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Research Article

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Prevalence of Metabolic Syndrome amongst Rwandan Patients with Epilepsy

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Abstract ***Purpose:*** Cardiovascular mortality and morbidity are more frequent in people with epilepsy than in general population. The explanation of that may be the change in biochemical components due to anti-epileptic drugs. We conducted this study to determine the prevalence of metabolic syndrome (MetS) and risk factors in adults with epilepsy emphasizing on respective anti-epileptic drugs patients were using.

Method: This was a cross-sectional study conducted from December 2018 to December 2019 in patients with epilepsy aged 18-60 years old who were on anti-epileptic drugs for at least two years. 1076 adult patients with epilepsy were selected to participate in this study. Participants were anthropometrically examined and fasting blood glucose and lipids were assayed. The study was conducted at Ndera Neuropsychiatric Hospital-CARAES Ndera in Rwanda.

Results: The final participant pool included 669 males, 58.5% and 447 females, 41.5%. The mean age of participants was 40.22±10.37 that of males was 40.20.04±10.34 and of females was 40.24.04±10.42. Using ATP III criteria, the crude prevalence of metabolic syndrome in people with epilepsy was 30.6% (329 subjects) and patients without metabolic syndrome were 747 (69.4%). Use of valproic acid (p=0.007), sedentary lifestyle (p=0.025), waist circumference>102cm (p=0.001), high triglycerides (p=0.001), high blood pressure (p=0.001), and fasting blood glucose >6.1mmol (p=0.001) were significantly associated with metabolic syndrome.

Conclusion: The MetS is highly prevalent among patients with epilepsy

Keywords Metabolic syndrome, epilepsy, prevalence

Introduction

The metabolic syndrome (MetS), a group of metabolic risk factors including hyperglycemia, dyslipidemia (elevated triglycerides, reduced high-density lipoproteins), elevated blood pressure, and obesity is increasingly becoming a global public health concern [1]. In general population, westernization characterized consumption of foods with fat and sugar content combined with less physical exercises are the leading causes of this syndrome [2] which is a great predicator of cardiovascular disease [3].

Compared with the general population, people with epilepsy have elevated rates of cardiovascular mortality and morbidity [4-5] which may be driven by metabolic changes. Studies have found that this patient group also has an increased risk of developing the metabolic syndrome [6] and obesity [7], both of which have been shown to be risk factors for vascular disorders [8-9].

The connection between the metabolic syndrome and epilepsy is emerging as a public health question of importance to both specialists and primary care practitioners [10]. So far few studies, with contradictory results, have investigated the presence of MetS in patients with epilepsy. Some of these studies targeted only specific groups of populations, such as females [10], young adults [11], children [12-13]; whereas others studied different metabolic side effects of AEDs on different organs, tissues and biochemical components of human body such as bone and calcium metabolism [14], glucose metabolism [15], mental health [16], blood components [17] and lipid metabolism [18].

We estimated the prevalence of MetS in Rwandan Patients with Epilepsy in a cross-sectional survey conducted from December 2018 and December 2019 at Ndera Neuropsychiatric Hospital-CARAES Ndera in Rwanda. Data on lifestyle and metabolic risk factors were conducted on adult patients aged 18 years old to 60 years old. We used the NCEP ATP III criteria to confirm MetS [19]. This study is the first to provide the estimate prevalence of MetS and risk factors in Rwandan patients with epilepsy.

Methods

Subjects

The study has been carried out in the Out-patients' Department of Ndera Neuro-Psychiatric Hospital, in Kigali, Rwanda. This study was carried out within a period of 12 months: From December 2018 to December 2019, we determine the prevalence of MetS and its individual components namely diabetes, hypertension, dyslipidemia and obesity in patients with epilepsy attending Ndera Neuro- Psychiatric Hospital. Consecutive enrolment was used as the sampling method. Study participants were adult volunteers diagnosed with epilepsy aged between 18 to 60 years attending the out-patients' clinic at Ndera Neuro-psychiatric Hospital who were under medication. Eligible study participants were only included in the study if they had no trait of MetS and no significant of chronic disease related to the component of MetS.

