THE HORMONAL CHANGES AMONG NIGERIAN WOMEN WITH EPILEPSY

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ABSTRACT

This study aims to compare the sex hormones between women with epilepsy (WWE) and their age-matched controls. We postulated that a difference in etiology, may be associated with an unexpected hormonal profile. A case control study carried out at the University College Hospital, Ibadan, South western, Nigeria involving seventy-five WWE and age-matched controls. Blood samples for hormonal evaluation follicle stimulating hormone (FSH), luteinizing hormone (LH), estrogen, progesterone and testosterone were taken twice from all the participants during their menstrual cycle. WWE had lower BMI (p: 0.004), cycle length (p: 0.014) and more menstrual pattern irregularities (p< 0.001.) In the pre-ovulatory phase, WWE had lower FSH levels when compared with controls, (p: 0.012). Further stratification shows a higher FSH levels among WWE on medication, (p: 0.003).In the mid-luteal phase, FSH level was lowest in WWE not on medication, WWE on medication had higher levels but lower when compared to the control group, p: 0.002. FWE had lower progesterone levels when compared with the control group, (p: 0.004) with no difference with use of AEDs. Testosterone levels were lower among those with symptomatic epilepsy, (p:0.012)WWE had lower progesterone, lower FSH and more menstrual abnormalities, compare to controls in our population.

Keywords: Hormonal Changes, Women, Epilepsy, Nigeria

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INTRODUCTION

The regular and synchronized release of various sex hormones ensures oocyte maturation, ovulation, and menstruation (Velíšková *et al,* 2010, Harden & Pennell 2013) Due to the cyclical nature of hormone release and the direct neuronal effects of oestrogen and progesterone or their metabolites, women are especially susceptible to the effects of these shifting hormones onseizure frequency and severity (Velíšková *et al,* 2010, Velíšková & DeSantis 2013). Thehormonal effects not only causes rapid changes in neuronal activity (Reddy 2013) but also long term changes from involvement of intracellular receptors that mediates gene expression at the nuclear level(Velíšková et al 2010, Harden & Pennell 2013).The relationship between epilepsy and sex steroid hormones has been explored with studies showing a bi-directional complex interdependence(Velíšková *et al,* 2010 Velíšková & DeSantis 2013). Progesterone has long been shown in several studies to have anti-seizure activities (Herzog *et al.* 2015,Younus & Reddy 2017 Pennell 2009). Reports have also postulated that progester one is the basis behind a lower incidence of epilepsy in women than men (Di Mai 2014). To this effect, progesterone has been linked to management of a number of brain related conditions e.g. traumatic brain injury (Harden & Pennell 2013 Velíšková & DeSantis 2013, Harden *et al.* 2006). Estrogen on the other hand is believed to have pro-convulsant and epileptogenic property (Sato & Woolley 2016. Velísková 2000). Intravenous infusions of estrogen is associated with rapid inter-ictal epilepti form activity in women with epilepsy (WWE), and seizures were exacerbated when estrogen was given prior to menstruation (Harden *et al*., 2006 Luef 2010). However, catamenial epilepsy in our routine epilepsy clinic is an uncommon occurrence despite prevalence as high as 78% (Herzog *et al.,* 2015 Herzog 2015). Also, result of an earlier study that showed no difference in the frequency of clinically significant sexual dysfunction between women with epilepsy (WWE) and their matched controls in

our cohort informed this study (Ogunjimi *et al.,* 2018). This study aims to compare the sex hormones between WWE and their age-matched controls. We postulated that a difference in etiology, with a higher prevalence of structural and/or acquired epilepsy in sub-Saharan Africa (Ba-Diop *et al.,* 2014, Preux & Druet-Cabanac 2005), may be associated with an unexpected hormonal profile.

