0.021
Diabetes mellitus	-0.838	0.466	-0.086	-1.797	0.073
Stressful life/depression (psychosocial)	-2.869	0.419	-0.317	-6.842	0
Exercise (times per week)	0.909	0.336	0.19	2.705	0.007
Seafood (fish, shrimp, etc.; servings per day)	-1.008	0.34	-0.152	-2.965	0.003
Sugary or salty food snacks or desserts (servings per day)	-1.224	0.38	-0.163	-3.219	0.001

3.2.3 Social and Psychological Issues

In terms of specific social and psychological issues (falling or staying asleep, feeling tired, poor appetite, feeling bad about oneself, trouble concentrating, speaking slowly, having negative thoughts, being nervous, feeling calm and peaceful, feeling depressed, feeling happy, feeling in the dumps, visiting friends and relatives, participating in community activities, taking care of other people, working in a similar job, working in different working conditions), there was a significant difference between pre- and post-diagnosis scores ($p<.05$) except for 'thoughts that you have the support of your family and friends' ($p=0.14$).

There was significant worsening of functional status from pre- to post-diagnosis. These activities include moving in and out of bed, walking indoors such as around the house, walking several blocks, walking one block or climbing up a flight of stairs, doing work around the house, running errands, driving a car or using public

transportation, and doing vigorous activities ($p<.05$). Climbing stairs and doing strenuous activities were most affected.

Social activities such as visiting relatives and friends, participating in community activities, taking care of other people, and performing work-related activities also worsened post-diagnosis. Following a diagnosis of heart disease, there were significant differences in terms of the patients feeling isolated, irritable, making unreasonable demands, and getting along well with other people ($p<.05$) In addition, there was a worsening of the feelings of satisfaction with sexual relationships, feelings about one's own health, staying in bed, and having to cut down on normal activities ($p<.05$).

4. Discussion

The present study aimed to determine whether cardiac disease diagnosis is associated with clinical depression prevalence and physical and social activity, as well as to identify its associations with other variables. Our findings revealed that the suspicion or diagnosis of cardiac disease is associated with a marked increase in depression prevalence. Patients who exercised had lower depression levels. In addition, there was a significant worsening of physical and social activities post-diagnosis.

In our sample, the prevalence of clinical depression increased from 1.7% to 36.6% following cardiac disease diagnosis (an increase of 34.9%; $p<.001$). This increase in depression from patients' premorbid states varied based on their health status and demographic or sociocultural circumstances. Variations in depression or depressive symptoms have been consistently reported. A large study reported that depression was prevalent in 9.3% of ambulatory patients with cardiac disease, 4.8% of the general population (Egede, 2007), 15–30% of patients post-myocardial infarction (Lichtman et al., 2008), and 19.3–33.6% of patients with heart failure (Tsu, 2012). It is also well known that depression can lead to treatment non-compliance as well as failure to make the necessary lifestyle changes (Martin, Williams, Haskard, & Dimatteo, 2005). Depression has also been associated with an increase in the probability of future cardiac events, less adherence to medication, and deterioration of overall quality of life (Brown & Bussel, 2011; Lichtman et al., 2008). Depression among patients with cardiac disease should, therefore, be recognised and managed early on since it is also considered a risk factor for coronary artery disease (CAD; Dhar & Barton, 2016).

Psychological factors such as hostility, anxiety, and depression significantly affect the development, clinical expression, and prognosis of heart disease (Ilić & Apostolović, 2002). In this study, there were no significant differences in mean depression scores among the different types of cardiac conditions. This result may be because of similar concerns regardless of the type of cardiac disease. In addition, among the evaluated demographics, only gender was significantly associated with depression, with females being the most affected. This is concerning, especially when our health care system displays no systemic, discriminatory practices. This finding may result from a subtle lack of focus on female health or a greater susceptibility to depression among females. Similar findings have been reported by the WHO (2012), with a prevalence of 70.7% and 55.5% in females and males, respectively. Such a difference in depression prevalence is undesirable because depression can lead to death and poorer outcomes after a cardiac event, placing females at more risk than males (Doering & Eastwood, 2011; McSweeney et al., 2016). According to the WHO, depression contributes to the global burden of disease (World Federation for Mental Health, 2012), especially among patients with CAD (Bahall, 2019; Lichtman et al., 2008). Poor management of risk factors increases the chances of developing CAD (Hobbs, 2004; Kromhout, Menotti, Kesteloot, & Sans, 2002), while controlling them has proven beneficial in its primary and secondary prevention (Hobbs, 2004; Kromhout, Menotti, Kesteloot, & Sans, 2002).

In this study, social support was associated with decreased depression, confirming Unützer and Park's (2012) findings. Moreover, diabetes, stress, and eating seafood and sugary foods were negatively associated with depression. While there is no clear link between food types and depression (Harvard Health Publishing: Harvard Medical School, 2018), this study revealed that sugary foods can increase depressive symptoms. Our results are consistent with Rutledge et al.'s (2014) finding that diet is associated with depression.

Further, exercise was negatively correlated with depression. Previous research has consistently shown the positive effects of exercise in minimising depression (Pozuelo, 2019) and it seems to be the single most important indicator of decreased depression and improved physical health. It has been reported that myocardial ischaemia can, in fact, lead to exercise intolerance and restrictions in physical activity (Pina et al., 2003). Nonetheless, exercising would increase patients' tolerance to physical activity, allowing them to achieve higher-intensity levels before reaching their angina or ischaemic electrocardiographic threshold (Boden et al., 2014).

Moreover, exercise is important in both primary and secondary prevention of cardiovascular disease. (Fletcher et al., 1996). In general, people who increase their physical activity after a myocardial infarction are more likely to survive subsequent episodes (Lawler, Filion, & Eisenberg, 2011; O'Connor et al., 1989). Patients' continued lack of exercise may result from a sedentary lifestyle, psychological fear, physical challenges resulting from their disease, or cultural norms.

Meanwhile, smoking, alcohol consumption, poor dietary habits, and lack of social support are also associated with depression (Pozuelo, 2019). Pozuelo (2019) found associations between depression and young age, increased comorbidities, higher weight, high body mass index, Hospital Anxiety and Depression Scale score, comorbid anxiety, physical inactivity, smoking, and being less likely to be partnered.

Lastly, there was a significant worsening of physical and social activities in this cohort of stable patients following diagnosis of cardiac disease.

This study has several limitations that should be taken into account when interpreting the results. First, the sample size is small and participants were selected from a single centre. Second, as the focus was on stable patients, attempts to generalise the findings to other groups of patients may be inappropriate. Third, we relied on patients' recall and subjective reports, which may not be completely reliable. Lastly, missing data from patients' records were excluded. This, however, does not diminish the value of the study, which focuses on psychosocial factors.

Cardiovascular disease, the number one cause of death in Trinidad and Tobago, necessitates an evaluation of depression and lifestyle practices to identify susceptible patients, particularly ones who can benefit from appropriate interventions such as exercise, social support, and healthy eating patterns.

5. Conclusion

Clinical depression is a major complication of cardiac disease. Exercise and social support are associated with diminished depression. Among stable patients, physical and social factors also worsen following cardiac disease diagnosis. Efforts must be made to identify and manage depression and other psychosocial factors in patients who have newly been diagnosed with cardiac disease.

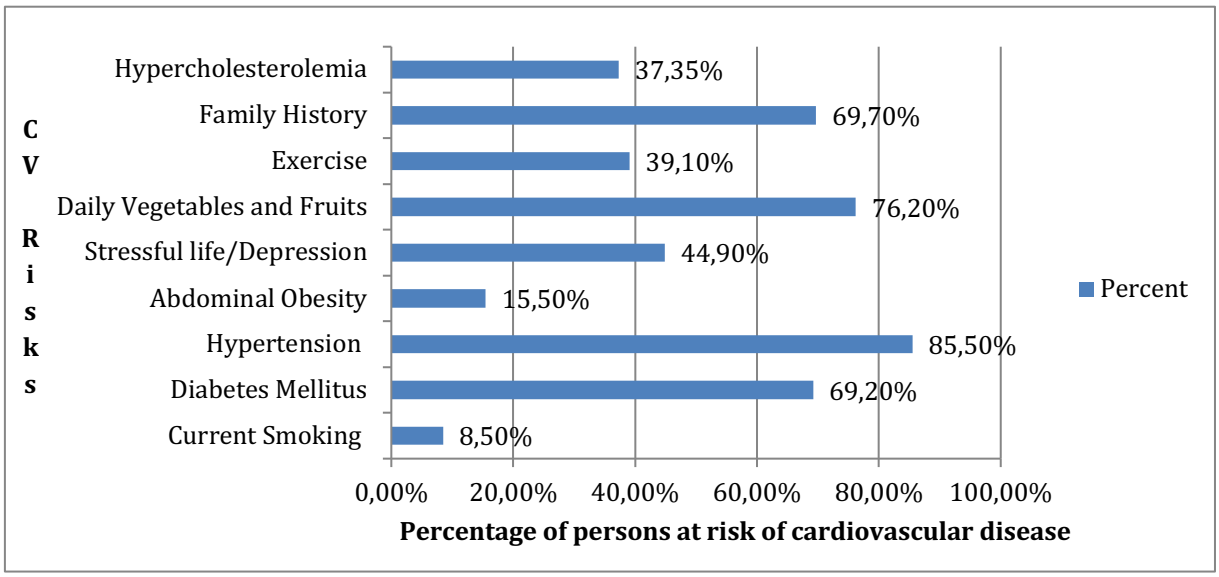

Figure 1. Cardiovascular (CV) risk prevalence (n=389).

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Antimicrobial Susceptibility Pattern of Urine Culture Isolates in a Tertiary Care Hospital of Karachi, Pakistan

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Abstract
Background: Urinary Tract Infections (UTIs) remain one of the leading causes of infection worldwide, andare a major health concern in developing countries, and lead patients to seek medical care. Recent reports have shown increasing resistance to commonly-used antibiotics. We aimed to study the isolates and their antibiotic resistance pattern in outpatients. Objective: The study was done in Karachi on outdoor patient urine samples, of patients with clinically suspected UTIs, in order to assess the antimicrobial susceptibility pattern of different organisms, which would help in deciding empirical antibiotic treatment and improving patient outcome. Materials and Methodology: 400 urine samples of patients clinically suspected to have UTI were collected directly from the bacteriology lab, out of which 77 were culture positive. The positive samples included 64 females and 13 males. Results: The most commonly isolated organism was *Escherichia coli (E.coli)*, followed by *Klebsiella species*. *Escherichia coli was* most sensitive to meropenem and nitrofurantoin (96.6%) whereas *Klebsiella* species were sensitive to several antibiotics excluding cotrimoxazole and the fluoroquinolones. Conclusion: *E.coli species* is the most common organism causing UTIs. Antimicrobial resistance is emerging against some antibiotics, and the current susceptibility patterns may be used locally for optimum therapeutic outcomes and for preventing antibiotic misuse.

Keywords: Antimicrobial Susceptibility, Urine Culture Isolates, Tertiary Care, Hospital

1. Introduction

Urinary tract infection (UTI) describes microbial colonization and infection of structures of the urinary tract. UTI is categorized by infection site as pyelonephritis (kidney), cystitis (urinary bladder), and urethritis (urethra), and can also be classified as uncomplicated or complicated [Ejrnæs K, (2011)]. Urinary tract infections are currently placed among the most widespread infectious diseases worldwide, with chronic and recurrent infections being troublesome [Matthew GB, Matthew AM, (2010)]. Clinical studies suggest that the overall prevalence of UTI is higher in women; less complicated UTIs in healthy women have an incidence of 50/1000/year. UTI varies with

age and gender, boys between the ages of 1-5 year suffers UTI more frequently and need to be evaluated efficiently [Gupta P, Mandal J, Krishnamurthy S, Barathi D, Pandit N (2015)].

Uropathogenic *Escherichia coli* (UPEC) are the primary etiologic agents, and the most common cause of urinary tract infections (UTIs) worldwide[R N Das, T S Chandrashekhar, H S Joshi, M Gurung, N Shrestha, P G Shivananda (2006); Ihsan A, Zara R, Safia A, Sajid M, Javid ID, (2015)]. *E.coli*pathotypes reside harmlessly in the human intestinal microenvironment but, upon access to sites outside of the intestine, become a major cause of human morbidity and mortality as a consequence of invasive UTI (pyelonephritis, bacteremia, or septicaemia) [Alteri CJ, Mobley HL (2015)]. The virulence factors of *E. coli* are multiple and unusually complex affecting pathogenicity in combination with one another. [Hegde A, Bhat GK, Mallya S, (2008)].*Escherichia coli* expresses multi-drug resistance. In the treatment of uncomplicated cystitis, the preferable antibiotics for empiric treatment include nitrofurantoin, trimethoprim/sulphamethoxazole, or ciprofloxacin. The alternate choices include cefuroxime and cefixime. For complicated and upper UTI cases in hospitalized patients, the antibiotics used are piperacillin/tazobactam and carbapenems[Jharna M, Srinivas AN, Buddhapriya D, Subhash CP, (2012)].

Antibiotic resistance among bacteria causing common infections is increasing in all regions of the world [Fair RJ, Tor Y. Antibiotics and bacterial resistance in the 21st century (2014)]. Infections are gradually becoming hard to treat, and may lead to therapeutic dead-ends [Moroh JLA, Fleury Y, Tia H, et al, (2014)]. The emergence of resistance to antibiotics illustrates the importance of using evidence-based strategies for treatment [Nickel JC, (2005)]. In UTI cases, antibiotic treatment is often started empirically before the results of urine culture and susceptibility testing are available. Appropriate antibiotic use in patients with UTI seems to reduce length of hospital stay and therefore favors patient outcomes and healthcare costs[Spoorenberg V, Hulscher ME, Akkermans RP, Prins JM, Geerlings SE, (2014)]. Hence, it becomes important to regularly monitor the resistance or susceptibility patterns of uropathogens, so that the guidelines for empirical antibiotic therapy can be improved to include antibiotics with low resistance, aiding clinicians in proper management of UTIs with minimal therapeutic failures[Sharma N, Gupta A, Walia G, Bakhshi R, (2016)]. The antibiotic resistance patterns have shown large inter-regional differentiation. The appropriate choice of antibiotic needs to be tailored based on the local susceptibility pattern[Prasada S, Bhat A, Bhat S, Shenoy Mulki S, Tulasidas S, (2019)]. Factors such as the type of UTI (complicated or uncomplicated), gender, age, and previous history of antibiotic therapy of each UTI patient should also be considered to find out the correct global data on susceptibility and for further appropriate treatments attempts [Alos JI (2005)]. Data provided by regional microbiology laboratories on the susceptibility patterns helps to choose the empirical choice of antimicrobials to treat UTI [McNulty CAM, Richards J, Livermore DM (2006), Car J (2006)]. Generally, the antimicrobial treatment is initiated before the laboratories results which may lead to the frequent misuse of antibiotics [Tambekar DH, Dhanorkar DV, Gulhane SR, Khandelwal VK, Dudhane MN, et al. (2006)].

All over the world, resistance against beta-lactam antibiotics is increasing due to Extended Spectrum Beta Lactamases (ESBLs) and Amp-c beta-lactamase production. Carbapenemases are plasmid-encoded and has reduced the activity of all penicillins, monobactams, cephalosporins and carbapenems[Arpin C, Dubois V, Coulange L, Andre C, Fischer I ,Noury P et al. (2003)]. Beta lactamases cause resistance to beta-lactam agents and are produced by different aerobic gram-negative bacteria (AGNB) [Aggarwal R, Chaudhary U, Sikka R (2004)]. ESBLs were discovered in 1980. The main reservoirs for these resistant organisms are hospital patients[Wiener J, Quinn J, Bradford P, Goering R, Nathan C, Bush K, (1999)].

Keeping in view the aforementioned considerations, this study was conducted with the aim of reviewing current antimicrobial sensitivity and resistance pattern in males and females of different age groups, therefore contributing to the prevention of therapeutic failures and antibiotic misuse in patients with UTI.

2. Materials and Methods:

2.1 Study area and population:

This cross-sectional study was carried out at the Ziauddin Hospital in Karachi, Pakistan. This hospital caters to the needs of patients from nearby urban and rural localities as well as from other parts of the province. The study included outdoor patients' urine samples collected over a period of one year from Jul 1, 2019 –Jun 30, 2020. The patients had clinical evidence of urinary tract infection as suggested by their physician. Culture and susceptibility reports were obtained directly from the micro-biology lab.

2.2 Sample size:

The urine samples of 400 patients comprising 315 females and 85 males were included in the study. Out of the 400 samples processed, 77 (19%) depicted bacterial growth, 28(7%) showed mixed flora, and the rest of the 374 (74%) samples were found to be sterile.

2.3 Sample collection and processing:

Patients were instructed to collect midstream urine sample in a bottle and give it to the laboratory for further processing. In the lab, the organisms were isolated and the colony count of each organism was measured. Culture results were interpreted as being significant and insignificant, according to the standard criteria. A growth of $>10^5$ colony forming units/mL was considered as significant bacteriuria.

2.4 Anti-microbial susceptibility testing:

17 antibiotics were tested as part of the study including, amikacin, amoxicillin-clavulanic acid, ampicillin, aztreonam, cefoperazone/sulbactam, cefixime, cefotaxime, ceftriaxone, colistin, co- trimoxazole, gentamicin, imipenem, meropenem, nitrofurantoin, ofloxacin/ciprofloxacin, polymixin and tazobactam/piperacillin. All the microscopic examinations involving identification of bacterial strains was performed by authorized laboratory technicians. Appropriate quality control strains were used to validate the results of the antimicrobial discs. The data was entered into Microsoft Excel and analyzed. The results were expressed as proportions and mean susceptibility was calculated for the antibiotics for each organism.

3. Results:

Table 1. Age and gender wise distribution of urine sample

Age (Years)	Gender		Total
	Female	Male	
0 – 20	7	1	8 (10.4%)
21 – 40	24	2	26 (33.8%)
41 – 60	17	1	18 (23.4%)
61 – 80	13	7	20 (26.0%)
81 – 100	3	2	5 (6.5%)
Total	64 (83.1%)	13 (16.9%)	77

3.1 Prevalence rate and frequency distribution of UTI among males and females in different age groups:

The total prevalence of UTI was found to be 83.1% in females and 16.9% in males as seen in Table 1, hence indicating a higher prevalence in femalepatients. The highest susceptible age group of UTI patients irrespective of gender was found to be 21-40 years (33.8%) followed by 61-80 years (26.0%), and then between 41-60 years (23.4%). The lowest prevalence of UTI was found in age groups of 0-20 years (10.4%), followed by 81-100 years (6.4%), irrespective of gender.

The prevalence of UTI differed in males and females according to age groups. The highest prevalence in females was found in the age group of 21-40 years, whereas elderly males in the age bracket of 61-80 years were mostly affected.

On the contrary, elderly females (81-100 years) were least affected by UTI. The least susceptible groups in males were those between 0-20 years and 41-60 years.

Table 2. Gender wise bacterial isolates

Bacterial Isolates	**Gender**				**Total**
	Female		**Male**		
	n	**%**	**N**	**%**	
Enterobacter Species	1	33.3%	2	66.7%	3
Enterococcus Species	3	100.0%	0	0.0%	3
Escherichia Coli	38	86.4%	6	13.6%	44
Klebsiella Species	12	80.0%	3	20.0%	15
Morganella Morganii	1	100.0%	0	0.0%	1
Pseudomonas aeruginosa	5	83.3%	1	16.7%	6
Serratia Species	1	100.0%	0	0.0%	1
Staphylococcal species	1	100.0%	0	0.0%	1
Streptococcus Group D	1	50.0%	1	50.0%	2
Streptococcus Species	3	100.0%	0	0.0%	3

3.2 Distribution frequency of isolated bacterial uropathogens:

As seen in table 2, among all the isolated bacterial uropathogens from UTI patients, *Escherichia coli* was found as the dominant bacteria with the highest prevalence, irrespective of gender. The second most prevalent isolate was *Klebsiella sp.* followed by *Pseudomonas. Enterococci sp, Enterobacter* and S*treptococcus sp.* had the same prevalence. The organisms with the lowest prevalence were found to be *Serratia sp.* along with *Morganella Morganii* and *Staphylococcal sp,* irrespective of gender.

3.3 Gender-wise distribution of uropathogens

The prevalence rate for the occurrence of different uropathogens among males and females had some variations. *Enterococcus species,* for example, was only seen in females (100%), whereas no isolates were found in males. *Morganella morganii, Serratia species, Staphylococcal* and S*treptococcal species* followed the same pattern.

On the other hand, some organisms had a higher prevalence in females as compared to males. These include *E. coli*with a prevalence of 86.4% in females and 13.6% in males, followed by *Pseudomonas aeruginosa*, the prevalence of which was 83.3% in females and 16.7% in males. *Klebsiella species* was also more prevalent in females (80%) and only 20% of the isolates were found in males.

Enterobacter species was the only organism which had higher prevalence in males (66.7%) than in females (33.3%). *Streptococcus groupD*was equally prevalent in males and females.

Table 3. Isolates from all the urine samples and their susceptibility pattern to antibiotics

ANTIBIOTICS	BACTERIAL ISOLATES												
	Citrobacter species	Enterobacter Species	Enterococcus Species	Escherichia Coli	Klebseiella Species	Morganella Morganii	Providencia Species	Pseudomonas aeruginosa	Salmonella species	Serratia Species	Staphylococcal species	Streptococcus Group D	Streptococcus Species
AMIKACIN	100.0%	80.0%	100.0%	87.9%	87.5%	100.0%	100.0%	100.0%	0.0%	100.0%	100.0%	100.0%	100.0%
AMOX-CLAV	100.0%	80.0%	100.0%	72.4%	81.3%	0.0%	100.0%	100.0%	0.0%	100.0%	0.0%	100.0%	100.0%
AMPICILLIN	100.0%	80.0%	80.0%	25.9%	87.5%	100.0%	0.0%	100.0%	100.0%	100.0%	100.0%	66.7%	100.0%
AZTREONAM	100.0%	40.0%	100.0%	37.9%	62.5%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
CEF-SUL	100.0%	100.0%	100.0%	87.9%	81.3%	100.0%	100.0%	100.0%	0.0%	100.0%	100.0%	100.0%	100.0%
CEFIXIME	100.0%	40.0%	100.0%	34.5%	62.5%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
CEFOTAXIME	100.0%	40.0%	100.0%	37.9%	62.5%	100.0%	100.0%	100.0%	0.0%	100.0%	100.0%	100.0%	100.0%
CEFTRIAXONE	100.0%	40.0%	100.0%	37.9%	62.5%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
COLISTIN	100.0%	80.0%	100.0%	84.5%	100.0%	100.0%	100.0%	100.0%	0.0%	100.0%	100.0%	100.0%	100.0%
CO-TRIMOXAZOLE	0.0%	80.0%	100.0%	50.0%	62.5%	100.0%	0.0%	100.0%	0.0%	100.0%	0.0%	100.0%	100.0%
GENTAMICIN	100.0%	80.0%	100.0%	81.0%	81.3%	100.0%	100.0%	100.0%	0.0%	100.0%	100.0%	100.0%	100.0%
IMIPENEM	100.0%	100.0%	100.0%	94.8%	93.8%	100.0%	100.0%	100.0%	0.0%	100.0%	100.0%	100.0%	100.0%
MEROPENEM	100.0%	100.0%	100.0%	96.6%	93.8%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
NITROFURANTOIN	100.0%	80.0%	80.0%	96.6%	68.8%	100.0%	100.0%	100.0%	0.0%	0.0%	100.0%	100.0%	100.0%
OFLOX/CIPRO	100.0%	60.0%	100.0%	46.6%	68.8%	0.0%	0.0%	66.7%	0.0%	100.0%	0.0%	100.0%	100.0%
POLYMIXIN	100.0%	80.0%	100.0%	84.5%	100.0%	100.0%	100.0%	100.0%	0.0%	100.0%	100.0%	100.0%	100.0%
TAZO/PIPERA	100.0%	100.0%	100.0%	87.9%	81.3%	100.0%	100.0%	100.0%	0.0%	100.0%	100.0%	100.0%	100.0%

Table 4. Isolates from all the urine samples and their resistance pattern to antibiotics.

ANTIBIOTICS	BACTERIAL ISOLATES												
	Citrobacter species	Enterobacter Species	Enterococcus Species	Escherichia Coli	Klebseiella Species	Morganella Morganii	Providencia Species	Pseudomonas aeruginosa	Salmonella species	Serratia Species	Staphylococcal species	Streptococcus Group D	Streptococcus Species
AMIKACIN	0.0%	20.0%	0.0%	12.1%	12.5%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
AMOX-CLAV	0.0%	20.0%	0.0%	27.6%	18.8%	100.0%	0.0%	0.0%	0.0%	0.0%	100.0%	0.0%	0.0%
AMPICILLIN	0.0%	20.0%	20.0%	74.1%	12.5%	0.0%	100.0%	0.0%	0.0%	0.0%	0.0%	33.3%	0.0%
AZTREONAM	0.0%	60.0%	0.0%	62.1%	37.5%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
CEF-SUL	0.0%	0.0%	0.0%	12.1%	18.8%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
CEFIXIME	0.0%	60.0%	0.0%	65.5%	37.5%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
CEFOTAXIME	0.0%	60.0%	0.0%	62.1%	37.5%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
CEFTRIAXONE	0.0%	60.0%	0.0%	62.1%	37.5%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
COLISTIN	0.0%	20.0%	0.0%	15.5%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
CO-TRIMOXAZOLE	100.0%	20.0%	0.0%	50.0%	37.5%	0.0%	100.0%	0.0%	0.0%	0.0%	100.0%	0.0%	0.0%
GENTAMICIN	0.0%	20.0%	0.0%	19.0%	18.8%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
IMIPENEM	0.0%	0.0%	0.0%	5.2%	6.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
MEROPENEM	0.0%	0.0%	0.0%	3.4%	6.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
NITROFURANTOIN	0.0%	20.0%	20.0%	3.4%	31.3%	0.0%	0.0%	0.0%	0.0%	100.0%	0.0%	0.0%	0.0%
OFLOX/CIPRO	0.0%	40.0%	0.0%	53.4%	31.3%	100.0%	100.0%	33.3%	100.0%	0.0%	100.0%	0.0%	0.0%
POLYMIXIN	0.0%	20.0%	0.0%	15.5%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
TAZO/PIPERA	0.0%	0.0%	0.0%	12.1%	18.8%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%

Tables 3 and 4 show the organisms' susceptibility and resistance pattern to the 17 antibiotics that were part of the study.

E.coli was most susceptible to meropenem and nitrofurantoin (96.6%), followed by imipenem (94.8%), cefoperazone/sulbactam, amikacin and tazobactam/piperacillin(87.9%). It was least sensitive to ampicillin (25.9%).

100% of*Klebsiella sp*were sensitive to colistin and polymixin, followed by imipenem and meropenem (93.8%), followed by ampicillin (87%) and amoxicillin-clavulanic acid (83%). They was least sensitive to aztreonam, cefixime, cefotaxime, ceftriaxone and co-trimoxazole (62.5%).

Pseudomonas was among those organisms which were 100% sensitive to most of the antibiotics. It was only resistant to one antibiotic, ofloxacin/ciprofloxacin (33.3%). *Streptococcus species* was the only organism that was 100% sensitive to all the antibiotics. *Streptococcus group D* followed a similar pattern except that it was somewhat resistant to ampicillin – 33% of the isolates.

The other organisms in this category include *Staphylococcal species* were 100% resistant to some antibiotics which included amoxicillin-clavulanic acid, co-trimoxazole and ofloxacin/ciprofloxacin.

Salmonella was sensitive to all antibiotics except ofloxacin/ciprofloxacin to which it was 100% resistant. Similarly*, Serratiasp.*was resistant to only nitrofurantoin. Other organisms which were 100% sensitive to most of the antibiotics include *Providencia sp,Morganella sp, Enterococcus* and C*itrobacter sp.*.