We excluded patients who were under 18 years' old because we used criteria from the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATPIII) which is for adults only. We also excluded candidates with malignancies, pregnancies, mental or legal incapacity that prevents them to give a valid consent or hinders them to fully participate in the whole process of this study or to comply with the study protocol.

Data Collection

Data were collected from patients who voluntarily agreed to participate in the study by signing a written consent form following a detailed explanation on the study. Participants were then interviewed and examined in a selected room for privacy and confidentiality. Demographic data, i.e. name, sex, age, and marital status and risk factors i.e. diabetes, hypertension, physical activity, smoking, and clinical measurement of height, weight and waist circumference were collected using structured questionnaires. The interview was carried out by the principal investigator and one research assistant (RA) who was trained before conducting the research.

Anthropometric Measurements

After filling up the questionnaire, anthropometric measurements were performed. Waist circumference was taken without outer clothing, using a non-stretchable tape measure at level of the uppermost edge of the hip bone on a light clothed abdomen with the tape parallel to the ground and recorded to the nearest 0.5 centimeters. Blood pressure was taken from the arm (brachial artery) from all respondents in the first encounter by using digital sphygmomanometer. Blood pressure measurements were performed in the sitting position with the arm supported at heart level and repeated after 5 minutes; the average of the two measurements was taken as a blood pressure. To calculate body mass index (BMI), subjects were weighted (kilograms) on scale full dressed but without shoes. Height (centimeters) was measured without shoes by a stadiometer. BMI was calculated as weight divided by height squared (kg/m^2).

Biochemical Tests

After an overnight fast, blood samples were collected with BD Vacutainer® Venous Blood Collection tubes. Five milliliters of venous blood were taken from the antecubital fossa and placed in empty sterile tubes. The blood samples were separated by centrifugation at 1000 × g for 15 min and the supernatant serum was collected. Serum levels of lipids [triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C)], fasting blood glucose were measured using commercially available kits (Roche System Reagents) by a Cobas C 311 autoanalyzer.

Statistical Analyisis

Data were entered and analyzed using the Statistical Package for Social Sciences (SPSS) version 24.0 software (SPSS Inc., Chicago, IL). Means of numeric variables were compared between groups by the Student's t-test. Proportions were compared by the Chi-square test. A multivariate logistic regression was used to determine the risk factors associated with MetS in patients with epilepsy. For tests and models, a *p*-value of less than 0.05 was taken for statistical significance.

Ethical clearance

Before the commencement of the study, ethical clearance was sought from Mbarara University of Science and Technology – Research Ethics Committee (MUST - REC). Ethical approval was also secured from both Rwanda National Health Research Committee (NHRC) and Rwanda National Ethics Committee (RNEC). We conducted our study in accordance with the guidelines of the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects. The information about the study was given to all study participants prior to interview and sample collection. A written and duly signed consent was obtained from all participants. Confidentiality was ensured for all individuals who participated in the study. The participation was fully voluntary devoid of any kind of intimidation or coercion and no participant was paid for participating in the study

Results

During the study period, 1076 adult patients with epilepsy meeting the inclusion criteria were carefully selected to participate in this study: They were 669 males, 58.5% and 447 females, 41.5%). The mean age of participants was 40.22±10.37 that of males was 40.20.04±10.34 and of females was 40.24.04±10.42. The distribution of age was 33.3% (n=358) between 18-35 years, 34.8% (n=374) between 36-45 years, 32.0% (n=344) between 46-60 years. Valproate treated patients were 328 (30.5 %), carbamazepine; 207 (19.2 %), leveracetam; 145 (13.5 %), phenytoin; 130 (12.1 %), phenobarbital; 135(12.5 %), clonazepam; 95(8.8 %) and topiramate treated patients were 36(3.3 %). Other clinical characteristics of participants are presented in table 1 and 2.

The crude prevalence of metabolic syndrome in people with epilepsy was 30.6% (329 subjects) and patients without metabolic syndrome were 747 (69.4%). Males with metabolic syndrome were 189 (17.6%) whereas females with metabolic syndrome were 140 (13.0%). The prevalence of metabolic syndrome weighted by age group was 9.0% (97) among the age group of 18-35 years old, 11.2% (120) among the age group of 36-45 years old and 30.6% (329) among the age group of 46-60 years old. Regarding individual components of MetS, 378 subjects (35.2 %) had high abdominal obesity, 316 subjects (29.4%) had high blood pressure, 155 subjects (14.4%) had diabetes mellitus, 283 subjects (26.3%) had Low HDLc, and 303 subjects (28.2%) had high level of serum triglycerides.

Table 1: Clinical characteristics of subjects with epilepsy with and without metabolic syndrome

	Total number of subjects (N=1076)	**Participants without metabolic syndrome [N = 747 (69.4%)]**	**Participants with metabolic syndrome [N = 329 (30.6%)]**	**p value**
Gender N (%)				0.655
Males	669 (58.5%)	440 (40.9%)	189 (17.6%)	
Females	447 (41.5%)	307(28.5%)	140 (13.0%)	
Age groups N (%)				0.214

18-35	358 (33.3 %)	261 (24.3%)	97 (9.0%)	
36-45	374 (34.8 %)	254 (23.6%)	120 (11.2%)	
46-60	344 (32.0 %)	252 (21.6%)	329 (30.6%)	
Antiepileptic drugs N (%)				0.066
Valproic acid	428(30.5 %)	209 (19.4%)	119 (11.1%)	**0.007**
Carbamazepine	207 (19.2 %)	140 (13.4%)	67 (6.2%)	0.534
Leveracetam	145 (13.5 %)	104 (9.7%)	41 (3.8%)	0.518
Phenytoin	130 (12.1 %)	97 (9.0%)	33 (3.1%)	0.799
Phenobarbital	135(12.5 %)	95 (8.8%)	40(3.7%)	0.171
Clonazepam	95(8.8 %)	74(6.9%)	21 (2.0%)	0.061
Topiramate	36(3.3 %)	28 (2.6%)	8 (0.7%)	0.268
Metabolic parameters (mean ±SD)				
FBG (mmol/L)	5.75±0.70	5.63±0.65	6.01±0.74	**0.001**
Total cholesterol (mmol/L)	3.78±0.88	3.75±0.82	3.84±0.98	0.141
LDLc (mmol/L)	3.20±1.18	3.09±1.11	3.44±1.28	**0.001**
HDLc (mmol/L)	1.15±0.20	1.18±0.19	1,09±0.20	**0.001**
Triglycerides (mmol/L)	1.34±0.58	1.25±0.53	1.54±0.62	**0.001**
Component of metabolic syndrome				
High abdominal obesity	378 (35.2 %)	182(16.9%)	196 (18.3%)	**0.001**
High blood pressure	316 (29.4%)	90 (8.4%)	101 (9.5%)	**0.001**
Diabetes mellitus	155 (14.4%)	84 (7.8%)	71 (6.6%)	0.001
Low HDLc	283 (26.3%)	144 (13.4)	139 (12.9%)	0.001
High triglycerides	303 (28.2%)	141(13.1%)	162 (15.1%)	0.001

Abbreviations: HDLc, high density lipoprotein cholesterol; FBG, fasting blood glucose; LDLc, low density lipoprotein cholesterol; N, number; SD, standard deviation; %, percentage. Bold values indicate the ones which have attained statistical significance.

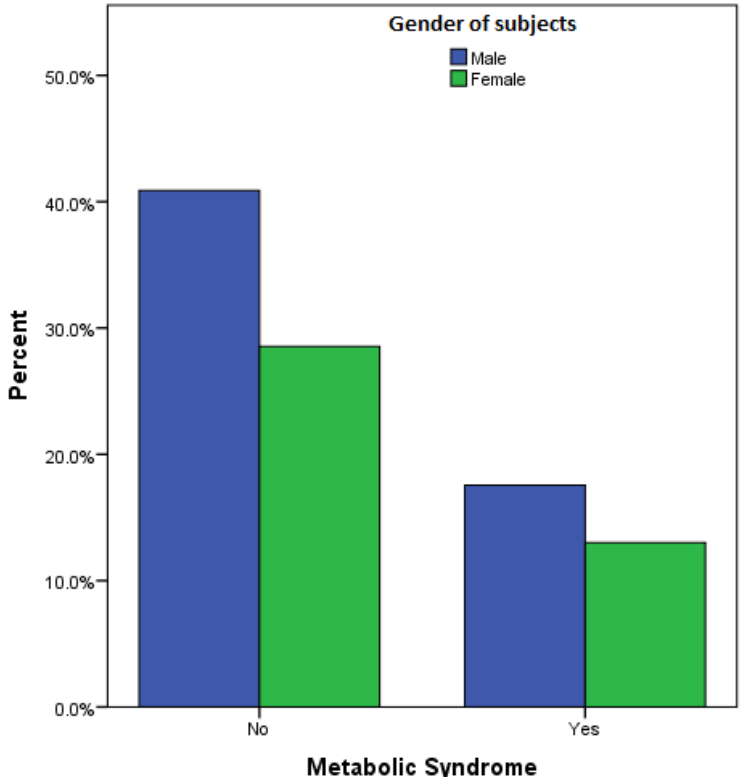

Figure 1: Prevalence of metabolic syndrome among males and females

Table 2: Comparison of clinical and metabolic parameters between males and females

	Males [N = 629 (58.5%)	**Females [N = 447 (41.5%)]**	**p value**
Age groups N (%)			0.812
18-35	214 (19.9%)	144(13.4%)	
36-45	215 (20.0%)	159 (14.8%)	
46-60	200 18.6%)	144 (13.4%)	
Ages in years, (mean ±SD)	40.20±10.34	40.24±10.42	0.950
Antiepileptic drugs N (%)			0.398
Valproic acid	199 (18.5%)	129 (12.0%)	
Carbazepine	126 (11.7%)	81 (7.5%)	
Leveracetam	81 (7.5%)	64 (5.9%)	
Phenytoin	77 (7.2%)	53 (4.9)	
Phenobarbital	72(6.7%)	63 (5.9%)	
Clonazepam	58 (5.4%)	37 (3.4%)	
Topiramate	16 (1.5%)	20 (1.9%)	
Metabolic parameters (mean ±SD)			
FBG (mmol/L)	5.74±0.69	5.75±0.72	0.805
Total cholesterol (mmol/L)	3.72 ±0.85	3.85+0.90	**0.017**
LDLc (mmol/L)	3.19±1.15	3.20+1.21	0.890
HDLc (mmol/L)	1.15±0.20	1.16±0.20	0.666
Triglycerides(mmol/L)	1.34±0.56	1.33±0.60	0.767
Component of metabolic syndrome			
High abdominal obesity	215 (20%)	163 (15.1%)	0.885
High blood pressure	112 (10.4%)	79 (7.3%)	0.763
Diabetes mellitus	97 (0.9%)	58 (5.4%)	0.260
Low HDLc	166 (15.4%)	117 (10.9%	0.937
High triglycerides	183 (17.0%)	120 (11.2%)	0.419

Abbreviations: HDLc, high density lipoprotein cholesterol; FBG, fasting blood glucose; LDLc, low density lipoprotein cholesterol; N, number; SD, standard deviation; %, percentage. Bold values indicate the ones which have attained statistical significance.

Regarding the occurrence of MetS in patients under different anti-epileptic drugs, we found that valproic acid was significantly associated with MetS (p=0.007). We didn't find any statistical significance between other AEDs and MetS, See table 5.1. Among 328 valproic acid treated patients, 119 (36.3%) patients had MetS. Among 207 carbamazepine treated patients, 67 (32.4%) had MetS. Among 145 levetiracetam treated patients, 41 (28.3%) had MetS. Among 135 phenytoin treated patients, 40 (29.6%) had MetS. Among 130 phenobarbital treated patients, 33 (25.4%) had MetS. Among 95 clonozepam treated patients, 21 (22.1%) had MetS. Among 36 topiramate treated patients, 8 (22.2%) had MetS.

Table 3: Frequency of metabolic syndrome in patients under different anti-epileptic drugs

		Metabolic Syndrome		
		No	**Yes**	**Total**
Valproic acid	*No*	538 (71.9%)	210 (28.1%)	748 (100.0%)
	Yes	209 (63.7%)	119 (36.3%)	328 (100.0%)
Carbamazepine	*No*	607 (69.9%)	262 (30.1%)	869 (100.0%)
	Yes	140(67.6%)	67 (32.4)	207 (100.0%)
Levetiracetam	*No*	643 69.1%)	288 (30.9)	931 (100%)
	Yes	104 (71.1%)	41 (28.3%)	145 (100%)
Phenytoin	*No*	652(69.3%)	289 (30.7%)	941 (100%)
	Yes	95 (70.4%)	40(29.6%)	135 (100.0%)
Phenobarbital	*No*	650 (68.7%)	296 (31.3%)	946 (100.0%)
	Yes	97 (74.6%)	33 (25.4%)	130 (100.0%)
Clonozepam	*No*	673 (68.6%)	308 (31.4%)	981 (100.0%)
	Yes	74 (77.9%)	21 (22.1%)	95 (100.0%)
Topiramate	*No*	719(69.1%)	321 (30.9%)	1040 (100.0%)
	Yes	28 (77.8%)	8 (22.2%)	36 (100.0%)
Total		**747 (69.4%)**	**329 (30.6%)**	**1076 (100.0%)**

In this study, a multivariate logistic regression analysis didn't reveal any significant correlation between the occurrence of MetS in patients with epilepsy and some clinical characteristic such as sex, age gender, family history of diabetes and family history of hypertension.

On another hand, a significant correlation was found between the occurrence of MetS and a quite number of components such us waist circumference (OR=1.067; *P*=0.001;95% CI, 1.052-1.016), fasting blood glucose(OR=1.810; *P*=0.001; 95%CI, 0.866-1.809), serum triglyceride (OR=2.797; *P*=0.001; 95% CI, 2.122-3.685), systolic blood pressure (OR=1.32; *P*=0.001; 95% CI, 1.018-1.046) and diastolic blood pressure (OR=1.102; *P*=0.001; 95% CI, 1.071-1.232).

Table 3: Multivariate analysis of risk factors associated with metabolic syndrome

Component	Odd ratio (OD)	*p*-value	95% confidence interval	
			Lower	Upper
Gender	1.272	0.128	0.933	1.734
Age	1.001	0.903	0.986	1.016
Waist circumference>102cm	1.067	**0.001**	1.052	1.016
Fasting blood glucose >6.1mmol	1.810	**0.001**	0.866	1.809
HDLc<1.03 mol	0.066	**0.001**	0.029	0.148
Triglyceride >130mol	2.797	**0.001**	2.122	3.685
Systolic blood pressure >130 mmHg	1.032	**0.001**	1.018	1.046
Diastolic blood pressure>85 mmHg	1.102	**0.001**	1.071	1.232
Family history of diabetes	0.978	0.906	0.029	0.148
Family history of hypertension	1.252	0.232	0.866	1.809

Discussion

This study determined the prevalence of MetS and cardiovascular risk factors in patients with epilepsy. The crude of MetS prevalence we found (30.6%) is higher than many other prevalence reported by surveys conducted in general population using ATPIII criteria; for instance in Ethiopia a reported prevalence was 10.0% in men and 16.2% in women [20], in South Africa, 18.5% [21], in Ghana, 15.0% [22], in Nigeria 25.2% [23], in Cameroon, 1.8%-1.9% [24], in Canada, 19.1% [25] etc. However some results from general population showed a higher prevalence than ours; for instance a community study from urban Eastern India reported an overall prevalence of 33.5% [26]. Studies conducted in patients already presenting components of metabolic syndrome reported similar prevalence as ours like the one which was looking at risk factors in obese children and adolescents in Dalmatia, Croatia (30.3%) [27], others studies reported higher prevalence than ours like a prevalence study conducted in overweight and obese outpatient children and adolescents in Brazil which reported alarming prevalence of 55.6% up to 74% [28].