MATERIALS AND METHODS

We conducted an observational study at the Neurology clinic, University College Hospital, Nigeria involving seventy-five WWE and forty-five controls of comparable ages between August 2015 and august 2016. The diagnosis of epilepsy was made clinically with electro encephalographic (EEG) features taken into consideration. Participants with a background chronic medical illness, features suggestive of pseudo-seizures, on oral contraceptives, pre-diagnosis of hypo-gonadism, structural gynecological anomalies, amenorrhea and those on hormonal replacement therapy were excluded. Ethical approval was obtained from the Joint Institution Review Committee (IRC) of the University College Hospital and the College of Medicine, University of Ibadan, Nigeria. An interviewer administered questionnaire administered by trained Neurologist was used to obtain socio-demographic variables and relevant clinical information from recruited participants which include epilepsy frequency, semiology, etiology and anti-epileptic drugs (AED) use. A Phoenix digital 16-channel EEG was used to obtain tracing in all participants. EEG recording lasted at least 45 minutes, with activation procedures including hyperventilation and photic stimulation. Detailed hospital records and medical history with focus on menstrual cycle characteristics was obtained from cases and controls.

A regular menstrual cycle was taken as 21-34 day duration (Amu & Bamidele 2014.). Blood samples for hormonal evaluation-follicle stimulating hormone (FSH), luteinizing hormone (LH), estrogen, progesterone and testosterone were taken from all participants twice during their menstrual cycle. The first sample was taken during the ovulatory phase on the 10^{th}-13^{th} day of the cycle. The second sample was withdrawn during the luteal phase on the 21^{st}-24^{th} day. Enzyme linked immune-sorbent assay technigue was used to determine the hormonal concentration. Data obtained were entered in Microsoft Excel for cleaning and subsequently transferred to Stata version 12 for analysis. The Pearson Chi-square or Fisher's exact (where the expected counts were less than five per cell) was used to assess categorical variable. Wilcoxon rank-sum and Kruskal Wallis test was used to determine continuous variable. The level of significance was $P < .005$.

RESULTS

The ages of participants ranged from 16-57 years with mean age of WWE and controls, 32.1 years (SD:± 9.3 years) and 31.2 years (SD: ±6.7 years) respectively; (t: -0.56, p-value: 0.575.) There was a significant difference in mean body mass index between both groups, 24.7 kg/m2 (SD: ±4.6 kg/m2) among WWE as opposed to 27.5 kg/m2 (SD: ±5.7 kg/m2) among controls; t: 2.97, p-value: 0.004. WWE and controls had similar gynecological features with respect to age at menarche (p: 0.959), bleeding days (p: 0.347) and frequency of dysmenorrhea (p: 0.072) but differ in cycle length and menstrual pattern with WWE having shorter cycle length (p: 0.014). The prevalence of menstrual disturbance among WWE in our cohort was 39.7% . Sixty p percent (60.3%) WWE admitted to normal menstrual flow as opposed to 97.5% controls (p< 0.001) with 18 (24.6%), and 11 (15.1%) WWE admitting to hypo-menorrhea, and hyper-menorrhea. See Table .

Table 1: Menstrual Related Characteristics

	WWE	Controls	Stat	p-value
Age, Mean (SD)	32.1 (9.3)	31.2 (6.7)	[1]-0.56	0.575
BMI, Mean (SD)	24.7 (4.6)	27.5 (5.7)	[1]2.97	0.004
Menarche, Mean (SD)	12.7 (1.9)	12.7 (1.8)	[1]0.05	0.959
Bleeding Days, Mean (SD)	4.7 (0.8)	4.9 (1.2)	[1]0.95	0.347
Dysmenorrhea, N (%)	46 (61.3)	20 (44.4)	[2]3.24	0.072
Cycle Length, Mean (SD)	27.1 (4.0)	28.9 (5.0)	[3]2.46	0.014
Normal Menstrual Flow, N (%)	44 (60.3)	39 (97.5)	[2]18.58	<0.001

[1]Independent student t-test (t-statistic). [2]Pearson Chi-square test (X^2). [3]Mann Whitney test (Z-score)

Among WWE, those on Anti epileptic Drugs (AED) had a shorter cycle length, 26.6 (±3.6) days; bleeding days, 4.6 (±0.8) days; and a higher frequency of dysmenorrhea, 40 (69.0%) when compared to those not on AED who had cycle length, 30.1 (±5.3) days, bleeding days, 5.3 (±0.7) days, and dysmenorrhea frequency of 6 (35.3%), p-values: p: 0.021, 0.031 and 0.012 respectively. Using the 2017 International League Against Epilepsy classification, of the studied subjects 38(50.7%) had combined,18 (24.0%) had generalized, 12 (16.0%) had focal unaware, and 7 (9.3%) had focal aware epilepsy. Of the 75 WWE; 39 (52.0%) had structural, 30 (40.0%) had idiopathic, 5 (6.7%) had infective, and one (1.3%) metabolic etiology. Concerning treatment, 58 (77.3%) were on AED - carbamazepine, all within 2 years since commencement, with 7 out of 58 (12.1%) admitting to poor medication adherence. 36 (51.4%) of the WWE had not attained seizure control, there was no statistical difference in seizure control between WWE not on medication and WWE on medication, X^2: 1.99, p: 0.159.

In the pre-ovulatory phase, WWE had lower FSH levels (5.8 mIU/ml; IQR: 3.2-11.7 mIU/ml) when compared with controls (8.3 mIU/ml; IQR: 6.3-13.0 mIU/ml), Z: 2.518, p: 0.012. Further stratification shows that WWE on medication had higher FSH levels (6.4mIU/ml; IQR: 3.7- 14.2 mIU/ml) when compared to WWE not on treatment (4.6 mIU/ml; IQR: 2.3 – 5.5 mIU/ml), p: 0.003. Controls had similar LH/FSH ratio with WWE on medication. However, WWE not on medication had a higher LH/FSH ratio (1.3mIU/ml; IQR: 0.7-10.3 mIU/ml) when compared to WWE on medication (0.9 mIU/ml; IQR: 0.5-1.1 mIU/ml). There was no significant difference in the levels of LH, estrogen, progesterone and E/P ratio between WWE with or without treatment . see Table2.

Table 2: Pre-ovulatory Phase Hormonal level

	WWE not on AEDs mIU/ml, Med (IQR)	WWE on AEDs mIU/ml, Med (IQR)	Controls mIU/ml, Med (IQR)	p
FSH	4.6 (2.3 – 5.5)	6.4 (3.7 – 14.2)	8.3 (6.4 – 13.0)	<0.001
LH	6.6 (4.6 – 41.0)	6.8 (4.7 – 16.3)	8.0 (6.2 – 10.3)	0.984
LH/FSH	1.3 (0.7 – 10.3)	0.9 (0.5 – 1.1)	0.9 (0.6 – 1.2)	0.026
Estrogen	80.9 (53.7 – 280.0)	74.6 (44.6 – 164.8)	80.5 (60–104.4)	0.673
Progesterone	1.0 (0.3 – 10.0)	0.7 (0.4 – 2.4)	0.9 (0.5 – 1.8)	0.438
E/P ratio	64.6 (21.9 – 142.0)	88.0 (54 – 248.2)	71.4 (47.9–124.1)	0.461

In the mid-luteal phase, FSH level was lowest in WWE not on medication (4 mIU/ml; IQR: 1.3- 6.2 mIU/ml), FWE on medication had higher levels (5.6 mIU/ml; IQR: 3.2-11.0 mIU/ml) but lower when compared to the control group (8.3 mIU/ml; IQR: 4.6-12.0 mIU/ml), p: 0.002. WWE on medication and those without however had similar progesterone level which was significantly lower than levels among the control group, (X2:10.9, p: 0.004). The E/P ratio was higher in WWE when compared to controls and among the WWE, those on medication had similar values compared to those without medications (X2: 13.0, p: 0.002). There was no significant difference in the levels of LH, LH/FSH ratio, estrogen, E/P ratio, and testosterone between WWE and controls levels of LH, FSH, progesterone and estrogen did not vary with epilepsy classification and were comparable in patients with idiopathic epilepsy and those with symptomatic epilepsy. However, testosterone levels were lower among those with symptomatic epilepsy (2.4 mlU/ml; IQR: 1.0-3.8 mlU/ml) when compared to those with idiopathic epilepsy (1.1 mIU/ml; IQR: 0.7-1.7 mIU/ml); p-value: 0.012. This occurs despite no difference in clinical outcome seen in the use of carbamazepine between both groups (73.3% vs. 76.9%)

DISCUSSION

The lower proportions of abnormal menstrual patterns in controls compared to WWE suggest an under lying hormonal abnormality among WWE and underscores the need to evaluate the effect of epilepsy and AEDs on menstrual cycles among women. Interestingly, the prevalence of menstrual disturbance among WWE in our cohort was similar to results from other studies (Amu & Bamidele 2014. