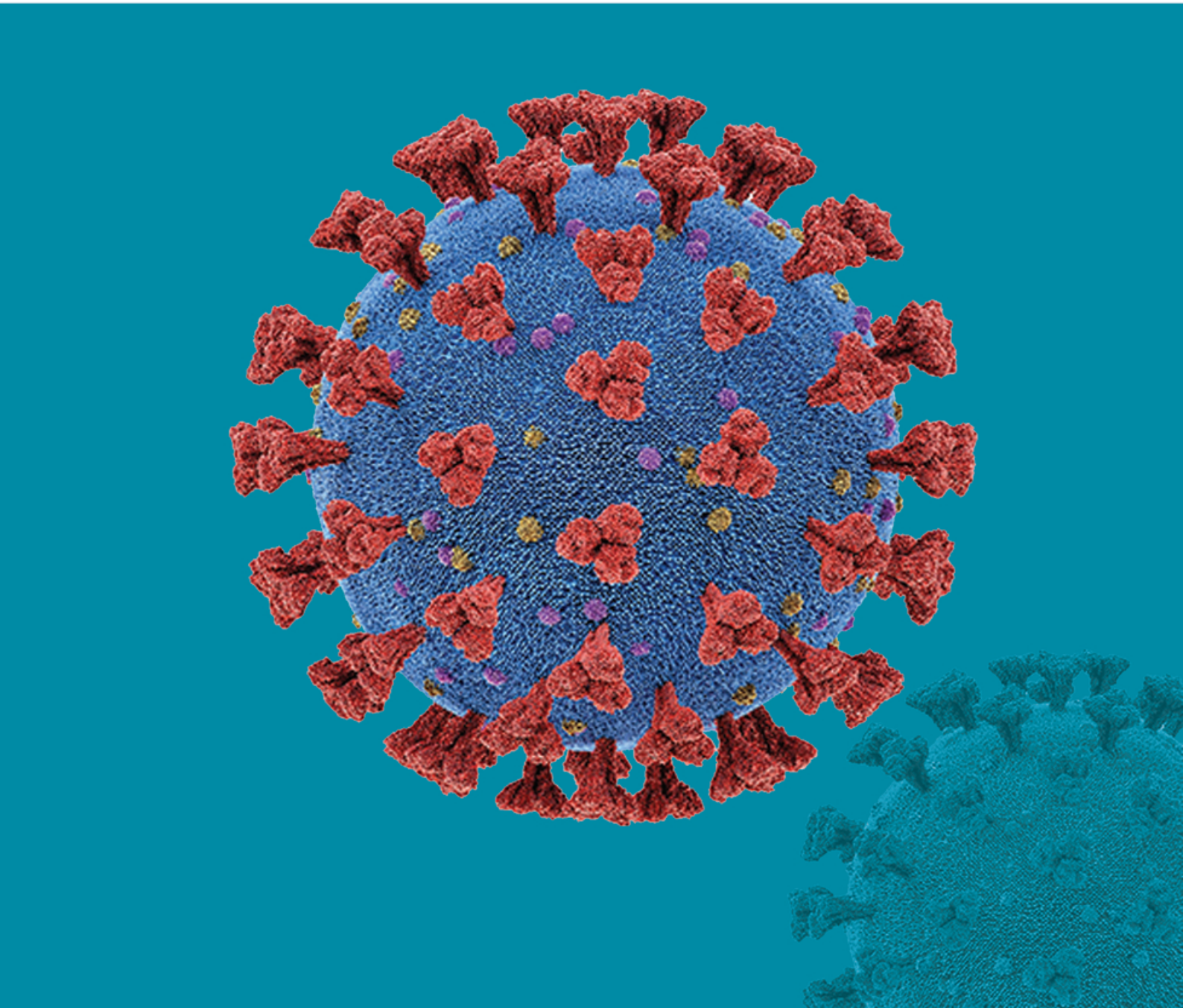
Volum 13 Number 02 May 2020

KHARTOUM MEDICAL JOURNAL

THE OFFICIAL JOURNAL OF THE FACULTY OF MEDICINE, UNIVERSITY OF KHARTOUM



KHARTOUM
MEDICAL JOURNAL
The Official Journal of the Faculty of Medicine, University of Khartoum
Published every four months

Address
P.O. Box 102, Khartoum, 11111 Sudan
E-mail:khartoummedicalj@gmail.com
E-mail:kmj@meduofk.net
Website:kmjuofk.com

Designed & set: Ahmed Hussien M

Ethical policies and procedures

- Any material submitted for publication in KMJ must conform to the ethical norms as defined by the Faculty of Medicine, University of Khartoum, Research and Ethical Committees.
- Research papers must be the result of original work and should not be submitted for publication elsewhere.
- Any related previously published work must be referred to by the author(s).
- Authors and co-authors are equally and completely responsible for their manuscripts and should all be aware of contents and have substantial contribution to the work done.
- Authors should accept full legal, moral, scientific and professional responsibility for their articles.
- Authors should include an acknowledgement of data, material or assistance they obtained and used that may otherwise lead to conflicts with other papers.
- Reviewers and readers are expected to report any duplication or fraud they recognize in a manuscript to the Editor-in-Chief. The Editorial Board will investigate the matter and take the appropriate action.
- KMJ reserves the right to accept or reject any article submitted for publication.

Khartoum Medical Journal Objectives

1. Provide a forum for scientific and clinical medicine publications.
2. Serve the medical community in Sudan and the region in the field of continuing medical education.
3. Offer opportunities for the publication of service-oriented research and disseminate information aimed at the promotion of health services.
4. Encourage the development of medical and allied sciences research.

CONTENTS

Original articles

Review article

ORIGINAL ARTICLE

The association of measures of adiposity: Body mass index, visceral adiposity index and lipid accumulation product with markers of Metabolic Syndrome in young adults

Rabab Elbashir,[1] Huda Mahgoub,[2] Nouralsalhin Abdalhamid Alaagib.[3*]

[1] *Department of Physiology, Faculty of Dentistry, University of Khartoum, Khartoum, Sudan*

[2] *Department of Physiology Faculty of Medicine University of Shendi, Shendi, Sudan*

[3] *Department of Physiology Faculty of Medicine, University of Khartoum, Khartoum, Sudan*

ABSTRACT

Background and objectives: Obesity and Metabolic syndrome (MetS) among young adults is increasing worldwide. This study investigated the relation between body mass index (BMI), waist circumference (WC), Visceral Adiposity Index (VAI) and Lipid Accumulation Product (LAP), as markers of obesity in young adults, with markers of MetS: blood pressure (BP), fasting blood glucose (FBG), plasma triglycerides (TG), high density lipoproteins (HDL), low density lipoproteins (LDL) and total cholesterol.

Methods One hundred and fifty young adults (66 male and 84 females) aged between 18-25 years volunteered to participate in the study. BP and anthropometric measurements including height, weight and WC were done. BMI was calculated as weight/hight^2 (kg/m^2). A fasting venous blood sample was taken to measure FBG, plasma TG, HDL, LDL and cholesterol. Lipid Accumulation Product (LAP) and Visceral Adiposity Index (VAI) were calculated.

Results Overweight and obese young adults had a significantly higher BP, higher LDL and lower HDL compared to normal weight subjects ((P=0.001), (P=0.005) and (P=0.0001), respectively. BMI showed highly significant positive correlation with BP (P=0.001) and LDL (P=0.005) and a highly significant negative correlation with HDL (P=0.001). WC associated positively with BP (P=0.0001) and negatively with HDL (P=0.0001).VAI and LAP showed a significant correlation with LDL (P=0.04) and a highly significant negative correlation with HDL (P=0.0001).

Conclusion Both BMI and WC are simple and cheap parameters which showed significant association with most of the markers of MetS in young adults. They can be used as predictors of MetS in young adults especially in communities with limited financial resources.

[*]***Correspondence to*** *nouralsalhin@gmail.com*

INTRODUCTION

Obesity especially visceral adiposity is a known risk factor for cardiovascular and metabolic complications.[1] Metabolic syndrome (MetS) is a clustering of risk factors including central obesity, insulin resistance, dyslipidemia and hypertension.[2] Individuals with these characteristics commonly manifest a pro-thrombotic and a pro-inflammatory state.[3] Patients with the MetS are at increased risk for developing atherosclerotic cardiovascular disease and type 2 diabetes mellitus.[4] Several definitions and clinical screening parameters have been proposed by various organizations to identify individuals with the MetS,[5] e.g. the World Health Organization (WHO), the International Diabetes Federation (IDF),[6] the American Heart Association/ National Heart, Lung, and Blood Institute. and the National Cholesterol Education Program–Adult Treatment Panel III (NCEP–ATPIII).[4] The most

commonly accepted is a recent consensus definition by the IDF. It includes abdominal obesity as a key, but not necessary component, elevations in serum triglyceride and glucose, increased blood pressure, and reduced levels of HDL cholesterol (HDL-C).[6] Several major organizations worked with IDF in an attempt to unify criteria (Table 1).[7] It was agreed that there should not be an obligatory component, but that waist measurement would continue to be a useful preliminary screening tool. Three abnormal findings out of five would qualify a person for the metabolic syndrome [6]

Table 1. Criteria for clinical diagnosis of the metabolic syndrome[7]

Measure	Categorical cut point
Elevated waist circumference [a]	≥ 102 cm in males ≥ 88 cm in females
Elevated triglycerides (drug treatment for elevated triglycerides is an alternate indicator [b])	≥ 150 mg/dL (1.7 mmol/L)
Reduced HDL-C (drug treatment for reduced HDL-C is an alternate indicator [b])	<40 mg/dL (1.0 mmol/L) in males <50 mg/dL(1.3mmol/L) in females
Elevated blood pressure (anti-hypertensive drug treatment in a patient with a history of hypertension is an alternate indicator)	Systolic ≥130 mmHg and/or diastolic ≥85 mmHg
Elevated fasting glucose [c] (drug treatment of elevated glucose is an alternate indicator)	≥ 100 mg/dL

HDL-C indicates high-density lipoprotein cholesterol.

[a] Waist circumference cut points used in the USA. Cut points for other populations are listed in the parent document.[6]

[b] The most commonly used drugs for elevated triglycerides and reduced HDL-C are fibrates and nicotinic acid. A patient taking one of these drugs can be presumed to have high triglycerides and low HDL-C. High-dose n-3 fatty acids presume high triglycerides.

[c] Most patients with type 2 diabetes mellitus will have the metabolic syndrome by the current criteria [6]

Yasir et al (2016) study in Sudanese university students showed that the prevalence of MetS among young adults was 16.6% as defined by NCEP-ATP III definition.[8] Obesity especially visceral adiposity is highly linked to the MetS risk factors. However, accurate measurements of visceral adiposity like magnetic resonance imaging, computed tomography and ultrasound are not usually available for most clinicians. In addition, the imaging techniques involved are expensive, may involve exposure to radiation and may need intensive training.[9] The methods used to define obesity differ between the various MetS definitions. The WHO panel defined the obesity component of MetS based on waist-hip ratio, or body mass index (BMI), while the IFD and NCEP-ATP III defined the obesity component of MetS by waist circumference (WC).[10] Amato et al (2010) modeled Visceral Adiposity Index (VAI) as a novel sex-specific index based on: WC, BMI, TG, and HDL. VAI is used as an indicator of visceral adipose function and was found to have a higher sensitivity and specificity than classical parameters such as WC and BMI.[11] VAI was found to be a valuable detector of insulin sensitivity and it showed strong positive association with all the components of MetS and cardio-metabolic risks [11] Therefore, VAI can be a good predictor of MetS in healthy young adults of both sex.[12]

Lipid Accumulation Product (LAP) is another index of obesity that estimates lipid over accumulation among adults; using a combination of WC and fasting TG.[13] LAP could be a reliable index in

early detection of MetS and cardiovascular diseases (CVD) in adults [14] and was found to be a better predictor for the incidence of CVD compared to BMI.[13] VAI, LAP and body adiposity index had a significant association with MetS independent of ethnic background and age[15] and they were effective screening markers for asymptomatic MetS in healthy adults aged 18 - 79 years.[16] Recently, Kavaric N et al (2018) reported that, LAP and VAI may not be better in evaluation of cardiometabolic risk in type 2 diabetes in comparison to the simple anthropometric indices and traditional lipid parameters.[17] VAI showed weaker although statistically significant correlations with objective ultrasound measurements of the thickness of visceral adipose tissue compared to WC,[18] WC and BMI were more accurate as markers of visceral adiposity in young adults than VAI and waist-hip ratio.[18]

Till now the obesity measure that is considered as a better indicator of MetS is still a matter of debate. There is a need to use simple affordable non-hazardous alternative indexes of visceral adiposity to substitute expensive imaging techniques. The aim of this study is to investigate the relation between BMI, WC, VAI and LAP as indicators of adiposity with markers of MetS, according to the definition of the International Diabetes Federation (IDF) [6] in young adults.

METHODS

This is a cross sectional descriptive analytical study carried out in the medical campus, University of Khartoum. One hundred and fifty healthy students aged between 18-25 years volunteered to participate in this study. Subjects with chronic health problems such as diabetes, hypertension, CVD, renal diseases and those who take medications that may affect the BP, plasma lipid or glucose were excluded. Smokers and alcohol consumer, pregnant women or those with history of amenorrhea were also excluded. This study was approved by the Ethical Committee of Faculty of Medicine, University of Khartoum. After explaining the purpose and method of study, each subject signed written informed consent and completed a questionnaire containing personal and medical history. Subjects attended early morning to the Physiology Department Laboratory (lab) after overnight fast for 10-12 hours. The following measurements were done:

- Anthropometric measurements including weight, height and WC were done by the investigator herself. The height (in cm) and weight (in Kg) of the participant were measured using a balance beam scale with a height rod (RGZ-120, China), with the subject standing wearing light clothes with bare feet and putting heals together. BMI (Kg/m^2) was calculated by dividing the weight (Kg) by the height in squared meters. WC (in cm) was measured by placing a flexible plastic, non-elastic measuring tape comfortably without compressing the skin around the exposed abdomen at a level midway between the lowest rib and the iliac crest with the subject standing on both feet and both arms hanging freely. Measurement was done at the end of normal expiration to the nearest 0.1 cm.[19]

- Arterial BP was measured by the same investigator for all participants at 8 o'clock in the morning using mercury sphygmomanometer (Mercurial Sphygmomanometer Desk Model, China) according to standardized method.[20] A larger cuff was used for obese subjects. Participants were first asked to relax for 5 minutes in a cool quiet room. The subject sat upright with uncrossed legs and the upper arm was positioned to be at the level of the heart. The systolic blood pressure (SBP) was defined as the appearance of the first sound (Korotkoff phase 1); and the diastolic blood pressure (DBP) was defined as the disappearance of the sound (Korotkoff phase 5).[20] Two measurements were recorded with at least two minutes interval between them and the mean of the two measurements was taken for statistical analysis.

- Venous blood sample was taken under aseptic condition from each participant by a qualified lab technician and the plasma was separated. Within less than one hour from the time of

collection the following investigations were done: fasting blood glucose (FBG) (mg/dl) was measured using enzymatic and colorimetric glucose oxidase method (Biosystems SA, Spain). Plasma cholesterol, HDL and LDL (mg/dl) were measure by spectrophotometer (Biosystems SA, Spain). TG (mg/dl) was measured by enzymatic colorimetric method (Spectrum, Egyptian Company for Biotechnology).

Lipid Accumulation Product (LAP) was calculated (in cm. mmol/L) by the following equations:

LAP for males = (WC [cm] - 65) × (TG concentration [m mol/L]).

LAP for females = (WC [cm] - 58) × (TG concentration [m mol/L]).[13]

Visceral Adiposity Index (VAI) was calculated for each participant by the following equations:

In males: VAI = [WC/ (39.68 + (1.88 × BMI)] × (TG/1.03) × (1.31/HDL).

In females: VAI= [WC/ (36.58+ (1.89×BMI)] × (TG/0.81) × (1.52 /HDL).[21]

Statistical analysis Results obtained were analysed using the Statistical Package Program for Social Sciences (SPSS) version 23. Comparison of means of markers of metabolic syndrome and means of adiposity measures between the three BMI groups was done using ANOVA test and P value <0.05 is considered significant. Correlations of adiposity measures with markers of metabolic syndrome were done using Spearman correlation.

RESULTS

One hundred and fifty young adult subjects were included in this study. Males constituted 44% (n=66) and females 56% (n=84). Their age ranged between 17- 25 years, and the mean age was 19.5±1.8. In this group of young adults BMI ranged between 18.4 - 39.8 Kg/m^2. Subjects were divided according to WHO classification into three BMI groups: normal weight with BMI = 18.5-24.99 kg/m2 (n=51), overweight with BMI = 25-29.99 kg/m2 (n=49) and obese group with BMI ≥30 kg/m2 (n=50).[22] In this study 13 subjects (8.7%) had MetS according to IDF criteria, 11 were obese and 2 were overweight.

Comparisons of markers of metabolic syndrome between the three BMI groups:

Markers of metabolic syndrome used in this study are those adopted by the International Diabetes Federation (IDF).[6] Results of this study showed that overweight and obese young adults had a significantly higher BP compared to normal weight subjects (P=0.001) (Table 2). Comparison of the means of lipid profile between the three groups, showed that overweight and obese groups had a higher LDL and lower HDL than normal weight group and the difference was statistically highly significant (P=0.005) and (P=0.0001), respectively. However, there was no significant difference in FBG, plasma cholesterol and TG between the three BMI groups (Table 2).

Table 2. Comparison of means of markers of metabolic syndrome between the three body mass index groups

Variable	Normal weight (n=51) (mean ± SD)	Overweight (n=49) (mean ± SD)	Obese (n=50) (mean ± SD)	P- Value
Systolic blood pressure	105.8±8.8	112.4±9.3	115.2±9.0	0.001**
Diastolic blood pressure	70.2±6.6	75.1±7.9	77.4±5.9	0.001**
Fasting blood glucose	92.8±7.7	88.9±11.9	89.4±12.4	0.14
Cholesterol	156.5±25.5	149.8±24.8	156.2±27.3	0.355
Triglyceride	77.3±17.8	74.2±21.3	81.1±23.7	0.27
Low density lipoprotein	62.4±18.9	77.2±28.9	79.8±34.6	0.005**
High density lipoprotein	79.4±16.2	32.9±7.8	35.9±8.2	0.0001**

* P value ≤ 0.05 is significant, ** P value ≤0.005 is highly significant. SD= standard deviation

Correlation of BMI with the measures of central adiposity showed that BMI had a highly significant positive correlation with the WC (P=0.0001), VAI (P=0.0001) and LAP (P=0.0001). Table 3 shows comparison of the means of measures of adiposity between the three BMI groups.

Table 3. Comparison of means of adiposity measures between the three body mass index groups

Variable	Normal weight n=51 (mean ± SD)	Overweight n=49 (mean ± SD)	Obese n=50 (mean ± SD)	P- Value
Waist circumference	74.3± 6.2	87.4±7.7	101.8± 10.6	0.0001**
Visceral adiposity index	.85±1.2	1.6±.74	1.7±.85	0.0001**
Lipid accumulation product	12.0±6.9	22.2±8.9	37.7±14.3	0.0001**

* P value ≤0.05 is significant, ** P value ≤0.005 is highly significant. SD=standard deviation

Correlation of obesity markers with selected markers of metabolic syndrome

are shown in Table 4. BMI, WC and LAP showed a highly significant positive correlation with: SBP (P=0.0001), DBP (P=0.0001) (Table 4). VAI showed significant positive correlation with: SBP (P=0.03) and DBP (P=0.04).

The correlation between BMI and lipid profile, showed that BMI had a highly significant negative association with HDL (P=0.0001) and a significant positive association with LDL (P=0.008). However, there was insignificant association between BMI with TG and cholesterol. WC associated positively with BP (P=0.0001) and negatively with HDL (P=0.0001). VAI and LAP showed highly significant positive correlation with TG (P=0.0001), significant correlation with LDL (P=0.04) and a highly significant negative correlation with HDL (P=0.0001).The correlations of BMI, WC, VAI and LAP with FBG were statistically insignificant (Table 4).

Table 4. Correlation of obesity markers with selected markers of metabolic syndrome

	Systolic blood pressure	Diastolic blood pressure	Fasting blood glucose	Cholesterol	TG	Low density lipoprotein	HDL
Body mass index	.448**	.450**	-.073	-.017	.067	.214**	-.585**
	.000	.000	.376	.834	.414	.008	.000
Waist circumference	.447**	.416**	-.089	-.064	.090	.155	-.515**
	.000	.000	.277	.437	.273	.059	.000
Visceral adiposity index	.180*	.168*	-.074	-.029	.424**	.163*	-.736**
	.03	.040	.367	.723	.000	.046	.000
Lipid accumulation product	.318**	.288**	-.072	-.012	.498**	.164*	-.400**
	.000	.000	.382	.882	.000	.045	.000

*P<0.05 is significant, **P<0.005 is highly significant. TG= Triglyceride HDL= High density lipoprotein

DISCUSSION

In this study adiposity measures including BMI, WC, VAI and LAP showed positive association with BP. Moreover, overweight and obese young adults had a significantly higher BP compared to normal weight subjects. The association of BMI with increased BP has been reported by a number of studies in children[23] and adults.[24-27] It has been found that subjects who gained weight in adulthood and those who remained obese from adolescence to young adulthood have increased

risk of hypertension (HTN).[26] The link between obesity and high BP was proposed to be through mechanisms that lead to increased sympathetic nervous system activity and/or via increased sodium retention by the kidneys.[25] Other suggested mechanisms for high BP in obese subjects include insulin resistance and hyperinsulinaemia,[28] higher levels of angiotensinogen and increased activity of the renin–angiotensin–aldosterone system[29] and leptin resistance.[30] In addition, excess adipose tissue produces high levels of free fatty acids (FFAs) which can increase the BP by increasing insulin resistance, sympathetic activity and oxidative stress. [25]

Body mass index is a common measure of weight status in most epidemiological studies.[10] However, its limited ability to discriminate between fat and lean body mass argue its efficiency in estimating the risk of obesity-related diseases.[10,13] Results of this study showed a significant difference in the means of adiposity markers between the three BMI groups. The correlations of BMI with the measures of central adiposity showed that BMI had a highly significant positive correlation with the WC, VAI and LAP. This indicates that BMI could be an acceptable measure of adiposity that can be used even in young adults. Comparable results were reported by Chakraborty et al (2007) who found that the specificity of detecting the obesity component of MetS by BMI alone is almost 100%, but the sensitivity of BMI is low.[10] They found that individuals with high BMI generally have large waist-hip ratio and wide WC, but the converse is not necessarily true. They concluded that central obesity is not always captured by a high BMI alone.[10] However, Yang et al (2008) showed that baseline BMI and age were the most significant predictors of MetS for both men and women.[31] It has been found that the mortality risk was higher in underweight and severely obese subject compared to normal or overweight ones.[32] Moreover, it has been found that WC and BMI were very highly correlated and can be considered similar in diabetes prediction[33] and have equally strong association with cardiovascular risks.[34] We found that BMI, had a highly significant positive correlation with: BP and a highly significant negative association with HDL (P=0.0001) and a significant positive association with LDL. Overweight and obese young adults had a significantly higher BP, higher LDL and lower HDL compared to normal weight subjects ((P=0.001), (P= 0.005) and (P= 0.0001), respectively). These findings are comparable to the results of Schuster et al (2014) study on young adults. They found a significant association between BMI with all the components of the metabolic syndrome, FBG, SBP, DBP, LDL and low HDL, in females and with DBP, TG and FBG in males.[12] Subjects with high BMI (overweight and obese subjects) were more likely to have HTN, dyslipidemia, and the MetS than normal-weight subjects.[24]

In this study WC, like BMI, showed a highly significant positive correlation with BP and negative correlation with HDL. WC measurement is an easy and cheap clinical parameter used for indirect evaluation of visceral fat. Zazai et al (2014) reported that WC is a valuable index of abdominal/visceral obesity in severely obese subjects (BMI>35 kg/m2). In their study WC was found to be associated with many metabolic variables independent of BMI.[35] Moreover, some studies suggested that WC may be superior to BMI as indicator of adiposity.[24,36,37] Abdulbari et al (2013) study on adult Qatari population found that WC at a cut-off point of 99.5 cm among men and 91 cm among women is a better predictor of MetS than BMI.[37] Another study done by Taylor et al (2011) showed that WC may identify those who have cardiometabolic disease risk factors despite being normal or overweight by BMI.[37] However, other studies reported that WC alone does not help in distinguishing between subcutaneous and visceral fat mass.[37,38] In addition, WC is age and gender as well as ethnicity dependent.[38] We suggest that both BMI and WC are good measures of obesity and obesity related complications. Similar results were reported by Borruel et al (2014); who found that WC and BMI were the most accurate surrogate markers of visceral adiposity in young adults.[18] In addition, Hou et al (2015) concluded that the combination of WC and BMI measures

was superior to the separate indices in identifying cardiometabolic and cardiovascular disease risk in Chinese adults [39]

In the present study VAI and LAP, like BMI and WC, showed positive association with BP and a highly significant positive correlation with TG (P=0.0001), significant correlation with LDL (P=0.04) and a highly significant negative correlation with HDL (P=0.0001). However, TG is one of the components of the formula for calculating VAI and LAP. Therefore, we considered its correlation with TG is a consequence of the calculation. A study done on Gujarati Asian Indians healthy adults aged 18–79 years concluded that VAI, LAP, and triglyceride/ high-density lipoprotein cholesterol (TG/HDL-C) ratio could be effectively used as a single surrogate marker for screening of asymptomatic subjects with MetS.[40] They found that the diagnostic accuracy of these markers was unaffected by age and gender of the individuals.[40] Guo et al (2016) reported a significant association between LAP and MetS, independent of ethnic background and age.[15] Another study done on adult males and females aged 18-65 years stated that LAP could be a reliable index in early detection of MetS and CVD. [14]

CONCLUSIONS

Obesity especially visceral adiposity is a known risk factor for cardiovascular and metabolic complications.[1] WC and BMI are simple, cheap measures of adiposity that are commonly used in clinical practice and were found to be as good as VAI and LAP. Therefore, they can be used as alternatives to the other biochemical or expensive adiposity markers. Both BMI and WC showed association with some markers of MetS in young adults and can be considered as predictors of MetS especially in communities with limited financial resources.

REFERENCES

1. Björntorp P. Visceral obesity: a "civilization syndrome". *Obesity Research* 1993;1:206-22.

2. Alberti KGM, Zimmet P, Shaw J. The metabolic syndrome - a new worldwide definition. *The Lancet* 2005;366:1059-62.

3. Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/ National Heart, Lung, and Blood Institute scientific statement. *Circulation* 2005;112:2735-52.

4. National CEPN. Third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III) final report. *Circulation* 2002;106:3143.

5. O'neill S, O'driscoll L. Metabolic syndrome: a closer look at the growing epidemic and its associated pathologies. *Obesity Reviews* 2015;16:1-12.

6. Alberti K, Eckel RH, Grundy SM, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention, National Heart, Lung and Blood Institute; American Heart Association, World Heart Federation, International Atherosclerosis Society, and International Association for the study of obesity. *Circulation* 2009;120:1640-5.

7. Grundy SM. Metabolic syndrome update. *Trends in Cardiovascular Medicine* 2016;26:364-73.

8. Yasir H, Tahir O, Leena B, Imam S. Metabolic syndrome and its association with obesity and lifestyle factors in Sudanese population. *Diabetes and Metabolic Syndrome* 2016;10:128-31.

9. Shuster A, Patlas M, Pinthus J, Mourtzakis M. The clinical importance of visceral adiposity: a critical review of methods for visceral adipose tissue analysis. *The British Journal of Radiology* 2012;85:1-10.

10. M Chakraborty B, Chakraborty R. Sensitivity and specificity of body mass index as a definition of the obesity component of metabolic syndrome. *Collegium Antropologicum* 2007;31:943-7.

11. Amato 1MC, Giordano C, Galia M, et al. Visceral Adiposity Index: a reliable indicator of visceral fat function associated with cardiometabolic risk. *Diabetes Care* 2010;33:920-2.

12. Schuster J, Vogel P, Eckhardt C, Morelo SDB. Applicability of the visceral adiposity index (VAI) in predicting components of metabolic syndrome in young adults. *Nutricion Hospitalaria* 2014;30:806-12.

13. Kahn HS. The "lipid accumulation product" performs better than the body mass index for recognizing cardiovascular risk: a population-based comparison. *BMC Cardiovascular Disorders* 2005;5:26.

14. Tellechea ML, Aranguren F, Martínez-Larrad MT, et al. Ability of lipid accumulation product to identify metabolic syndrome in healthy men from Buenos Aires. *Diabetes Care* 2009;32:e85-e

15. Guo S-x, Zhang X-h, Zhang J-y, et al. Visceral adiposity and anthropometric indicators as screening tools of metabolic syndrome among low income rural adults in Xinjiang. *Scientific Reports* 2016;6:36091.

16. Joshi H, Shah K, Patel P, et al. Novel indexes for diagnosing metabolic syndrome in apparently healthy Gujarati Asian Indians: a cross-sectional study. QJM: *An International Journal of Medicine* 2016;109:717-22.

17. Kavaric N, Klisic A, Ninic A. Are visceral adiposity index and lipid accumulation product reliable indices for metabolic disturbances in patients with type 2 diabetes mellitus? *Journal of Clinical Laboratory Analysis* 2018;32:e22283.

18. Borruel S, Moltó JF, Alpañés M, et al. Surrogate markers of visceral adiposity in young adults: waist circumference and body mass index are more accurate than waist hip ratio, model of adipose distribution and visceral adiposity index. *PloS One* 2014;9:e114112.

19. Consultation WE. Waist circumference and waist-hip ratio. Report of a WHO Expert Consultation Geneva: World Health Organization. 2008:8-11.

20. Thomas G. Pickering JEH, Lawrence J. et al Recommendations for blood pressure measurement in humans and experimental animals. AHA Scientific Statement. 2004.

21. Amato MC, Giordano C, Galia M, et al. Visceral Adiposity Index: a reliable indicator of visceral fat function associated with cardiometabolic risk. *Diabetes Care* 2010;33:920-2.

22. WHO. Obesity and overweight Geneva: http:// www. WHO. Int/mediacentre/ factsheets / fs340/en; 2014.

23. Flynn J. The changing face of paediatric hypertension in the era of the childhood obesity epidemic. *Paediatric Nephrology* 2013;28:1059-66.

24. Janssen I, Katzmarzyk PT, Ross R. Waist circumference and not body mass index explains obesity-related health risk. *The American Journal of Clinical Nutrition* 2004;79:379-84.

25. Papathanasiou G, Zerva E, Zacharis I,et al. Association of high blood pressure with body mass index, smoking and physical activity in healthy young adults. *The Open Cardiovascular Medicine Journal* 2015;9:5.

26. Suglia SF, Clark CJ, Gary-Webb TL. Adolescent obesity, change in weight status, and hypertension: racial/ethnic variations. *Hypertension* 2013;61:290-5

27. Frey F. Body-mass-index, blood pressure, and serum cholesterol in young Swiss men: an analysis on 56784 army conscripts. *Swiss Medical Weekly* 2009;139(3536).

28. Kim J-a, Montagnani M, Koh KK, Quon MJ. Reciprocal relationships between insulin resistance and endothelial dysfunction: molecular and pathophysiological mechanisms. *Circulation* 2006;113:1888-904.

29. Kalupahana NS, Massiera F, Quignard-Boulange A, et al. Overproduction of

angiotensinogen from adipose tissue induces adipose inflammation, glucose intolerance, and insulin resistance. *Obesity* 2012;20:48-56

30. da Silva AA, do Carmo JM, Hall JE. Role of leptin and CNS melanocortins in obesity hypertension. *Current Opinion in Nephrology and Hypertension* 2013;22:135

31. Yang F-Y, Wahlqvist ML, Lee M-S. Body mass index (BMI) as a major factor in the incidence of the metabolic syndrome and its constituents in unaffected Taiwanese from 1998 to 2002. *Asia Pacific Journal of Clinical Nutrition* 2008;17:339-51.

32. Flegal KM, Graubard BI, Williamson DF, Gail MH. Excess deaths associated with underweight, overweight, and obesity. *JAMA* 2005;293:1861-7.

33. Vazquez G, Duval S, Jacobs Jr DR, Silventoinen K. Comparison of body mass index, waist circumference, and waist/hip ratio in predicting incident diabetes: a meta-analysis. *Epidemiologic Reviews* 2007;29:115-28.

34. Kromhout D, Geleijnse JM, Boer JM, Verschuren WM. Body mass index and waist circumference predict both 10-year nonfatal and fatal cardiovascular disease risk: study conducted in 20 000 Dutch men and women aged 20–65 years. *European Journal of Cardiovascular Prevention & Rehabilitation* 2009;16:729-34

35. Zazai R, Wilms B, Ernst B, Thurnheer M, Schultes B. Waist circumference and related anthropometric indices are associated with metabolic traits in severely obese subjects. *Obesity Surgery* 2014;24:777-82.

36 Bener A, Yousafzai MT, Darwish S, Al-Hamaq AO, Nasralla EA, Abdul-Ghani M. Obesity index that better predict metabolic syndrome: body mass index, waist circumference, waist hip ratio, or waist height ratio. *Journal of Obesity* 2013;2013.

37. Taylor SA, Hergenroeder AC. Waist circumference predicts increased cardiometabolic risk in normal weight adolescent males. *International Journal of Paediatric Obesity* 2011;6:e307-11.

38. Després J-P, Lemieux I, Bergeron J, et al. Abdominal obesity and the metabolic syndrome: contribution to global cardiometabolic risk. *Arteriosclerosis, Thrombosis, and Vascular Biology* 2008;28:1039-49.

39. Hou X, Lu J, Weng J, et al. Impact of waist circumference and body mass index on risk of cardiometabolic disorder and cardiovascular disease in Chinese adults: a national diabetes and metabolic disorders survey. *PLoS One* 2013;8:e57319.

40. Taverna MJ, Martínez-Larrad MT, Frechtel GD, Serrano-Ríos M. Lipid accumulation product: a powerful marker of metabolic syndrome in healthy population. *European Journal of Endocrinology* 2011;164:559-67.

Quality of life among adolescents with epilepsy: An outpatient based study, Khartoum, Sudan

Sarah E.Mohamed,[1] Inaam N. Mohamed [2,3*]

[1]*Neurology Unit - Soba University Hospital, Khartoum, Sudan*

[2]*Neurology Division, Department of Paediatrics and Child Health, Faculty of Medicine, University of Khartoum, Khartoum, Sudan.*

[3]*Neurology Unit, Gafer Ibn Auf Specialized Hospital for Children, Khartoum, Sudan.*

ABSTRACT

Background The term "Quality of Life (QOL)" refers to the physical, psychological and social aspects of health. Several studies attempted to measure the QOL among epileptic patients using either generic or specific instruments. In adolescents the impact of epilepsy on life style and QOL is even more evident. The objective of this study is to measure the QOL and to identify the effect of gender, epilepsy classification, antiepileptic drugs (AEDs) and control of seizures on QOL in adolescent patients with epilepsy.

Methods This is a cross-sectional, observational study, conducted in outpatients at Gafer Ibn Auf Specialized Hospital and Soba University Hospital. Fifty patients were enrolled in the study and the QOL was measured using the tool Quality of Life in Epilepsy for Adolescents (QOLIE-AD-48). Data was analysed using statistical package for social sciences (SPSS).

Results The quality of Life total mean score for patients was 78.95±12.9. The highest mean score was for school behaviour domain (88.83±24.56) and the lowest score was for stigma (68.08±19.18). Males with epilepsy had higher score for QOL as compared to females. Patients in basic school had significantly higher total QOL score than those in high school. The total score for QOL is significantly lower in patients with generalized-motor-tonic-clonic seizures, non-compliance to AEDs, on polytherapy and those with partial response to treatment ($p < 0.05$).

Conclusion Epilepsy has impact on quality of life in adolescents with epilepsy especially in the stigma and attitude towards the disease domains. Psychological evaluation and intervention are of great value to help patients cope with their illness. Transitional clinic to take over the care of adolescent patients for easy transfer to adulthood care is recommended.

[*]***Correspondence to*** *inaamgashey@gmail.com, Inaam.gashey@uofk.edu*

INTRODUCTION

Quality of life (QOL) is a broad concept incorporating in a complex way the person's physical health, psychological state, level of independence, social relationships, personal beliefs and their relationship to salient features of the environment.[1] Paediatric epilepsy is a very complex neurological condition primarily characterized by unexpected, episodic, and chronic nature of seizures, as well as different developmental, psychological, behavioural, educational, and social difficulties. As such, paediatric epilepsy has pervasive impacts on all aspects of a child's life.[2] Many studies compared the impact of epilepsy and other chronic illnesses and almost all found that impact due to epilepsy is significantly more.[3] In adolescents the effect is even more, as adolescence is a time of significant transition in terms of biological changes, alteration in one's role and development of appropriate and healthy peer relationships.[4] The objective of this study is to measure the Quality Of Life (QOL) using the tool Quality of Life in Epilepsy for Adolescents (QOLIE-AD-48) and to identify the effect of

age, gender, epilepsy type, Anti- Epileptic Drugs (AEDs), control of seizures, on QOL in adolescent patients with epilepsy.

METHODS

This is a cross-sectional outpatient-based study, conducted at the neurology outpatient departments (OPD) at Gafer Ibn Auf Specialized Hospital for Children, Khartoum, and Soba University Hospital (The teaching hospital for Khartoum University). The clinics were carried out once per week, with a total number of 60-70 patients per week. Patients with confirmed diagnosis of epilepsy for a minimum of six months with no other chronic co-morbidities or impaired cognition and their age range 13 - 18 years were included. Fifty patients were enrolled in the study during the period of 6 months.

CASE DEFINITION

Epilepsy: A diagnosis of epilepsy in this study is retained if the patient had at least two or more epileptic seizures unprovoked by any immediate cause.[5]

Good response to AEDs: In this study good response referred to patients, who were free of seizures for the last six months,

Partial response to AEDs: In this study partial response referred to patients, who had history of seizure in the last six months,

Epilepsy Classification: For each patient, epilepsy was classified using the International League Against Epilepsy (ILAE) Commission on classification and terminology 2017 Report.[6] Factors considered in the classification included seizure type (s) based on descriptive semiology and personal interview, elector-encephalograph (EEG) and neuro-imaging findings.[5]

Investigations: The EEGs were done using the 10-20 system with photic stimulation and hyperventilation procedures done when indicated; none of the patients had undergone a video-telemetry EEG or an ambulatory EEG recording as these are unavailable in the study setting. The majority of patients (89%) had awake EEGs and very few EEGs were done whilst sleep or sleep deprived. The EEGs were interpreted and reported by an adult neurophysiologist.

Treatment: Treatment decisions were made by paediatric neurologists as per the international recommendations for the specific seizure type, taking into consideration the age of the patient, sex, tolerability, formulations, availability and affordability of AEDs in our setting. Other modalities of treatment e.g. ketogenic diet and epilepsy surgery are not available in Sudan. We tried at least two first-choice AEDs in monotherapy before using a polytherapy regimen.

Variables: Sex, age at onset of seizure, type of epilepsy, number of AEDs, epilepsy control and compliance.

Data analysis

Data analysis was performed using SPSS software version 23. The quantitative variables were presented as mean and standard deviation (SD). Qualitative variables were described in the form of frequency and percentage. Standard test of significance was used. P Value of <0.05 was considered significant.

Study tool

A designed questionnaire was completed by self–interview. It included demographic data, epilepsy classification, epilepsy treatment and variables that may affect the QOL such as age at onset of epilepsy, epilepsy type, seizures control, AEDs, polytherapy, compliance, parents' education, socioeconomic status and schooling.

Quality of Life in Epilepsy for Adolescents (QOLIE-AD-48). [7]

To measure the QOL we used the Quality of Life in Epilepsy for Adolescents (QOLIE-AD-48) questionnaire after taking permission from the Quality of Life International Epilepsy (QOLIE) Development Group. The QOLIE-AD-48 was developed in 1999 under the guidance of a panel of seven experts in the field (QOLIE-AD Advisory Group) and has been used in many studies in Nigeria, United Kingdom, Canada, USA and many other countries.[8] The questionnaire contains 48 items in 8 subscales: epilepsy impact (12 items), memory-concentration (10 items), attitudes toward

epilepsy (4 items), physical functioning (5 items), stigma (6 items), social support (4 items), school behavior (4 items), health perceptions (3 items), and total summary score. The total summary score was calculated and transformed linearly into scales of 1-100 points, using the scoring manual for QOLIE-AD-48. A higher value represents better functioning and wellbeing. The health-related quality of life scores was presented as mean and SD.

Ethical Approval

Ethical approval was obtained from the Ethical Committee, Sudan Medical Specialization Board. Permission was granted from the two hospitals concerned and a written consent was taken from the caregiver and/or patient, after explanation of the study purpose in simple Arabic language.

RESULTS

Fifty patients with epilepsy were enrolled in the study. The mean age was 13.63±2.35 years. Twenty-eight (56.0%) were males and 22(44.0%) were females with a male to female ratio of 1.3:1. Forty (80.0%) patients were in basic main stream school, seven (14.0%) high school and three (6.0%) patients were off school because of their illness. Eleven (14.0%) patients had first attack of seizure after the age of 10 years, 12 (24.0%) between 5-10 years, 17 (34.0%) between 1-5 years and 10 (20.0%) at less than one year of age.

Epilepsy was classified according to the International League against Epilepsy (ILAE-2017) classification. Twenty seven (54.0 %) patients had generalized motor seizures, eight (16.0%) focal motor with impaired awareness, six (12.5%) focal motor with intact awareness, five (10.0%) focal non motor with intact awareness, two (4.0%) had generalized non motor seizures, one (2.0%) focal non motor with impaired awareness and one (2.0 %) patient had unknown onset type of seizure (Table 1).

Mono-therapy was prescribed for 28(56.0%) patients, while 12 (24.0%) were on two antiepileptic drugs (AEDs) and 10 (20.0%) patients on three AEDs. Forty-five (90.0%) patients had good compliance to treatment, while five (10.0%) were non-compliant. Thirty-six (72.0%) patients showed good response to AEDs and 14 (28.0 %) patients showed partial response to AEDs.

Quality of Life total mean score for patients was 78.95± 12.9. The highest subscale mean score was for school behavior domain, which was 88.83±24.56 followed by physical functioning (87.70±20.24), health perception (82.35±19.19), epilepsy impact (82.53±20.04), social support (80.38±31.89), memory and concentration (80.58±17.71), attitude towards epilepsy (70.50±27.47) and the lowest score was for stigma (68.08±19.18). This difference is found to be statistically significant (P =0.0001) (Table 2).

Males with epilepsy had higher score for QOL in physical functions, attitude and health perception domains as compared to females ($p < 0.05$), although females had higher scores in social support domain; this difference was not of statistical significance. There is no difference between males and females in the epilepsy impact, memory concentration and school behavior domains (Figure). Overall, males with epilepsy had higher QOL total scores than females; the mean total score for males was 85.6 and 78.2 for females. Using t-test these differences were found to be statistically significant ($p < 0.05$). Patients in basic (primary) school had significantly higher total score QOL than those in higher school ($p < 0.05$). Using non-parametric test – independent samples - the total score for QOL is significantly lower in patients with generalized-motor-tonic clonic seizures, non-compliance to AEDs, on polytherapy and had partial response to treatment ($p < 0.05$). There was no significant effect of age at epilepsy onset on total score for QOL ($p > 0.05$).

Table 1. Classification of epilepsy among adolescent with epilepsy (n=50)

	Focal Onset	Number (%)	Generalized onset	Number (%)
Seizures classification	**A. Focal Motor**		**A. Motor onset**	
	1. Aware	6(12.0)	1. Tonic Clonic	20(40.0)
	2. Impaired Awareness	8(16.0)		
	B. Focal Non-Motor		**B. Non-Motor Onset**	
	1. Aware	5(10.5)	1. Atypical Absence	1(2.0)
	2. Impaired Awareness	1(2.0)	2. Myoclonic	1(2.0)
	Focal to bilateral tonic clonic	5(10.5)		
	Unknown Motor –Tonic Clonic	2(4.0)		
	Unclassified	1(2.0)		

Table 2. The Mean and Standard Deviation of Quality of Life Domains (QOL) (n=50)

QOL Domains	Mean Score	Standard Deviation	Skewness
1- School Behaviour	88.83	24.2	-3.1
2- Physical Functions	87.70	20.2	-1.7
3- Epilepsy Impact	82.52	20.0	-1.2
4- Health Perception	82.34	19.1	-1.3
5- Memory Concentration	80.58	17.7	-.93
6- Social Support	80.37	31.8	-1.4
7- Attitude towards epilepsy	70.49	27.4	-.91
8- Stigma	68.08	19.1	0.02
9- Total Score	78.95	12.9	-1.1

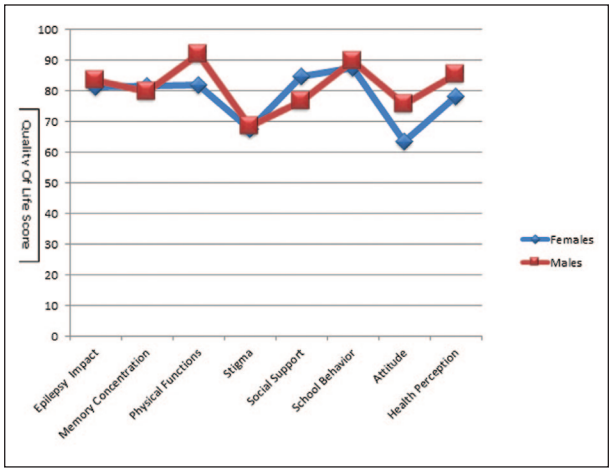


Figure. Comparison between male and female QOL total score (n=50) P =0.0001

DISCUSSION

Adolescence, the transition from childhood to adulthood, is a period marked by puberty, novelty seeking, sexual and social identification, and solidifying personality traits. In this turbulent and fragile life stage, a chronic medical disorder, such as epilepsy, can stigmatize, and impair independence, social functions, peer relations, self-esteem, mood, and cognition.[9-12] Epilepsy can significantly affect the quality of life (QOL) at this age not only because of its chronicity, need for regular medications, and their side effects, but also due to prejudices and social conventions that is still adherent to it.[13] The objectives of epilepsy management has focused on seizure control with minimal or no adverse medication effect, whereas the leading of normal life style and hence the importance of assessing QOL has not be addressed in similar weight. This is particularly true for Sudanese children, where the QOL is probably affected by the social stigma; usage of traditional and religious medicine and wrong believes that are still surrounding epilepsy in our communities.[13] Quality of Life in adolescents with epilepsy reflects their understanding of their disease, adaptation, acceptance of own selves, acceptance of their role and position in the community and it reflects their perception of wellbeing from their own respect.[14]

The concept of quality of life is difficult to define because of its multi-dimensional aspects and it is difficult to quantify. According to WHO the main domains of QOL are the physical domain, which includes independence in activities of daily living and symptoms of disease; the psychological domain, involving emotional, cognitive and behavioral status; and the social domain, how people perceive their role and relationship with other people.[15-16] Because many of the components of QOL cannot be observed directly, they are typically assessed according to classical principles of item-measurement theory.[17] Psychometric tools are used to explore each domain using group of questions. Full assessment of QOL issues in adolescent with epilepsy is complex, due to diversity in maturation, experience and independence in this age group. Inputs like aetiology, family history, position of the adolescent, family dynamics, society acceptance all plus any environmental, emotional or physical inputs contribute to the final QOL in this age group.

The present study showed that Sudanese adolescents with epilepsy had QOL score of 78.95±12.9 when assessed by a population-specific tool (QOLIE-AD-48). We found a few studies that corroborate with our results; one is the study of Wu et al who identified a high level of QOL of adolescents with epilepsy in China and a report by Natha´lia et al from Brazil.[18-19] In contrast to relatively low QOL reported from Egypt, Iran, India and Brazil.[20-22] The lowest scores were observed in stigma and attitude toward epilepsy domains (70.49+7.4) (68.08+19.1), respectively, which was similarly reported from Egypt by Mohammed et al[20] and Gunawan et al from Indonesia.[23] The stigma associated with epilepsy and the community perception of illness has a negative impact in QOL in adolescent with epilepsy as their seizures gave them the sense of insecurity, inequality, and hence isolation, restriction of capabilities and low expectations in life. The highest score was observed in school behaviour domain; this was also reported from India by Nagrathnam et al.[24]

In this study older adolescents (16-18 years) had lower QOL than younger ones (<16 years), and females had lower QOL than do males. This was similarly reported by Orrin Devinsky et al who stated that female adolescents had significantly

lower QOL. Older adolescents reported worse overall QOL than did their younger counterparts. Older adolescents were also more likely to perceive a greater negative impact on life and general health and had more negative attitudes toward epilepsy. Adolescent boys and girls may show different sensitivities to various quality-of-life domains.[25]

In this study patients at primary schools had higher scores for QOL than those in higher schools; this can be explained by the high peer pressure and difficult competitive environment among adolescents, but both have better QOL scores than those who quit the school at some point during their illness. Mohammed et al [20] and Natha´lia F et al [19] reported that the quality of life is better in educated compared to non-educated adolescents with epilepsy.

Patients on polytherapy had lower QOL when compared to patients on monotherapy, Abbas et al, [26] Nagarathnam et al [24] and Mohammed et al [20] correlated the poor QOL with polytherapy too. Patients with generalized tonic clonic seizures had poorer QOL when compared to other seizure types which was similarly reported in the literature.[27-29] As patients with generalized tonic clonic seizures experience injury, incontinence, fear and postictal stage; this might lead to more emotional distress than other types of epilepsy.

In this study patients with good-control epilepsy reported a high score on total QOL which was similar to other reports.[30-31] This is because seizure control could have its direct effect on psychological functioning and self-esteem; and a low level of distress and anxiety, as well as better adjustment to the disease.

The limitation of this study is that the results represent only the test population located in a particular geographical area - outpatient based, consisting of a medically and socially homogeneous population.

CONCLUSION

Poorer overall QOL on the QOLIE-AD-48 tool was predicted by age, sex, and generalized-motor-tonic clonic seizures, polytherapy and poor compliance to AEDs. These factors collectively suggest that specific features can identify adolescents at high risk for poor QOL among our population.

RECOMMENDATIONS

Epilepsy has an impact on quality of life in adolescents with epilepsy. Psychological evaluation and intervention by trained psychologists is of great value to help them cope with their illness. Transitional clinic to take over the care of adolescents with epilepsy for easy transfer to adulthood care is recommended. In such clinic a multidisciplinary team must be established and should involve paediatricians, neurologists, health educator nurses, psychologists, psychiatrists and social workers.

Acknowledgements. Our thanks to all patients who participated in this study and to their care-givers.

REFERENCES.

1. Stevanovic N, Tadic I. Health-related quality of life in children and adolescents with epilepsy: A systematic review, Epilepsy in children. *International Journal of Advanced Robotic System* 2011; 978:681-682.

2. Beilmann A, Napa A, Sööt A, Talvik I, Talvik T. Prevalence of childhood epilepsy in Estonia. *Epilepsia* 1999; 40:1011-9.

3. Hills MD. The psychological and social impact of epilepsy. *Neurology Asi*a 2007; 12:10-2.

4. Ronen Streiner GDL, Rosenbaum P. Health-related quality of life in childhood epilepsy: moving beyond seizure control with minimal adverse effects. *Health and Quality of Life Outcomes* 2003; 1:36.

5. Berg AT, Berkovic SF, Brodie MJ, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE commission on classification and terminology, 2005–2009. *Epilepsia* 2010; 51:676–685.

6. Fisher RS, Cross JH, French JA, et al. Operational classification of seizure types by

the International League against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology. *Epilepsia* 2017; 58:522-530.

7. Cramer JA, Westbrook L, Devinsky O, et al. Development of a quality of life inventory for adolescents: The QOLIE-AD-48. *Epilepsia* 1999; 40: 1114-1121.
8. Ferro MA, Avison WR, Karen Campbell M, Speechley KN. The impact of maternal depressive symptoms on health-related quality of life in children with epilepsy: A prospective study of family environment as mediators and moderators. *Epilepsia* 2011; 52:316-25.
9. Donnellan MB, Trzesniewski KH, Robins RW, Moffitt TE, Caspi A. Low self-esteem is related to aggression, antisocial behaviour and delinquency. *Psychological Science* 2005; 16:328-35.
10. Diehl M, Hay EL, Risk and resilience factors in coping with daily stress in adulthood: The role of age, self-concept incoherence, and personal control. *Developmental Psychology* 2010; 46:1132.
11. McEwen MJ, Espie CA, Metcalfe J, Brodie MJ, Wilson MT. Quality of life and psychosocial development in adolescents with epilepsy: a qualitative investigation using focus group methods. *Seizure* 2004; 13:15-31.
12. Ferro MA, Ferro AL, Boyle MH. A systematic review of self-concept in adolescents with epilepsy. *Journal of Paediatric Psychology* 2012; 37:945-58.
13. Inaam N Mohamed, Hyder Babeker. Traditional and spiritual medicine among Sudanese patients with epilepsy. *Sudanese Journal of Paediatrics* 2013; 13: 31-37.
14. Herodes M, Qun A, Haldre S, Kaasik AE. Epilepsy in Estonia: a quality-of-life study. *Epilepsia* 2001; 42:1061-73.
15. Hills MD. The psychological and social impact of epilepsy. *Neurology Asia* 2007; 12:10-2.
16. Spangenberg JJ, Lalkhen N. Children with epilepsy and their families: Psychosocial issues. *South African Family Practice* 2006; 48:60-3.
17. Frisen, A. Measuring health-related quality of life in adolescence. *Acta Paediatrica* 2007; 96: 963-968.
18. Wu D, Ding D, Wang Y, Hong Z. Quality of life and related factors in Chinese adolescents with active epilepsy. *Epilepsy Research* 2010; 90: 16–20.
19. Natha´lia F Siqueira, Fernando LBB. Oliveira Jorge A Siqueira, Elisabete Abib et al. Quality of Life in Epilepsy: A Study of Brazilian Adolescents. *Plos One* 2014; 9:e106879
20. Mohammad MS, Hemeida SA, Rabah AM. Health status and quality of life in epileptic children and adolescents. *Egypt J Neurol Psychiat Neurosurg* 2010; 47:83-92.
21. Zamani G, Shiva S, Mohammadi M, Gharaie JM, Rezaei N. A survey of quality of life in adolescents with epilepsy in Iran. *Epilepsy and Behaviour* 2014; 33:69-72.
22. Devinsky O, Westbrook L, Cramer J, et al. Risk factors for poor health-related quality of life in adolescents with epilepsy. *Epilepsia* 1999; 40:1715-20.
23. Gunawan P, Limanto T, Saharso D. Age decreases the quality of life in adolescents with intractable epilepsy correspondence. *Universa Medicina* 2015;34:104-111

24 Nagarathnam M, Shalini B, Vijayalakshmi V, Vengamma B, Latheef SA. Predictors of quality of life among adolescents with epilepsy in the state of Andhra Pradesh. *Neurology India* 2017; 65:1019.

25. Orrin Devinsky, Lauren Westbrook, Joyce Cramer, et al. Risk Factors for poor health-related quality of life in adolescents with epilepsy. *Epifepsia 1999*; 40: I715- 1720.

26. Abbas Z, Elseed MA, Mohammed IN. The quality of life among Sudanese children with epilepsy and their care givers. *Sudanese Journal of Paediatrics* 2014;14:51-9.

27. Leonardi M, Ustun T, The global burden of epilepsy. *Epilepsia* 2002;43:21-25

28, Sidenvall R, Forsgren L, Heijbel J. Prevalence and characteristics of epilepsy in children in northern Sweden. Seizure-European. *Journal of Epilepsy* 1996; 5:139-46.

29. Ziegler RG, Erba G, Holden L. Dennison H. The coordinated psychosocial and neurologic care of children with seizures and their families. *Epilepsia* 2000; 41:732-43.

30. Smith ML, Elliott IM, Lach L. Cognitive skills in children with intractable epilepsy: comparison of surgical and nonsurgical candidates. *Epilepsia* 2002; 43:631-7.

31. Høie B, Sommerfelt K, Waaler PE, et al. Psychosocial problems and seizure-related factors in children with epilepsy. *Developmental Medicine and Child Neurology* 2006; 48:213-9.

Laparoscopic appendicectomy in children: specimen coiling prevention using safe and simple technique to retrieve the appendix in a glove finger

Abdelbasit E. Ali,* Motaip H. Alrawili

Department of Paediatric Surgery, King Saud Medical City, Riyadh, Kingdom of Saudi Arabia

ABSTRACT

Background Removal of the appendix from the peritoneal cavity following laparoscopic appendicectomy (LA) can be challenging. Several techniques have been described to extract the appendix. The use of a glove finger to remove the appendix is well known, however, it may prove to be difficult due to coiling and clubbing of the appendix inside the glove finger at the exit site. Occasionally the glove finger is damaged during this procedure with a resultant wound soiling and potentially wound infection.

Objectives To enable easy retrieval of the appendix and avoid complications.

Methods The 3rd Endo-loop ligature - that is coming out with the appendix - is left long and grasped to facilitate keeping the appendix straight during its removal in the glove finger. The records of all the children who underwent LA using this modified technique in our department in the period between February 2017 and March 2020 were reviewed retrospectively.

Results In 48 cases out of 151 LA, the appendix was extracted using this technique. Their ages ranged between 2-13 years. Complications related to the technique were observed in three patients (6.25%), one patient had a slipped ligature and two patients had fragmented necrotic appendices.

Conclusion Leaving a long ligature on the specimen is a simple, safe, inexpensive, easy and effective technique to control, straighten and retrieve the appendix in a glove finger.

Correspondence to aliabdelbasit@hotmail.com, *abdulbasit.e@ksmc.med.sa*

INTRODUCTION

Laparoscopic Appendicectomy (LA) is one of the most commonly practiced procedures in children. Removal of the appendix from the peritoneal cavity following LA can be challenging and several techniques have been described for this purpose. The use of a commercially available specimen retrieval bag,[1,2] a glove finger[3,4] or a direct delivery of the grasped appendix through the port[5] is common practice. It is important to ensure safety and to minimise wound contamination during the procedure.[6]

The use of a glove finger to remove the appendix is well known, however, appendix retrieval by this method may be associated with difficulties, such as coiling of the appendix inside the glove finger (Figure 1a and`1b) and complications due to glove disruption and wound contamination.[1,3] Therefore, and to avoid such complications, there is a need to introduce modifications to improve the technique of appendix retrieval.

Objective To describe a modification to the glove finger technique to remove the appendix following laparoscopic appendicectomy in paediatric patients.

METHODS

The total number of children who underwent appendicectomy in our institution in the period between February 2017 and March 2020 was documented. Open appendicectomies were excluded and the records of all children who

underwent LA were reviewed retrospectively. Of this group, the study included all children who underwent laparoscopic appendicectomy using a modified technique in which, to retrieve the appendix, a glove's middle finger was used as a specimen bag while leaving a long appendicular ligature tail projecting out of the glove to help maintaining a straight appendix. An informed consent was obtained from parents.

The technique

Following the use of three Endo-loop ligatures to tie off the proximal end of the appendix (two placed at the base, and a 3rd one placed approximately 1cm further distal to the base), the technique involves leaving a long 3rd Endo-loop ligature tail (approximately 5 cm) mounted on the proximal end of the mobilized appendix.

Following appendicectomy between the basal, stump ligatures and that at the proximal end of the appendix, the specimen is inserted into a glove finger with the appendicular tip introduced first. The ligated proximal end of the appendix with the long thread would be close to the open end of the glove finger. The glove fingers, together with the projecting ligature tail, are controlled with a grasper that is applied transversely, sealing the walls close to the open end of the glove finger (Figure 2). Care must be exercised to avoid catching any appendicular tissue in the process. The graspers, with the controlled end of the glove finger, are pulled into the port before removing the port and the glove finger through the wound. This technique will ensure that the appendix will remain straight and prevent its coiling during the attempt of extraction (Figure 3).

When exteriorised, and if there is still difficulty to remove the glove finger and its content, the appendix can be controlled and retrieved from the glove finger by clipping and pulling the protruding free end of the ligature thread while the glove grasper is released. It is important to control the open edges of the glove finger with an artery clip before carefully releasing the Endo-grasper to avoid spillage of the glove finger contents into the wound.

RESULTS

Out of a total of 231 paediatric appendicectomy procedures carried out in our institution during the study period, we performed 151 laparoscopic appendicectomies, of which 48 were completed using this modified technique. Patients' ages ranged from 2 to 13 years. The appendix was extracted using this technique in all the 48 cases. Complications related to the technique were observed in three patients (6.25%), one patient had a slipped ligature and two patients had tissue avulsion of fragmented necrotic appendix (Table).

Table. Appendicectomy series in 38 Months (February 2017 – March 2020)

Observation	Numbers
Appendicectomy total No.	231
(Open + Laparoscopic)	F:M 1:1.15
Laparoscopic appendicectomy	151
	F:M 1.2:1
Median age (Range) in years	9 (2-13)
Technique under study applied in	48
	F:M 1.1:1
Complications	3 (6.25%)
- Slipped ligature	1
-Avulsed/Fragmented appendix	2

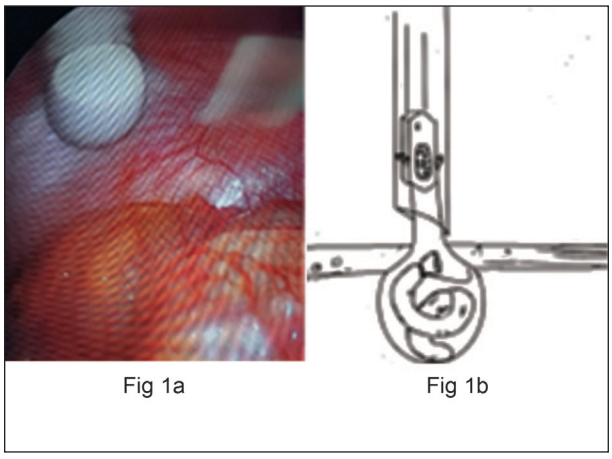


Figure 1a. and 1b. Appendix-delivery in a glove finger, the ball in the left upper part of the picture (1a) indicates that retrieval through the wound is obstructed by a coiling appendix inside the glove finger (1b).

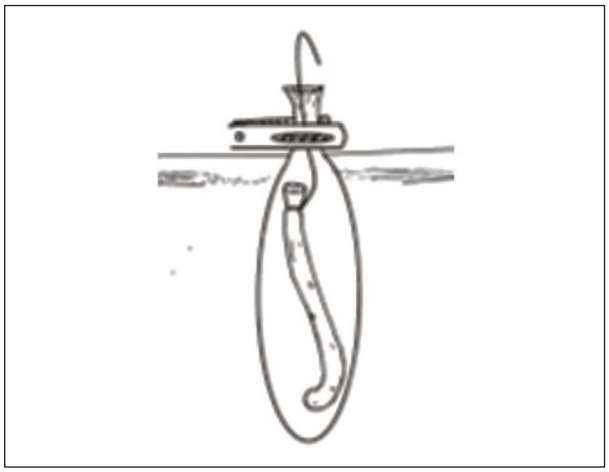


Figure. 2. Schematic representation of the technique of appendicular retrieval in a glove finger with a long ligature allowing control of a straight appendix to facilitate the removal step.

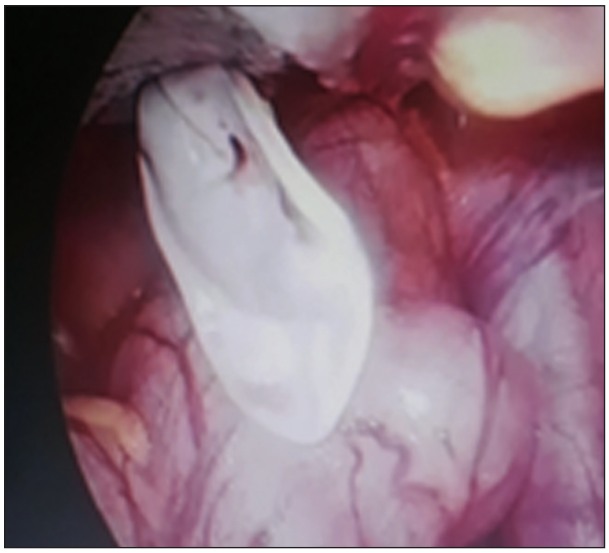


Figure. 3. Appendix delivery in a glove finger, easy retrieval is enabled by maintaining the appendix straight inside the glove finger.

DISCUSSION

Laparoscopic appendicectomy is a common surgical procedure in children. Several methods were described to facilitate removal of the specimen from the peritoneal cavity, and protect the retrieval site from exposure to the inflamed appendix during the procedure.[1,2,6,7] However, these techniques are attended with drawbacks including elevated costs, large surgical wounds and high contamination risks.[3]

The use of a glove finger to remove the appendix is well known.[3,4] It is available, cheap, safe and simple to use. However, removing the appendix in a glove finger (particularly when it is bulky or when using a small-sized port) may be associated with difficulty due to coiling and clubbing of the appendix inside the glove finger. Surgeons frequently struggle to deliver the appendix at this point in the operation. Widening the wound may be necessary for safe removal of an intact glove finger and its content, thus adding unnecessary and avoidable operative time. Occasionally the glove finger is damaged during this procedure with a resultant wound contamination and potential wound infection.

To avoid such complications, a modified technique which helps achieve a simple, safe and easy retrieval of the appendix is described in this study. When a tightly ligated Endo-loop ligature thread on the proximal end of the appendix is left projecting and grasped carefully within the glove finger, it ensures the appendix is kept straight during the course of extraction through the port or through the wound. By so doing, the procedure is conducted with least difficulty in appendix retrieval as it eliminates the specimen-delivery-obstruction that results from coiling of the appendix which frequently occurs has it been left uncontrolled inside the glove finger and, as such, it saves time frequently wasted in this step of the procedure. Perhaps this time gain can be measured in a further prospective study comparing this modified technique with other LA specimen retrieval techniques. Besides, the modified technique minimises the wound contamination that may result from any damage of the glove finger due to excessive manipulation during a difficult extraction.

We believe that there is an additional advantage in using this modified technique. Introducing the tip of the appendix first will reduce the glove finger edges exposure to the soiled appendicular lumen at the proximal end of the appendix which will result in contamination of the port inlet and, consequently, the wound. The technique is, however, not without potential complications.

Complications.

Proximally: Ligature slippage: to avoid slippage of the ligature from the appendix, the surgeon should: a) ensure leaving a stump. To achieve this, the appendix should not be cut very close to the ligature and b) ensure application of a tightly secured ligature. For the body of the appendix: integrity of the appendix is a factor of the degree of tissue necrosis. A friable necrotic appendicular avulsion, appendicular disruption or fragmentation can be avoided by gentle handling. The two cases in this study in which fragmentation of the appendix during retrieval took place, both had necrotic appendix that was attempted to be removed through a 5 mm-port-wound, but neither of them resulted in a spillage or wound contamination. No wound infection has been documented in this series.

For the distal end: when there is a clubbed appendix, or one that contains an impacted faecolith, wound extension around the port (not around an impacted glove finger) to obtain an adequate opening size is recommended. Alternatively, in the situation where maximum diameter of the appendix is identified preoperatively by imaging (ultrasound or CT scan), it is advisable to use an appropriate port size to facilitate a safe removal of the appendix.[8]

CONCLUSION

During laparoscopic appendicectomy, leaving a long ligature on the specimen is a simple, safe, inexpensive, easy and effective technique to control, straighten and retrieve the appendix in a glove finger. It reduces the retrieval time and minimises the risk of wound infection.

Acknowledgment. The authors would like to acknowledge Dr Muhammad Azhar for drawing the illustrations in Figures 1 and 2.

REFERENCES

1. Alder AC, Minkes RK. Paediatric appendicitis: treatment and management. www.medscape.com, updated: Oct 25, 2018. Cited March 31, 2020

2. Jain PK, Sedman P. Appendix retrieval after laparoscopic appendectomy: a safe and inexpensive technique. *Surg Laparosc Endosc Percutan Tech* 2003;13:322–324

3. Sagaon MM, Hamitaga F, Hurnilow Y. Appendix extraction after laparoscopic appendectomy in children: An easy, safe, and inexpensive technique. *Journal of Paediatric Surgery* 2016;51(2):341–343.

4. Nazir S, Bulanov A, Shanazarian M, Magruder JK. Glove-finger extraction technique for laparoscopic appendectomy:high-quality cost-conscious surgery. Society of the American Gastrointestinal and Endoscopic (SAGE) surgeons. 2016 Jan. www.sages.org/meetings.

5. Saad M. Fisherman's technique, introducing a novel method for using the umbilical port for removal of appendix during laparoscopic appendectomy. *Surg Laparosc Endosc Percutan Tech* 2007;17(5):422-4.

6. Fields AC, Lu P, Palenzuela DL, Bleday R, Goldberg JE, Irani J, et al. Does retrieval bag use during laparoscopic appendectomy reduce postoperative infection? *Surgery* 2019;165(5):953-957.

7. Mazziotti MV, Minkes RK. Paediatric appendectomy. www.medscape.com. Updated: Nov 12, 2015, Cited March 30, 2020.

8. Jung CY, Bae JM. Trocar size selection for trans-trocar appendix removal in laparoscopic appendectomy. *J Minim Invasive Surg* 2014;17(1):1-4 https://doi.org /10.7602 /jmis. 2014.17.1.1.

Incidence, indications, and risk factors of reopening after cardiac surgery in a tertiary cardiac centre, Sudan: Retrospective observational study

Fatimah Azhari Gasmalla Gadeltayeb,[1*] Elfatih M. Malik,[1] Elamin E. Elnur[2]

[1] *Faculty of Medicine, University of Khartoum, Khartoum, Sudan*

[2] *Faculty of Medicine, University of Bahri, Khartoum North, Sudan*

ABSTRACT

Background Chest re-opening after cardiac surgery is a surgical approach that is performed for diagnosing and managing some postoperative complications. The rate of reopening of patients undergoing cardiac surgery varies between 2% to 6%. The most frequent indication for reopening is bleeding after surgery, cardiac tamponade, cardiac arrest and redo surgery. Several risk factors have been associated with reopening including age, sex, body mass index (BMI), New York Heart Association NYHA class, diabetes mellitus, cardiopulmonary bypass and aortic cross clamp time. The aim of this study is to determine the incidence, indications, and risk factors of reopening after cardiac surgery.

Methods In this retrospective observational study, a total of consecutive 638 patients who underwent cardiac surgery in Ahmed Gasim cardiac centre in 2017 were included.

Results Thirty-nine out of the 638 surgeries done were reopened. The incidence of reopening was 61 per 1000 in all age groups: 90 per 1000 in adults, and 34 per 1000 in paediatrics. Among the 39 reopening cases, bleeding was the most frequent indication for reopening. Multivariate analysis by logistic regression revealed that having NYHA class II gave odds ratio (OR) = 24.767 (95% confidence interval (CI) = 1.048 – 585.3), previous cardiac surgery OR = 13.9 (95% CI = 1.013 – 193.3), having diabetes mellitus OR = 4.885 (95% CI = 1.251 – 19.056), longer cardiopulmonary bypass time OR = 1.012 (95% CI = 1.00 – 1.024), preoperative aspirin intake OR = 3.528 (95% CI = 1.062 – 11.720), and warfarin therapy OR = 12.790 (95% CI = 1.594 – 102.3).

Conclusion In Ahmed Gasim cardiac centre, the incidence of reopening after cardiac surgery was found to be relatively higher than the international records. Reopening was mostly performed for management of postoperative bleeding. Factors associated with increased risk of reopening included: cardiac failure assessed by NYHA classification, previous cardiac surgery, diabetes mellitus; anti-thrombotic therapy and longer bypass time.

[*]***Correspondence to*** *fatimah91.fa@gmail.com.*

BACKGROUND

Although open cardiac surgeries have a large impact on reducing the morbidity and mortality among people with cardiac disease, yet they have serious complications in both short and long term. Most of the short term complications of open cardiac surgeries are associated with the use of cardiopulmonary bypass machine, type of surgical intervention, and peri-operative medications .These complications include: postoperative arrhythmia, haemorrhage, cardiac tamponade and surgical wound infections.[1] Part of these complications may indicate early reopening of the chest in the first few days following cardiac surgery for diagnostic and therapeutic interventions.

Indications of reopening after cardiac surgery include: postoperative hemorrhage, tamponade, cardiac arrest, sternal osteomyelitis or mediastinitis,

sternal dehiscence, and redo-surgery.[2] Risk factors of reopening after cardiac surgery include: age, BMI, emergency operation, peri-operative anticoagulant, use of cardiopulmonary bypass machine, and bypass time.[3] Morbidity and mortality levels are high among patients undergoing reopening surgery compared to those undergoing only the primary cardiac operations. The mortality rate related to reopening is estimated to be as high as 43%, half of which happens during operation. The most frequent complication of reopening is stroke.[4]

There is no previously published data from Sudan investigating the incidence and indications of reopening after cardiac surgery. This study is expected to provide data about reopening in one of the biggest cardiac centres in Sudan.

METHODS

This study is a retrospective observational study conducted in the Centre of Cardiac Surgery and Kidney Transplantation in Ahmed Gasim Hospital, a tertiary hospital located in Bahri locality, Khartoum State, Sudan. Types of heart surgery performed in the centre included arterial grafts, valves replacement, vascular surgery and paediatric operations for congenital heart defects. All the cohort of consecutive open cardiac surgeries from January 2017 to January 2018 was included in the study. The data was collected from the hospital records.

Ethical approval was obtained from the Ethical Committee, Faculty of Medicine, University of Khartoum. Permission for data collection was obtained from Ahmed Gasim Hospital administration.

Statistical analysis

The data was analyzed using Statistical Package for Social Sciences (SPSS) version 20. Tests of normality for numeric data were performed and the data was normally distributed. Categorical data was expressed in frequencies and percentages, and numerical data as mean ± standard deviation (SD). Association between reopening and possible risk factors had been tested by univariate analysis using independent t test for comparing the means of numerical data. Chi square and Fisher's exact tests were used for categorical data. Multivariate analysis was conducted for further test of associations; using logistic regression possible risk factors were compared to reopening status. For all statistical tests, a p values at $\alpha < 0.05$ was regarded as statistically significant.

RESULTS:

Out of the total of consecutive 638 patients, 378 (59.2%) were males and 260 (40.8%) were females, with age range from 39 days to 81 years. The socio-demographic characteristics of the patients are listed in Table.1.

Table 1. Socio-demographic characteristics of patients in the study group

Criteria		Frequency	Percent
Age: (n=638)			
≥18 years		327	51.3
<18 years		311	48.7
Sex: (n=638)	Male	387	59.2
	Female	260	40.8
Occupation: adults (n=310)*			
Unemployed		172	55.5
Self-employed		98	31.6
Employees		40	13.0
Marital status: adults (n=301)*			
Single		35	14.4
Married		245	78.8
Divorced		3	0.8
Widowed		18	6.0

Residency (by State): (n=582)*		
- Blue Nile	106	18.2
- Darfur	22	3.8
- Kassala	61	10.5
- Khartoum	254	43.6
- Kurdofan	45	7.7
- Northern	94	16.2

*There is some missing information

Indications of reopening

The percentage and incidence of reopening in cardiac surgery patients in the study group is shown in Table 2. Bleeding was the most frequent indication of reopening, which occurred in 30 (77%) out of 39 patients who underwent reopening; followed by cardiac tamponade (n=4, 10%), cardiac arrest (n=4, 10%) and redo surgery in 2 (4%) patients

Table 2. Percentage and incidence of reopening in cardiac surgery patients in the study group

Age group	Total number of patients	Frequency of reopening	Percent of reopening	Incidence per 1000
All age groups	638	39	6.1	61
Paediatrics	327	11	3.4	34
Adults	311	28	9.0	90

Risk factors for reopening

Association between reopening and multiple factors was established using chi square test for categorical variable (Table 3) and independent t test (Table 4) for comparing the mean of continuous variables. A statistically significant p value of < 0.05 was estimated for analysis of age, NYHA classification, previous open cardiac surgery, type of cardiac surgery performed, diabetes mellitus, tuberculosis, previous myocardial infarction, preoperative exposure to aspirin and warfarin. Further testing of association was done by logistic regression for age, NYHA classification, type of the primary operation, previous open cardiac surgery, diabetes mellitus, hypertension, renal insufficiency, tuberculosis, previous myocardial infarction, cardiopulmonary bypass time, preoperative exposure to aspirin and warfarin. Logistic regression results are shown in Table 5.

Table 3. Baseline characteristics of cardiac surgery patients using chi square and Fisher's exact tests

Risk factor		Reopening		Parsons chi	P value
		Yes (n=39)	No (n=599)	Square/Fisher exact value	
Sex	Male	26	352	0.947	0.330
	Female	13	247		
NYHA	NYHA I	6	198	16.922	0.001*
classification	NYHA II	13	241		
	NYHA III	10	62		
	NYHA IV	2	3		
Priority of surgery	Elective	38	591	2.103	0.435
	Urgent	1	6		
	Emergency	0	2		

Past sternotomies	Yes	2	6	5.011	0.025*
	No	37	591		
Diabetes mellitus	Yes	13	118	4.579	0.039*
	No	25	480		
Hypertension	Yes	9	113	0.528	0.523
	No	29	485		
Renal insufficiency	Yes	1	2	4.016	0.169
	No	37	598		
Tuberculosis	Yes	2	2		
				13.888	0.019*
	No	36	596		
Previous MI	Yes	5	27	5.586	0.036*
	No	33	571		
Previous stroke	Yes	0	4	0.256	0.781
	No	38	594		
Aspirin	Yes	12	83	8.809	0.006*
	No	26	515		
Heparin	Yes	0	3	0.192	0.831
	No	38	595		
Warfarin	Yes	4	12	10.575	0.012*
	No	34	586		

*indicates statistically significant p value using Chi square or Fisher exact test at α <0.05 levels, MI=myocardial infarction, NYHA=New York Heart Association.

Table 4. Baseline characteristics of cardiac surgery patients using independent t test

Criteria	**Reopening Mean ± SD**		**P value**
	Yes	**No**	
Age (years)	45.2 ± ٢٤,٥٥	25.1 ± 25.85	0.001*
EF**	56.96 ± 11.33	59.19 ± 9.58	0.230
LVEDD**	8.6 ± 8.50	47.01 ± 10.77	0.472
CPB time	100.5 ± ٣٨,٠٣	99.6 ± 50.2	0.936
Aortic cross clamp time	74.2 ± 38.16	66.8 ± 43.03	0.396

*indicates statistically significant p value using independent t test at α <0.05 level,

** Variables measured for adult patients only. SD = Standard deviation,

EF = Ejection fraction, CPB = cardiopulmonary bypass, LVEDD = left ventricle end diastolic dimensions,

Table 5. Binary logistic regression (B) of reopening and potential risk factors in the study group

	B	Standard Error	Wald	Df	P value	Exp(B)	95% CI for Exp(B)	
							lower	Upper
Bypass time	0.012	0.006	3.653	1	0.056	1.012	1.000	1.024
NYHA			8.987	3	0.029			
NYHA I	2.042	1.485	1.890	1	0.169	7.704	0.419	141.572
NYHA II	3.209	1.614	3.956	1	0.047*	24.767	1.048	585.336
NYHA III	0.953	1.529	0.388	1	0.533	2.592	0.129	51.902
Age	0.010	0.016	0.396	1	0.529	0.990	0.961	1.021
Previous surgery	2.639	1.340	3.879	1	0.049*	13.993	1.013	193.339
Diabetes mellitus	1.586	0.695	5.211	1	0.022*	4.885	1.251	19.065
Hypertension	0.665	0.738	0.811	1	0.368	1.944	0.457	8.268
Renal Insufficiency	24.48	40192.933	0.000	1	1.000	3205041629.000	0.000	
Tuberculosis	23.98	26311.147	0.000	1	0.999	26000595672.779	0.000	.
Previous acute MI	0.06	0.896	0.002	1	0.968	1.037	179	6.002
Aspirin	1.261	0.613	4.235	1	0.040*	3.528	1.062	11.720
Warfarin	2.549	1.062	5.754	1	0.016*	12.790	1.594	102.630

*Indicates statistically significant p value using binary logistic regression at $\alpha < 0.05$ level.
Df = degree of freedom, MI=myocardial infarction, NYHA= New York Heart Association

DISCUSSION

In this study, the incidence of reopening after cardiac surgery was found to be 61/1000 or 6.1% for all age groups, which is approximating the incidence of 5.6% estimated in a similar Nigerian study that also included all age groups from 1 month to 52 years.[5] Among adult patients we found an incidence of 90/1000 or 9% which is much higher than that reported in almost all of the reviewed literature, in which incidence rate varied from 2% to 6%.[6-8] Variation in incidence may be due to several factors such as patients' age, co-morbidities, pre-surgery and intra-surgery anticoagulation therapy, surgical techniques and individual surgical skills of surgeon.

Although paediatric cardiac surgeries are more associated with postoperative morbidity and mortality than in adults, our finding of incidence of reopening in paediatrics of 3.4% are lower than incidence in adults but are comparable with the finding of many other paediatrics studies; an incidence of 3.9% was reported from a similar Indonesian study.[8] However, a higher reopening incidence of 5.1% was estimated among paediatric patients who underwent cardiac surgery with cardiopulmonary bypass and 7.4% among patients without cardiopulmonary bypass.[9] Less anti-thrombotic administration among paediatrics compared to adults may be a possible explanation of the lower incidence of reopening among paediatrics; as anti-thrombotic therapy is associated with increase in the risk of reopening after cardiac surgery.

In this study, the most frequent indication of

reopening was postoperative bleeding in 79%, followed by cardiac tamponade (10%), cardiac arrest (10%), and redo-surgery in 2.5% of patients. These findings are comparable with similar study where bleeding was the indication of reopening in 70.4% of cases followed by cardiac tamponade in 23% and both bleeding and tamponade in 5.9% of cases.[7] A higher finding was reported in another study in which bleeding was the indication in 92.8% of cases.[6]

Regarding risk factors for reopening, the findings of this study were consistent with the findings reported elsewhere. Cardiopulmonary bypass was found to be significantly associated with increased risk of reopening in many studies.[6,7,11,12] This finding may be explained by the fact that cardiopulmonary bypass affect the platelets and haemostasis, which increases the risk of bleeding which is the main indication of reopening.[13] Past history of cardiac surgery leading to mediastinal fibrosis that may advance around the great vessels increases the risk of blood vessels injury in subsequent cardiac surgeries. Our findings of association between previous cardiac surgeries and reopening is also reported in many other studies.[6,14]

As NYHA classification is used for clinical categorization of heart failure, it is usually higher in patients with high surgical risk.[6] In this study, the multivariate analysis finding of significant association between NYHA classes and increased risk of reopening after cardiac surgery was consistent with a results of a similar study that aimed to identify the risk factor of massive bleeding and subsequent reopening risk.[15] However, these findings are in disagreement with other studies where no significant association was found between NYHA class II-IV and risk of reopening after cardiac surgery.[6,13,16,17]

Preoperative administration of anti-thrombotic agents, specifically aspirin and warfarin, significantly increases the risk of reopening after cardiac surgery as they both increase bleeding risk and subsequent need of re-exploration. This association was also found in many other studies.[18,19] Diabetes mellitus was also found to increase the risk of reopening after cardiac surgery in similar study and that is consistent with our findings.[8]

Limitations:

Because our findings reflect routine clinical practice at only one single institution, this study carries the possibility of biases in patient, surgeon, or centre selection, as well as in the reopening decision. The use of multiple statistical tests increased the probability that associations might have been due to chance alone.

The retrospective feature of the study resulted in some missing information during data collection; a future conduction of similar prospective study will be more beneficial.

CONCLUSIONS

In this study, the overall incidence of reopening estimated from a single institutional experience was found to be consistent with what had been reported previously by others, but incidence in adults was higher than what had been provided by most of the reviewed literature. Bleeding was found to be the most frequent indication of reopening. This study re-emphasizes the known pre- and intra-operative risk factors or reopening after cardiac surgery. Cardiac failure assessed by NYHA classification, previous cardiac surgery and longer bypass time were significantly associated with increased risk of reopening.

Acknowledgements

We acknowledge the help of Mr. Sulman from Ahmed Gasim Hospital for his help in medical record search, and also the help of El-Awab, Lamis, and Amjad in some parts of data collection and for their support throughout this work.

REFERENCES

1. Williams NS, Bulstrode CJK, O'Connell PR. Bailey and Love's Short Practice of Surgery London:Crc Press; 2008.
2. Cheng DCH, David TE. Perioperative care in cardiac anaesthesia and surgery. Pennsylvania,:Lippincott Williams & Wilkins; 2006.

3. Karthik S, Grayson AD, McCarron EE, Pullan DM, Desmond MJ. Re-exploration for bleeding after coronary artery bypass surgery: risk factors, outcomes, and the effect of time delay. *The Annals of Thoracic Surgery* 2004;78(2):527-34.

4. Unsworth-White MJ, Herriot A, Valencia O, et al. Re-sternotomy for bleeding after cardiac operation: a marker for increased morbidity and mortality. *The Annals of Thoracic Surge*ry 1995;59(3):664-7.

5. Falase B, Sanusi M, Majekodunmi A, Ajose I, Idowu A, Oke D. The cost of open heart surgery in Nigeria. *Pan African Medical Journal* 2013;14(1)61

6. Ruel M, Chan V, Boodhwani M, et al. How detrimental is re-exploration for bleeding after cardiac surgery? *The Journal of Thoracic and Cardiovascular Surgery 20 17;154(3):927-35.*

7. ÄŒanÃ¡dyovÃ¡ Jl, Zmeko Da, MokrÃ¡Ä et al. Re-exploration for bleeding or tamponade after cardiac operation. *Interactive Cardiovascular and Thoracic Surgery* 14(6):704-7.

8. Ranucci M, Bozzetti G, Ditta A, et al. Surgical re-exploration after cardiac operations: why a worse outcome? *The Annals of thoracic sur*gery 2008;86(5):1557-62.

9. Murni IK, Djer MM, Yanuarso PB, et al. Outcome of pediatric cardiac surgery and predictors of major complication in a developing country. *Annals of Paediatric Cardiology* 2019;12(1) : 38-44

10. Agarwal HS, Wolfram KB, Saville BR, Donahue BS, Bichell DP. Postoperative complications and association with outcomes in paediatric cardiac surgery. *The Journal of Thoracic and Cardiovascular Surgery* 2014;148(2):609-16. e1.

11. Dacey LJ, Munoz JJ, Baribeau YR, et al. Re-exploration for haemorrhage following coronary artery bypass grafting: incidence and risk factors. *Archives of Surgery* 1998;133(4):442-7.

12. Miana LA, Atik FA, Moreira LF, et al. Risk factors for postoperative bleeding after adult cardiac surgery. *Brazilian Journal of Cardiovascular Surgery* 2004;19(3):280-6

13. Biancari F, Mikkola R, Heikkinen J, et al. Individual surgeon's impact on the risk of re-exploration for excessive bleeding after coronary artery bypass surgery. *Journal of Cardiothoracic and Vascular Anaesthesia* 2012;26(4):550-6.

14. Okonta KE, Rajan S. Re-exploration after open heart surgery at the Madras Medical Mission, Chennai, India. *Journal of the West African College of Surgeo*ns 2011;1(2):1.-17

15. Long SS, Pickering LK, Prober CG. Principles and practice of paediatric infectious diseases. *Shock* 2003;20(1):98.

16. Haneya A, Diez C, Kolat P, et al. Re-exploration for bleeding or tamponade after cardiac surgery: impact of timing and indication on outcome. *The Thoracic and Cardiovascular Surgery* 2015;63(01):051-7.

17. Biancari F, Mikkola R, Heikkinen J, Lahtinen J, Airaksinen KE, Juvonen T. Estimating the risk of complications related to re-exploration for bleeding after adult cardiac surgery: a systematic review and meta-analysis. *Eur J Cardiothorac Surg* 2012; 41:50–5.

18. Deja MA, Kargul T, Domaradzki W, et al. Effects of preoperative aspirin in coronary artery bypass grafting: a double-blind, placebo-controlled, randomized trial. *The Journal of Thoracic and Cardiovascular Surgery* 2012;144(1):204-9. e3.

19. Kincaid EH, Monroe ML, Saliba DL, et al. Effects of preoperative enoxaparin versus unfractionated heparin on bleeding indices in patients undergoing coronary artery bypass grafting. *The Annals of Thoracic Surgery* 2003;76(1):124-8.

REVIEW ARTICLE

Psychogenic non-epileptic seizures: Review of recent developments

Abdelgadir H. Osman,[1*] Sabah M. Alsharief,[2] Ahmed A Osman,[3] Hassab Elrasoul Siddig[4]

[1]*Psychiatric Department, Faculty of Medicine, University of Khartoum, Khartoum, Sudan.*

[2]*Sudan Medical council, Khartoum, Sudan.*

[3]*Academic Hospital, Khartoum, Sudan*

[4]*Alnileen Medical Centre, Khartoum, Sudan.*

ABSTRACT

The Psychogenic Non-epileptic Seizures (PNES) Task Force of the International League Against Epilepsy (ILAE) highlighted, important barriers to PNES service development in low income countries. This involves access to diagnosis and treatment (estimated to affect 60-80% of patients), lack of diagnostic services, psychological treatment, and money for treatment, as well as stigma/lack of awareness or information.

To bridge such gaps in our country, we undertook an evidence based review to summarize current, clinical semiology, underlying aetiology, diagnosis, and management for patients with PNES. The intention is to improve the care of patients, and to steer discussion in clinical and scientific arena with the purpose of developing integrated services in low resource country. For this review, Medline and PsycINFO database searches were undertaken for articles with keywords addressing nonepileptic seizures, pseudo-seizures, dissociative seizures and functional neurological disorder. We distilled the consensus views, most supported evidence to inform future service development.

[*]***Correspondence to*** *abdelgadir1159@yahoo.com, abdelgadir.osman@uofk.edu*

Black cover

Psychogenic non-epileptic seizures (PNES) are events (of motor, behaviour, sensations and emotions) that resemble epileptic seizures, without evidence of characteristic epileptic discharges on electroencephalography (EEG).[1,2] The underlying mechanism for such events are thought to have a psychological origin, classified in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) as a conversion disorder.[3] About one in five patients first presenting to a seizure clinic is diagnosed with PNES, yet represent a diagnostic challenge because they sometimes intermingle with real seizures in patients diagnosed with epilepsy.[4,5] This poses a challenge to neurologists, leading to meticulous investigations and unnecessary medication for sufferers. Thus, diagnosis of PNES comes after systematic exclusion of any underlying neurophysiological disorder, which on average takes four years to conclude.[6,7] Moreover, diagnosis of PNES should be based on positive affirmation of psychological disturbance, as exclusion alone proved to be elusive; since back in the mid-1960s Slater published his pivotal article on patients that received a diagnosis of Hysteria and were found later on to have suffered from an underlying organic illness.[8] Slater found that 50% of what was diagnosed 10 years earlier as hysteria, later emerged to have underlying neurological disorder, such as demyelinating disease, myasthenia gravis and tumour in situ. However, with advances in investigation techniques, such misdiagnoses were found less frequent.[9,10] In 2011, a consensus clinical practice statement based on an international survey of experts carried out by the Commission on Neuropsychiatric Aspects of Epilepsy of the International League Against Epilepsy (ILAE) ranked psychogenic nonepileptic seizures (PNES) among the top three neuropsychiatric problems with anxiety/depression and psychotic disorder.[11]

Epidemiology

Socio-demographic correlates

About 75% of patients diagnosed with this condition are female. PNES disorders most frequently start in late adolescence or early adulthood, although seizures may first manifest in children as young as five years and in older people; however, the usual pattern are young females of Low socio-demographic background, with history of sexual trauma.[1,2] This said, many studies in Arabic and Sudanese culture report significantly less traumatizing sexual events and lower levels of dissociative psychopathology than individuals from specialized treatment centres in the Europe.[12,13] Dissociative phenomena have been documented in many non-western societies where psychiatric models of dissociation are less dominant and the ethos and metaphors for illness and healing differ from those employed in the industrialized west.[14]

Epidemiological data from poorer countries are virtually lacking altogether. However, studies from industrialised countries estimates that 10% of adults with PNES have concurrent epilepsy. Approximately 70% of patients with PNES have other psychogenic disorders.[15] Patients with learning disability, head injury, and those who had previously been sexually abused were also more likely to report flashbacks and emotional triggers of their PNES. Several more recent studies have highlighted the fact that PNES are also associated with autonomic arousal.[15,16] Up to 50% of patients with PNES report a precipitating event that might also be associated with epilepsy. Up to 70% of patients report antecedent trauma, which is of a sexual nature in up to 40%.[17,18]

Front-line doctors usually over diagnose epilepsy especially if the presentation is acute. This leads often to late diagnosis of PNES patients. The time between the onset of symptoms and diagnosis could exceed several years. The costs of myriad of laboratory, electrophysiological, and imaging studies searching for the cause usually take extensive amount of time and resources. It is estimated that around 20 % of patients referred to epilepsy centres for refractory epilepsy have PNES.[19,20]

Aetiological Factors

Psychogenic non-epileptic seizures do not have a single aetiology, they are often, products of several different causal pathways interact to produce the disorder. Therefore, these are discussed as model of understanding for the underlying aetiological mechanisms.

Psychoanalytic

Conversion disorder is associated with conflicts or recent stressors, and its symptoms manifest as a result of channelling of unresolved psychological conflict and distress into loss of function. Often conversion manifest into neurological symptoms, though the aetiology and mechanism of this are unclear. Psychological states are thought to play a role as well as a history of trauma, and abuse, though by no means invariably. Therefore, PNES is seen as one manifestation of conversion disorder, often associated with a range of psychiatric co-morbidities, including depression, anxiety and personality disorders.[21,22]

Neurobiological model

More recently a neurobiological model of conversion includes hypo-activation of the supplementary motor area and relative disconnection from areas that select or inhibit movements and are associated with a sensory area.[23,24] This model is a focus of intense research with functional neuroimaging but it is still too early for a conclusive theory.

Physiological Model

Panic symptoms in PNES are mostly somatic, with affective symptoms less common. Meta-analysis showed hyperventilation moderately successfully induces PNES events. Goldstein and Mellers, for example, found that patients with PNES reported more somatic symptoms of anxiety during their attacks than patients with epilepsy, although they did not seem to experience subjectively higher levels of anxiety during their seizures. As PNES patients reported more agoraphobic-type avoidance

behaviour than those with epilepsy, PNES were interpreted as a dissociative response to anxious arousal.[25,26]

Learning theory

Some researchers found that patients with PNES were six times more likely to report having witnessed someone in a seizure before experiencing their own first seizure than those with epilepsy. Therefore, PNES is viewed as a leant behaviour to adopt a sick role at adversity with high level of suggestibility.[27]

Integrative Cognitive Model (ICM)

This model brings together existing theories within a single explanatory framework, leading to a number of novel hypotheses. Based on an established theory of "medically unexplained symptoms" (MUS), the ICM suggests that the observable and subjective elements of PNES result from the automatic execution of a learnt mental representation of seizures typically in the context of a high level inhibitory dysfunction resulting from chronic stress, arousal and other factors that compromise high level processing.[28,29]

Clinical semiology and presentation

History taking is essential to capture patients' experience of the seizure as often patients do not just tell the clinician what they experience in their seizures. They also show how they deal with the challenge of having to communicate about their seizure experiences interpersonally.[30,31] Patients' subjective seizure symptoms give important clues about the nature and aetiology of the seizures. For instance, patients with PNES were shown to have greater recall aspects of an ictal examination than those who were tested after a complex partial epileptic seizures.[32-34] Numerous signs have been described, in many studies, with a systematic review indicating that the most reliable indicators of PNES are long duration, occurrence from apparent sleep with EEG-verified wakefulness, fluctuating course, asynchronous movements, side-to-side head or body movement, closed eyes during the episode, ictal crying, memory recall and absence of postictal confusion.[35,36] No individual observation can provide a firm basis for a diagnosis of PNES in isolation and all of these "typical" features of PNES could, conceivably, be observed in epileptic seizures. Important practical clinical semiology for PNES collated from multi-sources is shown in Table.

Faint attacks, "Swoon" type events should raise suspicion of PNES if prolonged over a minute. One should bear in mind a differential diagnosis of vasovagal or cardiac syncope. Atonic ES are much shorter and typically occur in the epilepsies with other seizure types, for example, Lennox- Gastaut syndrome.[37] However, four distinct groups of clinical presentations for PNES have been validated based on eleven signs and symptoms, which are frequently found in PNES: Hyper-motor (H), Akinetic (A), Focal Motor (FM), and with Subjective Symptoms (SS). Uttering of words in PNES occurs during or after seizures, and may be complex, with emotional content to their vocalization, whereas in ES it occurs at the beginning, usually primitive, and has no affective content.[28,38]

Diagnosis

The diagnosis of PNES may be based on different combinations of data. Good history from patients, witness reports, clinician observations, and ictal and inter-ictal EEG, and ictal video is used for the diagnosis; rarely requiring functional imaging for diagnostic determination. The video EEG (vEEG) confirms the nature of the recorded episode with a high degree of diagnostic certainty.[39] One should bear in mind that, a normal inter-ictal EEG does not exclude epilepsy or confirm PNES. Similarly, an abnormal inter-ictal EEG does not confirm epilepsy or exclude PNES. The ILAEs Task Force recognizes that not all sites, around the world have access to vEEG and clinicians and patients may have to make treatment choices (for instance, about stopping inappropriate antiepileptic drugs or commencing psychological treatment) when the diagnosis is not completely certain.[13] In such situation different level of diagnostic certainty may be used. These levels include, in ascending order, "possible", "probable", "clinically established" and "documented".[40] Each

level increases with the combination of witness and EEG. For instance for "possible" diagnosis, one requires a witness or self-report description of clinical semiology of PNES, while "probable" is when a video recording is checked by a clinician confirming typical semiology of PNES with inter-ictal or sleep deprived EEG showing no epileptiform activity. "Clinically established" level is when experienced clinician confirms diagnosis via video or in person combined with clear ambulatory or ictal EEG during ictus / event. "Documented" attack is when the PNES semiology is confirmed by vEEG in a background of positive history of PNES attacks.[40,41]

Table. Salient Clinical features differentiating Epileptic Seizure (ES) from PNES*

Character	ES	PNES	Reference	Remarks
Length of seizure	Often1minute or less	More than 5 minutes	24,27	Be aware of TLE and FLI
Seizure type	Tonic clonic or other types	Pelvic thrusting with eye closure or swoon attacks	27,28,29	
Vocalization	Primitive at the beginning	During and after seizure complex of emotional connotation	33,38	
Tongue biting	When happens could be on edge	On the tip less bizarre	24,27,35	
Urine incontinence	Of positive significance	Unlikely, could happen	35,40	Consciously induced in PNES
Stressful event/ trauma	can occur	Available in most cases	62,69	In West Sexual trauma
Mood	Low grade symptoms in 30%	Moderate to severe depressive and Anxiety Disorders over 50%	68,69	Poor differentiating
Antidepressant	Do not affect seizures	Can resolve seizures in over 50%	69,70,71	Good

*PNES=Psychogenic non-epileptic seizures

Differential diagnosis

Many patients with PNES experience such symptoms to a degree sometimes difficult to distinguish clearly between some PNES and panic attacks.[41,42] However, it appears that panic symptoms may be experienced differently during PNES, sometimes associated with hyperventilation.

Agoraphobic-type avoidance behaviour often seen in therapy setting with PNES more than those with epilepsy, PNES was interpreted as a dissociative response to anxious arousal, syncope and epilepsy (91%) and between syncope and PNES (94%).

For diagnostic purposes of non-epileptogenic seizures, several conditions could come in the interplay. Those consciously produced seizures for unconscious reasons (forms of factitious disorder), and physiologic seizure-like activity secondary to medical conditions belong to separate categories.[43] Unconsciously produced symptoms for unconscious reasons, as in conversion disorder, which include a great variety of neurological presentations, includes a whole array of neurological presentations

involving motor, sensory, and coordination abnormalities. Even though this phenomenon probably represents one of those cornerstone diagnostic modalities that act as pivotal point in swinging patient care between specialties; in many instances the diagnosis is not an exact science posing a challenge for both neurologists and psychiatrists. Still close liaison with mental health team constitutes the best care pathway.[44] Length of psychogenic seizures frequently exceeds 5 minutes; these patients would more likely have a history of chronic pain or fibromyalgia, depression and dissociative states.[45] Other factors include history of childhood sexual, emotional or physical abuse, history of unipolar depression or anxiety disorders, along with somatoform and conversion disorders.[46]

History taking from patients and relatives play crucial role. Eliciting and interpreting the patient's history is the most important contribution that the clinicians make to the diagnostic process .Thorough clinical history elicits whether there is likely to be one or more types of habitual event. The video allows comparison of the recorded events with those previously reported to ensure they are the same and that all event types have been captured.[47] Patients with PNES preferentially focus on the circumstances in which their seizures occurred or the consequences of their seizures.

Investigations

Electrophysiology and electrocardiogram (ECG)

In the differential diagnosis of seizures, the combination of vEEG with the history of patients and witnesses offers a diagnostic "gold-standard" with high levels of certainty and excellent interpreter reliability.[48,49] Diagnostic certainty for PNES Consensus group of International League against Epilepsy (ILAE) recommended staged approach to PNES diagnosis. Using a consensus review of the literature: these included history, EEG, ambulatory EEG, vEEG/monitoring, neurophysiologic, neuro-humoral, neuroimaging, neuropsychological testing, hypnosis, and conversation analysis. The diagnosis is often a longitudinal process, and that can be reviewed on the long-term clinical course.[13,50]

The concurrent recording of ECG during vEEG is essential. Ictal heart rate is higher and the ictal heart rate increase is more rapid in epilepsy than in PNES.[51] Unlike that seen in ES, the heart rate increase in PNES is usually commensurate with the physical activity involved in the seizure. Many patients do not have seizures in an observed setting. Outpatient ambulatory EEG may be useful in this circumstance, particularly if there is a caregiver who can give good descriptions of the events that have been recorded or can provide video recordings of them.[51]

Neuroimaging

Neuroimaging findings are of modest differential diagnostic value at present. Lesions with epileptogenic potential (such as mesial temporal sclerosis) are more commonly found in patients with epilepsy, but have also been described in patients with PNES and are clearly not sufficient for a diagnosis of epilepsy. More recently, structural and functional imaging studies in patients with PNES have documented changes in cortical and cerebellar regions at group level.[52]

Biochemical and Hormonal

Raised prolactin (PRL) serum level was demonstrated by Cragar et al, to be in favour of true ES. They reviewed many studies prior to 2002, concluding that the absence of PRL rise predicts PNES with a mean sensitivity for PNES of 89%.[53] However, later on, a well-structured study reported, raised serum PRL levels in PNES group up to 26.3% in comparison to true seizure group of 58.8%. While reporting lower percentage of 12% for simple partial ES. They concluded that the difference in percentage of patients with abnormal prolactin levels between these groups was not found to be significant.[54] Reasons for "false positive" PRL tests in PNES group include treatment with dopamine antagonists and some tricyclic antidepressants, breast stimulation, and syncope. "False negatives" occur with use of a dopamine agonist, or with status epilepticus, because PRL has a short half-life and may attenuate in postictal release. PRL may also

fail to rise after frontal lobe ES. In conclusion, it is useful adjunct of differentiation between PNES and true ictus seizure if absolute serum PRL rise is twice of prior ictus level, which will be in favour of true ictus event if test is conducted 10-20 minutes after onset .

Management

Communicating diagnosis to patient

The way how the diagnosis is communicated to patient has been shown to have a bearing on the patient engagement with treatment and future prognosis. Thus, the diagnosis must be communicated in a respectful and empathic manner. One of the recommendations is to explain the mechanisms involved in dissociation. So that the patient is not made to feel that he was cheating, malingering or attention seeking. In the contrary, often, it's due to psychological distress and trauma that expresses itself via the specific symptoms. This may help patients feel that they are being taken seriously and that the seizures are not a pretence. Patients who see a possible association between previous life events (as well as their current life situation) and the seizures, find it easier to accept the diagnosis and are more receptive to further treatment services.[55,56]

Cognitive Behavioural Therapy (CBT)

Cognitive behavioural therapy helps people learn skills they can use to change their thoughts and behaviours related to PNES symptoms. Many forms of CBT exists, however, the one evaluated by Goldstein et al, was based on a fear escape-avoidance model that views PNES as dissociative responses to cues (cognitive/emotional/physiological or environmental) that have been associated with extremely distressing or life-threatening experiences (e.g., abuse or trauma) and which had produced unbearable feelings of fear and distress at an earlier point in the person's life.[57,58] Conducting a functional behavioural analysis, assessing external stressors and internal triggers with the aim of promoting health and wellness, and preparing for life after completing the intervention. The therapy addresses connections between mood, cognitions, and the environment, as well as patients' automatic thoughts, catastrophic thinking, maladaptive schemas, and somatic misinterpretations. All executed coupled with learning relaxation techniques to unwind any anxiety provoked by memory of stressors.

Individual psychotherapy

The working model of PNES centres around three cardinal features: (a) the importance of trauma, (b) the chronicity of symptoms, and (c) the wide range of symptoms experienced by individual patients. Interpersonal and psychodynamic therapy involves working with a therapist to talk through emotional struggles or conflicts that can lead to PNES. By using therapy to talk through emotional issues, a person may improve relationships and social functioning and lower their day-to-day emotional distress. By lowering distress, a person may be less likely to have PNES.[59,60]

Trauma based work, eye movement desensitization and reprocessing and Hypnotherapy

Eye movement desensitization and reprocessing (EMDR) has a strong evidence base for the treatment of posttraumatic stress disorder, there is no evidence for its use as a primary intervention in patients with PNES beyond the case series level.[61]

Behaviour therapy

Agreed targets are set with the patient following behavioural functional analysis. Then the therapist uses positive reinforcement for seizure-free behaviour and occasional use of punishment or negative reinforcement to reduce inappropriate behaviour. This has been reported to lead to a reduction in PNES frequency, anxiety, depression symptoms and symptoms of post-traumatic stress disorder.[62]

Psychopharmacology

The pharmacologic treatment of patients should begin with early tapering and discontinuation of AEDs, which are an ineffective treatment for people with lone PNES, unless a specific AED. Co-morbid mood disorders, anxiety, somatoform

disorder has been reported to constitute over 80% in some studies.[63] Open-label trials of antidepressants in patients with conversion disorders have shown some response Phase III controlled studies of the benefit of psychotropic in patients with PNES; however, have not been conducted, and apart from anecdotal reports, their effect is unknown.[64,65]

Treatment Maintenance

Coordinated care approach between therapist patients and involved parties should prevent further unnecessary interventions, investigations, or treatments. Given the association of PNES with serious and pervasive conditions such as borderline personality disorder, co-morbid mood disorders, post traumatic stress disorder (PTSD) and somatoform disorder. Many patients may lead tortuous course with remissions and relapses with considerable disabling symptoms.[66,67] However, therapist should always remain optimistic as many recovers along the course of follow up, including those with co-morbid borderline personality disorder.[68]

Psychiatric co-morbidities

Increased rates of several psychiatric disorders have been reported in PNES, including depression, anxiety and panic disorders. Some theories suggest panic and/or hyperventilation have aetiological roles in PNES. Conversion Disorder criteria in DSM-5 have been changed by guiding users to make a positive diagnosis based on symptom presentation and by relegating a psychological stressor.[69] Patients diagnosed with conversion disorder are not feigning the signs and symptoms. Despite the lack of a definitive organic diagnosis, the patient's distress is very real and the physical symptoms the patient is experiencing cannot be controlled at will.[70,71] One should always assess the mood with patients presenting with PNES, due to considerable comorbidity of depression, anxiety, and somatisation. The latter is a condition in which a person experiences physical symptoms that are inconsistent with or cannot be fully explained by any underlying general medical or neurological condition. Preoccupation with these symptoms leads to excessive distress in the patient.[72]

Prognosis

Favourable outcomes have been reported from non-Western cultures, provided underlying stressors are addressed head on at an early stage. However, a multivariate analysis, suggested a poor outcome was predicted by expectation of non-recovery, non-attribution of symptoms to psychological factors and the receipt of health related benefits at the time of the initial consultation.[73] Many factors play role in predicting outcome. Early diagnosis of the condition and prompt treatment are determinant factors to good outcome; whilst late diagnosis is thought to lead to chronicity of symptoms and co-morbidity. Addressing underlying psychopathology, traumatic events that may have precipitated, predisposed or perpetuated the condition lead to better outcome, in comparison with patient only treated pharmacologically.[73,74]

CONCLUSION

Much is now known about the bio-psychosocial underpinnings of PNES; yet, sufferers are not having adequate access to healthcare provisions, with gaps in close liaisons between different concerned specialties. Providing a clear diagnosis of PNES and assessing the co-morbidities are essential in understanding the patient and gaining her/his therapeutic engagement. Communicating to the patient that the seizures have a psychological aetiology and are not epilepsy may stop PNES in the short-term, but does little to improve associated psychological morbidity, distress, or health-related quality of life. Therefore, addressing patients underlying psychological traumas and stressors are essential part of full recovery. Treatment specifically addressing PNES is required in most patients.[74,75] It is important that every endeavour should be made to reduce delay in diagnosis of PNES. Moreover, all effort should be made to improve the transition of care from neurology to mental health treatment and psychology.

REFERENCES

1. Anderson JR, Nakhate V, Stephen CD, Perez DL. Functional (psychogenic) neurological

disorders: assessment and acute management in the emergency department. *Semin Neurol* 2019;39:102–114. https://doi.org/10.1055/s-0038-1676844

2. Duncan S, Razvi S Mulhern. Newly presenting psychogenic nonepileptic seizures: incidence, population characteristics, and early outcome from a prospective audit of a first seizure clinic *Epilepsy Behav* 2011;20:308-311

3. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington VA: American Psychiatric Publishing; 2013.

4. Daum C, Hubschmid M, Aybek S. The value of "positive" clinical signs for weakness, sensory and gait disorders in conversion disorder: a systematic and narrative review. *J Neurol Neurosurg Psychiatr* 2014;85:180–190. https://doi.org/10.1136/jnnp-2012-304607

5. Brechje Dandachi-FitzGerald, Björn van Twillert, Peter van de Sande, Yindee van Os Rudolf WHM Ponds. Poor symptom and performance validity in regularly referred hospital outpatients: Link with standard clinical measures, and role of incentives, *Psychiatry Research* 2016; 239:47-53.

6. Benbadis SR, Agrawal V, Tatum WO. How many patients with psychogenic nonepileptic seizures also have epilepsy? *Neurology* 2001;57: 915 – 7.

7. Hickie I.B, Scott J, Hermens DF, et al. Clinical classification in mental health at the cross-roads: which direction next?. *BMC Med* 2013;11:125. https://doi.org /10. 1186/1741-7015-11-125

8. Slater ET. Diagnosis of 'hysteria'. *Br Med J* 1965;i:1395-9

9. Crimlisk HL, Bhatia K, Cope H, et al. Slater revisited: 6 year follow up study of patients with medically unexplained motor symptoms. *Br Med J* 1998;316:5826.

10. Kerr MP, Mensah S, Besag F, et al. International consensus clinical practice statements for the treatment of neuropsychiatric conditions associated with epilepsy. *Epilepsia* 2011;52:2133–2138.

11. Ali A Asadi-Pooya, Michael R Sperling. Epidemiology of psychogenic nonepileptic seizures. *Epilepsy and Behaviour* 2015;46;60-65.

12. Kanemoto K, Lafrance WC, Duncan R, et al. PNES around the world: where we are now and how we can close the diagnosis and treatment gaps-an ILAE PNES Task Force report. *Epilepsia Open* 2017; 2: 307– 16.

13. Hafeiz HB. Hysterical conversion: a prognostic study. *Br J Psy*chiatry 1980;136:548–551

14. Somer E, Ross C, Kirshberg A, Shawahdy R, Ismail S. Dissociative disorders and possession experiences in Israel: a comparison of opiate use disorder patients battered Arab women and a non-clinical group. *Transcult Psychiatry* 2015;52(1):58–73. https://doi.org/10.1177/1363461514552584.

15. Fiszman SV, Alves-Leon R.G, Nunes DA, Isabella I. Figueira Traumatic events and posttraumatic stress disorder in patients with psychogenic nonepileptic seizures: a critical review *Epilepsy Behav* 2004;5:818-825.

16. Rothbaum E, Foa Hembree E. Reclaiming your life from a traumatic experience: a prolonged exposure treatment program workbook. New York: Oxford University Press; 2007

17. Pick S, Mellers JD, Goldstein LH. Dissociation in patients with dissociative seizures: relationships with trauma and seizure symptoms. *Psychol Med* 2017;47(7):1215-1229.

18. Bègue I, Adams C, Stone J, Perez DL. Structural alterations in functional neurological disorder and related conditions: a software and hardware problem? *Neuroimage Clin* 2019 ; https://doi.org/10.1016/j.nicl.2019.101798.

19. Heintz CEJ, van Tricht MJ, van der Salm SMA, et al. Neuropsychological profile of psychogenic jerky movement disorders: importance of evaluating non-credible cognitive performance and psychopathology. *Journal of Neurology, Neurosurgery and Psychiatry* 2013; 8;862-867. 10.1136/jnnp-2012-304397, 84,

20. Kalogjera-Sackellares D. Psychodynamics and psychotherapy of pseudoseizures. Carmarthen: Crown House Publishing Ltd; 2004.

21. Bowman ES, Markand ON. Psychodynamics and psychiatric diagnoses of pseudoseizure subjects. *Am J Psychiatry* 1996;153:57– 63.

22. Duncan R, Razvi S, Mulhern S. Newly presenting psychogenic nonepileptic seizures: incidence, population characteristics, and early outcome from a prospective audit of a first seizure clinic. *Epilepsy Behav* 2011;20:308–11.

23. Markus Reuber. The aetiology of psychogenic non-epileptic seizures: Toward a biopsychosocial model, *Neurologic Clinics* 2009;4:909-924. 10.1016/j.ncl.2009.06.004.

24. Markus Reuber, Richard J Brown, Understanding psychogenic nonepileptic seizures: Phenomenology, semiology and the Integrative Cognitive Model. *Seizure* 2017;44:199-205. 10.1016/j.seizure.2016.10.029.

25. Richard J Brown, Markus Reuber, Towards an integrative theory of psychogenic non-epileptic seizures (PNES). *Clinical Psychology Review* 2016;47:55-70. 10.1016/j.cpr.2016.06.003.

26. Ghaffar O, Staines WR, Feinstein A. Unexplained neurologic symptoms: an fMRI study of sensory conversion disorder. *Neurology* 2006; 67(11):2036 –2038

27. Goldstein LH, Mellers JD. Recent developments in our understanding of the semiology and treatment of psychogenic nonepileptic seizures. *Curr Neurol Neurosci Rep* 2012:12: 436-444.

28. Erba G, Giussani G, Juersivich A, et al. The semiology of psychogenic nonepileptic seizures revisited: Can video alone predict the diagnosis? Preliminary data from a prospective feasibility study. *Epilepsia* 2016;57(5):777-785.

29. Magaudda A, Laganà A, Calamuneri A, et al. Validation of a novel classification model of psychogenic nonepileptic seizures by video-EEG analysis and a machine learning approach. *Epilepsy Behav* 2016;60:197-201.

30. Stone J, Zeman A, Simonotto E, et al. FMRI in patients with motor conversion symptoms and controls with simulated weakness. *Psychosom Med* 2007; 69(9): 961–969.

31. Ali A, Asadi-Pooya Zahra Bahrami, Maryam Homayoun. Natural history of patients with psychogenic nonepileptic seizures. *Seizure* 2019 10.1016/j.seizure.2019.02.006.

32. Rawlings GH, Reuber M. What patients say about living with psychogenic nonepileptic seizures? a systematic synthesis of qualitative studies. *Seizure* 2016; 41: 100–11.

33. Reuber M, Rawlings GH, Schachter S. In our words: personal accounts of living with non-epileptic seizures (the Brainstorms Series). New York, NY: Oxford University Press; 2018.

34. Butler C, Zeman A Z. Neurological syndromes which can be mistaken for psychiatric conditions. *J Neurol Neurosurg Psychiatry* 2005; 76 i31-i38

35. Gelauff J, Stone J, Edwards M, Carson A. The prognosis of functional (psychogenic) motor symptoms: a systematic review. *J Neurol Neurosurg Psychiatry* 2014;85:220–226.

36. White PD, Rickards H, Zeman AZ. Time to end the distinction between mental and neurological illnesses. *Br Med J* 2012;344: e3454-10.1136/bmj.e3454.

37. Valente KD, De Paola L, Palmini A, et al. The approach to patients with psychogenic nonepileptic seizures in epilepsy surgery centers regarding diagnosis, treatment, and education.

Epilepsy Behav 2017;68:78-83.

38. Rawlings GH, et al. Panic symptoms in transient loss of consciousness: frequency and diagnostic value in psychogenic nonepileptic seizures, epilepsy and syncope *Seizure* 2017;48:22-27

39. Bakvis P, Roelofs K, Kuyk J, et al. Trauma, stress, and preconscious threat processing in patients with psychogenic nonepileptic seizure. *Epilepsia* 2009;50:1001-1011

40. LaFrance WC, Baker GA, Duncan R et al. Minimum requirements for the diagnosis of psychogenic nonepileptic seizures: a staged approach. *Epilepsia 2013*; 54:2018.

41. Hendrickson R, et al. Panic attack symptoms differentiate patients with epilepsy from those with psychogenic nonepileptic spells *Epilepsy Behav* 2014;) 37:210-214.

42. Bakvis P, Spinhoven P, Putman FG, Zitman K Roelofs. The effect of stress induction on working memory in patients with psychogenic nonepileptic seizures, *Epilepsy Behav* 2010; 19:448-454.

43. Whitehead K, Reuber M. Illness perceptions of neurologists and psychiatrists in relation to epilepsy and nonepileptic attack disorder. *Seizure* 2012;21:104 – 9.

44. Aamir S, Haymayon S, Sultan S. Behaviour therapy in dissociative convulsion disorder. *J Depress Anx*iety 2011; 1: 1– 4.

45. Ali A Asadi-Pooya, Fateme Ziyaee. Outcome of patients with psychogenic nonepileptic seizures with limited resources: A longitudinal study. *Seizure* 2018;59:1-4.

46. Curt LaFrance W, Markus Reuber, Laura H Goldstein. Management of psychogenic nonepileptic seizures. *Epilepsia* 2013;54:53-67.

47. Devinsky O, Gazzola D, LaFrance WC Jr. Differentiating between nonepileptic and epileptic seizures. *Nat Rev Neurol* 2011;7:210–220.

48. Duncan R. Psychogenic nonepileptic seizures: diagnosis and initial management. *Expert Rev Neurother* 2010;10:1803–1809.

49. Goldstein LH, Deale AC, Mitchell-O'Malley SJ, Toone BK, Mellers JDC. An evaluation of cognitive behavioural therapy as a treatment for dissociative seizures: a pilot study. *Cogn Behav Neurol* 2004;17: 41– 49.

50. Goldstein LH, Chalder T, Chigwedere C, et al. Cognitive-behavioural therapy for psychogenic nonepileptic seizures: a pilot RCT *Neurology* 2010;74:1986–1994.

51. Kellett S, Bennett D, Ryle T, Thake A. Cognitive analytic therapy for borderline personality disorder: therapist competence and therapeutic effectiveness in routine practice. *Clin Psychol Psychother* 2011;23

52. Goldstein LH, LaFrance WC Jr, Chigwedere C, Mellers JDC, Chalder T. Chapter 29. Cognitive behavioural treatments. In SC Schachter, WC Lafrance (Eds) Gates and Rowan's nonepileptic seizures. 3rd ed. Cambridge, New York: Cambridge University Press; 2010b: pp. 281–288.

53. Cragar DE, Berry DT, Fakhoury TA, Cibula JE, Schmitt FA. A review of diagnostic techniques in the differential diagnosis of epileptic and nonepileptic seizures. *Neuropsychol Rev* 2002;12:31–64.

54. Shukla G, Bhatia M, Vivekanandhan S, et al. Serum prolactin levels for differentiation of nonepileptic versus true seizures: limited utility. *Epilepsy Behav* 2004;5:517-21.

55. Carlson P, Nicholson Perry K. Psychological interventions for psychogenic non-epileptic seizures: a meta-analysis. *Seizure* 2017;45:142-150.

56. Stone J, LaFrance WC, Brown R. et al. Conversion disorder: current problems and potential solutions for DSM-5. *J Psychosom Res* 2011;71:369–376.

57. Guthrie E, Creed F, Dawson D, Tomenson B. A controlled trial of psychological treatment for the irritable bowel syndrome. *Gastroenterology* 1991;100:450– 457.

58. Hall-Patch L, Brown R, House A, Howlett S, Kemp S, Lawton G, Mayor R, Smith P, Reuber M. Acceptability and effectiveness of a strategy for the communication of the diagnosis of psychogenic nonepileptic seizures. *Epilepsia* 2010;51:70–78.

59. Harden CL, Ferrando SJ. Delivering the diagnosis of psychogenic pseudoseizures: should the neurologist or the psychiatrist be responsible? *Epilepsy Behav 2001*;2:519– 523.

60. Hogberg G, Pagani M, Sundin O, et al. Treatment of post-traumatic stress disorder with eye movement desensitization and reprocessing: outcome is stable in 35-month follow-up. *Psychiatry Res* 2008;159:101– 108.

61. Hopp JL, LaFrance WC Jr. Cognitive behavioural therapy for psychogenic neurological disorders. *Neurologist* 2012;18:364– 372.

62. Howlett S, Reuber M. An augmented model of brief psychodynamic interpersonal therapy for patients with nonepileptic seizures. *Psychother Theory Res Pract Training* 2009;46: 125– 138.

63. Howlett S, Grunewald RA, Khan A, Reuber M. Engagement in psychological treatment for functional neurological symptoms – barriers and solutions. *Psychother Theory Res Pract Training* 2007;44: 354– 360.

64. Kelley SD, Benbadis S. Eye movement desensitization and reprocessing in the psychological treatment of trauma-based psychogenic non-epileptic seizures. *Clin Psychol Psychother* 2007;14:135–144.

65. Goldstein LH, Mellers JD, Landau S, et al. Cognitive behavioural therapy vs standardised medical care for adults with dissociative non-epileptic seizures (CODES): a multicentre randomised controlled trial protocol. *BMC Neurol* 2015;15:98.

66. M Reuber R, Pukrop AJ, Mitchell J, Bauer CE Elger. Clinical significance of recurrent psychogenic nonepileptic seizure status. *J Neurol* 2003;250:1355-1362.

67. Bravo TP, Hoffman-Snyder CR, Wellik KE, et al. The effect of selective serotonin reuptake inhibitors on the frequency of psychogenic nonepileptic seizures: a critically appraised topic. *Neurologist* 2013;19(1):30-33.

68. Pintor L, Baillés E, Matrai S, et al. Efficiency of venlafaxine in patients with psychogenic nonepileptic seizures and anxiety and/or depressive disorders. *J Neuropsychiatry Clin Neurosci* 2010;22(4):401-408.

69. LaFrance WC Jr, Baird GL, Barry JJ, et al. NES Treatment Trial (NEST-T) Consortium. Multicenter pilot treatment trial for psychogenic nonepileptic seizures: a randomized clinical trial. *JAMA Psychiatry* 2014;71(9):997-1005.

70. Bodde NM, Janssen AM, Theuns C, et al. Factors involved in the long-term prognosis of psychogenic nonepileptic seizures. *J Psychosom Res* 2007;62:545 – 51.

71. McKenzie P, Oto M, Russell A, et al. Early outcomes and predictors in 260 patients with psychogenic nonepileptic attacks. *Neurology* 2010; 74: 64 – 9.

72. Bravo TP, Hoffman-Snyder CR, Wellik KE, et al. The effect of selective serotonin reuptake inhibitors on the frequency of psychogenic nonepileptic seizures: a critically appraised topic. *Neurologist* 2013;19(1):30-33.

73. Pintor L, Baillés E, Matrai S, et al. Efficiency of venlafaxine in patients with psychogenic nonepileptic seizures and anxiety and/or depressive disorders. *J Neuropsychiatry Clin Neurosci* 2010;22(4):401-408.

74. Carton S, Thompson PJ, Duncan JS. Non-epileptic seizures: patients' understanding and reaction to the diagnosis and impact on outcome. *Seizure* 2003;12:287–294.

75. Arain AM, Hamadani AM, Islam S, Abou-Khalil BW. Predictors of early seizure remission after diagnosis of psychogenic nonepileptic seizures. *Epilepsy Behav* 2007;11: 409–412.

Instructions to Authors

Authors are advised to read these instructions carefully. Adhering to the format of the journal guidelines will facilitate and limit the time needed for the processing of the paper.

Types of papers

Please specify the type of paper submitted for publication. The journal accepts the following categories: original articles, short communications, case reports, review articles, letter to the editor, medical news and quiz cases relevant to medical education.

Covering letters

1. Should specify the type of paper according to the first paragraph of this document.
2. If the authors wish, they can include in the covering letter information on related publications.
3. All authors should sign the covering letter.
4. Address all correspondence to:-

   The Editor, Khartoum Medical Journal, P.O.Box 102, Khartoum, Sudan.

   E.mail:kmj @meduofk.net

   E-mail:khartoummedicalj@gmail.com

Copyright

Submission of original articles for publication is an undertaking by the author/s that:-

1. The manuscript is not under consideration for publication elsewhere.
2. The manuscript is original, truthful and free of fabrication, fraud or plagiarism.
3. All authors have read the manuscript, agree to its contents and share in the responsibility of its publication.
4. All authors have made a substantial contribution to the work submitted e.g. conception and design, experimental work or clinical studies, analysis and interpretation of data, drafting and critical editing. Contributions such as obtaining material or other support does not justify authorship.
5. All funding and support for the work should be acknowledged.
6. Any part of the manuscript not owned by the authors requires that permission should be obtained by the authors from the owner of the copy right.
7. All papers published by the journal will be KMJ copyright.
8. Please also supply information or related papers in press or submitted for publication elsewhere.

The manuscript

1. Use of English Language according to Oxford English Dictionary style.
2. Formatting the manuscript: should be typed, double spaced, with margins not less than 3 cm.
3. The title should not be more than 100 characters and spaces.
4. The abstract should not be more than 250 words presented as follows: objectives or background – about 50 words, methods about 60 words, results about 60 words and conclusion about 60 words.
5. System of international units should be used. Equivalents may be given in parenthesis. Symbol and abbreviations: A Guide for Biological and Medical Editors and Authors, 5th Edition, 'London, Royal Society of Medicine Press 1999'.
6. Tables should be on separate pages.
7. Legends for tables and figures should be submitted separately.
8. Please supply two hard copies of manuscript, tables and figures as well as a digital copy which may be sent through the e-mail.

Illustrations

1. Illustrations should be kept to the minimum. Illustrations in color are acceptable; however, an extra charge may be required to be paid by authors.

2. Care should be taken that illustrative material may have to be reduced in size to fit pages or columns. It is recommended that the size of figures to be about 12.5x20 cm.
3. All illustrations should be numbered on the reverse side and the tope of the figure indicated.
4. Graphics should be clear, camera-ready and all symbols explanations included on the figure or in the legend.
5. Permission to reproduce illustrations or tables should be obtained by the authors and submitted with the manuscript.

Statistical analysis

1. Statistical methods used should be clearly identified and if necessary described.
2. Means and standard errors of the mean and P values should be given to two decimal places.

References

1. Please use the Vancouver Style as shown below.
2. References should be listed numerically by order of their appearance in the text.

The Vancouver Style of Reference Formatting

With the growth of medical knowledge and research, it had become necessary that the formatting of reference citation both within the text of scientific writing and in reference lists should be widely agreed. The first steps to establish a uniform system for formatting manuscripts and references were begun by the Conference of Biological Editors in 1960. The International Committee of Medical Journal Editors (CMJE) held a meeting in Canada in 1979 to launch a uniform style of reference formatting for medical journals and proposed the Vancouver Style. Since then the major medical journals have adopted the 'Uniform requirements for manuscripts submitted to biomedical journals'[(1)], a common style for presentation of papers for publication.

- The justification of an internationally accepted style of reference citation can be summarized as follows:-
- Correct and complete referencing of scientific and medical publications is an essential component of the 'scientific method' when recording the outcome of research.
- To facilitate formatting scientific papers for more efficient peer reviews and publications.
- An unambiguous system of referencing allows other researchers and reviewers of manuscripts to access the cited literature to validate claims and arguments.
- To successfully secure research funding, the research proposal including the existing literature on which it is based should be convincing and easily accessed by reviewers.
- Uniform and complete citation formats facilitates quotation and reference compilation for researchers and postgraduate students.

The following is a summary to supplement the Instructions to Authors for referencing of manuscripts submitted to KMJ. It is based on the Vancouver Style and is the preferred referencing format for writing of dissertations, theses and other referenced writing in the Faculty of Medicine, University of Khartoum:-

1. References should be numbered consecutively throughout the text in the order in which they appear.
2. No references should be included in the abstract.
3. Identify references in the text, tables and legends by numerals in parenthesis e.g. (1), (2,3) or (3-6).
4. When citing authors in the text, acknowledge only the first author where there are three or more authors, e.g. Smith et al (1998) stated that ….(1).
5. Where there are two authors cite both, e.g. Adam and Ehsan (2003) reported that ….(2). Note that numerals in parenthesis at the end of a sentence are written before the full stop.
6. The list of references should begin on a new page and given the numbers which indicate order of citation.
7. All authors should appear in the list of references i.e. all references are listed in full.
8. Where more than 6 authors are registered, write

the first 3 authors followed by et al.

9. The order of author/s initials, punctuation, title of article, year, journal title – in accepted abbreviated form, volume and page numbers, constitute a full reference citation. The following are examples of commonly used reference sources:

Reference in journals

General format including punctuation,

Author/s, title of article, title of journal (in italics with no full stops), year; volume number: page numbers.

e.g. Rose ME, Huerbin MB, Melick J, JK et al. Regulation of interstitial excitatory amino acid concentrations after cortical contusion injury. Brain Res 2002; 935: 40-6.

References in books

Author(s) of a book

General format including punctuation.

Author(s) Title: sub-title. Edition. Place of publication: Publisher; Year

e.g. Guyton AC, Hall JE. Textbook of Medical Physiology. 10th Ed. Philadelphia: Saunders; 1990.

Author(s) of a chapter in a book

General format including punctuation

Author(s) of the chapter. Title: sub-title of chapter. In: Author(s) (or editors) of the book. Title: sub-title of book. Place of publication: Publisher; Year; page numbers.

Elmunshid HA. Special senses. In: Sukkar MY, Elmunshid HA, Ardawi MS, editors. Concise Human Physiology 2nd Edn. Oxford: Blackwell Science; 2000.p.401-23.

Reference on-line

Example (from The Michener Institute for Applied Health Sciences, Learning Resource Centre: Irc@ michenere.ca).

Book on the Internet

Foley KM, Gelband H, editors. Improving palliative care for cancer [monograph on the Internet]. Washington: National Academy Press; 2001 [cited 2002 Jul 9]. Available from: http://www.nap.edu/books/o309074029/html/.

Internet homepage/website

Cancer-Pain.org [homepage on the Internet]. New York: Association of Cancer Online Resources, Inc.; c2000-01 [updated 2002 May 16; cited 2002 Jul 9]. Available from: http://www.cancer-pain.org.

For a fuller range of examples of citation from other sources of references, there are innumerable sites on the internet. Please also consult the publications cited in KMJ instructions to authors and the references cited below:-

1. Uniform requirements for manuscripts submitted to biomedical journals: writing and

Volum 13 Number 02 May 2020

CONTENTS

Original articles

Review article