Some studies that were looking on prevalence of metabolic syndrome in certain categories of patients with epilepsy found closely related prevalence: Nair et al reported a prevalence of 29.5% in young adults Indian with epilepsy [11], and Rakitin et al., reported a prevalence of 25.8% in Estonian adults patients with epilepsy who were under VA treatment [29] . Other studies reported higher prevalence: Jiajia Fang et al. reported a MetS prevalence of 47% among Chinese obese patients with epilepsy on VA [30] and Verrotti et al. after conducting their study in Italian overweight epileptic patients treated with VA, reported that 43.5% of their study participants patients had MetS [13].

In our study, all age groups had different frequencies of MetS however this difference didn't reach statistical significance (9.0% in 18-35 years old group, 11.2% in 36-45 years old group, and 30.6% in 46-60 years old group, *p*=0.214). In this regards, if we compare our results with results from other studies conducted among patients with epilepsy elsewhere, we are in agreement with Jiaji Fang et al. who also didn't find significant difference of MetS across age groups [31]. However our results disagrees with results of Nair et al. who found significant higher prevalence of MetS in oldest age group [6].

In our study, men and women were all affected though with different proportions [189 subjects (17.6%) versus 140 subjects (13.0%), *p*=0.655)]. This can be interpreted that AEDs and other risk factors like sedentary life and

unhealthy lifestyle can trigger MetS in people with epilepsy regardless of their gender and age group. Our resultants are therefore concordant with results published by Verroti et al., Nair et al, Jiaji Fang et al who also found no difference of MetS between males and females [6, 13, 31]. However, Prasad et al reported significant gender differences with higher prevalence of MetS in females compared to males (42.3% vs 24.9%) [26].

We observed that across all age groups, valproic acid (VA) treated patients are more prone to develop MetS than other EADs treated patients (11.1%, p=0.007). The least prevalence of MetS was found in topiramate treated patients (0.7%, p=0.268). This confirms earlier reports from several studies which emphasize that the use of VA for treating epilepsy is linked with high probability of experiencing metabolic and hormonal disturbances [21-22, 32-38].

Regarding individual components of MetS, we found that the most prevalent one was the high abdominal obesity with diabetes mellitus being the least prevalent. However, in some general population studies, the most frequent MetS component was low serum HDL cholesterol in women and elevated high blood pressure (HBP) in men [21, 24]. Similar results have been found by other investigors [39] and abdominal obesity was significantly correlated with MetS (p=0.001).

Increased abdominal obesity have constantly been reported by several researchers working on studies patients with epilepsy who are under AEDs medication especially VA [10], [13], [40–42] and current evidence supports that abdominal obesity is a predictive of metabolic risk factors [7, 43, 46-47]. In our study, HBP was the second most MetS individual component we found. According to Jiaji Fang et al, HBP was also found to be very common in Chinese obese patients with epilepsy on VA. VA causes MetS in some patients but not all. Genetic factors and several molecular pathways of energy homeostasis might influence the occurrence of MetS [13]. Our study showed that the prevalence of hyperglycemia was 14.4 % which suggests that hyperglycemia is higher among patients with epilepsy than in general population. The Rwanda Non-communicable Diseases Risk Factors Report released in 2015 pointed out that in the general population of Rwanda, impaired fasting glucose levels and raised blood glucose affect 3.1% of the population in Rwanda [48]. Hyperglycemia may be due to drugs which are known to cause hyperglycemia like VA or due to combination of MetS risk factors commonly found among patients with epilepsy like obesity and lower exercise capacity that make body cells less sensitive or resistant to insulin.

Conclusion

This is the first study of this nature to look at the prevalence of metabolic syndrome and risks factors among patients with epilepsy in Rwanda. Results of our study form an informative tool for clinicians and other police makers in management of epilepsy in Rwanda. Understanding the prevalence of metabolic syndrome and other metabolic abnormalities among patients with epilepsy is immensely useful to practitioners to help affected patients to undergo risk reducing interventions. This also lays a good foundation for further research like interactions of AEDs and other medications, markers of genetic susceptibility of MetS in patients with epilepsy etc.

Disclosure statement

The authors declare that they have no competing interests

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