4. Discussion:

The age and gender distribution of the patients diagnosed with UTI followed the natural epidemiological pattern of UTI, with young females being the most affected group, which is related to the difference between the male and female genitourinary systemsin anatomy and microflora. This study highlights the current scenario of UTI and the anti-microbial susceptibility pattern in the urban and rural settings of other cities in the developing world. In females of all age categories, *E. coli* is the most frequently isolated uropathogen which correlates with other studies [Nys S, van Merode T, Bartelds AIM, Stobberingh EE (2006); Hazarika J, Baruah K, (2018); Nys S, (2005)]. It is followed by*Klebsiella sp.*which is also the second most commonly isolated organism in various studies[George CE, Norman G, Ramana GV, Mukherjee D, Rao T (2015); Prakash D, Saxena RS (2013); Somashekara SC, Deepalaxmi S, Jagannath N, Ramesh B, Laveesh MR, Govindadas D, et al (2014)].

Increasing antimicrobial resistance has been documented in this study as well as globally [Claudia V, Francesca L, Maria PB, Gianfranco D, Pietro EV, et al. (2014); Kashef N, Djavid GE, Shahbazi S (2010); Karlowsky JA, Jones ME, Thornsberry C, Critchley I, Kelly LJ, et al. (2001); Rajalakshmi V, Amsaveni V (2011); Sharifian M, Karimi A, Tabatabaei SR, Anvaripour N (2006); Haghi-Ashteiani M, Sadeghifard N, Abedini M, Soroush S, Taheri-Kalani M, et al. (2007); Rashed Marandi FRM, Saremi M (2008)]. The tendency to self-medicate, noncompliance with treatment, financial constraints and lack of education on the part of patients; the sale of antibiotic drugs without proper prescription and failure to educate patients on the part of pharmacists; negligible surveillance of susceptibility patterns, poor regulatory controls over antibiotics and a lack of will to make a change on part of health care system, and administering antibiotics before obtaining samples for culture, failure to educate patients and poor prescribing practices on part of physicians are among many factors that lead to injudicious and inappropriate use of antibiotics, hence causing the rapid development of resistance [World Health Organization. The World Health Report 1996; World Health Organisation. National Action Plan on Antimicrobial Resistance (NAP-AMR) 2017-2021. New Delhi, India: World Health Organisation Country Office for India; 2017; Laxminarayan R, Chaudhury RR (2016). Porter G, Grills N (2016).].

The above study shows that *E.coli* is most susceptible to meropenem and nitrofurantoin, but it also showed a high sensitivity to amoxicillin-clavulanic acid (72.4%) and hence this maybe the preferred oral drug of choice in *E.coli* positive patients. On the contrary we see that *E.coli* is most resistant to ampicillin (74.1%), and 53% of the isolates were resistant to ofloxacin/ciprofloxacin, therefore these may be excluded in the empiric treatment of *E.coli* positive patients.

For *Klebsiella sp*, which is the second most common uropathogen, a high susceptibility to commonly used antibiotics (amoxicillin and amoxicillin-clavulanic acid) was noted, however, 33% of the isolates were resistant to ofloxacin/ciprofloxacin, and several of the studies quoted above have shown an increased resistance to fluoroquinolones. The resistance of 33% of *Pseudomonas sp* and 40% of *Enterobacter sp* to fluoroquinolones also

depicts the widespread use of these antibiotics, even in the absence of a prescription. The 100% resistance of *Citrobacter sp* to cotrimoxazole may be due to the widespread use of this drug in the community.

Resistance to antibiotics is a leading cause of therapeutic failures all over the world. This study was therefore aimed at studying the antimicrobial resistance trends and aiding clinicians in deciding the appropriate empirical treatment, hence improving patient outcome. This may also help in preventing the misuse of antibiotics in UTI patients. A unified antibiotic protocol is necessary to restrict the use of antibiotics injudiciously in order to prevent resistance and reduce the complications of UTI arising from the use of resistant drugs. Since thos was a cross-sectional study, further regular monitoring and a continuous review of antibiograms is also necessary to track changes in etiological agents and antimicrobial patterns to help in empirical treatment.

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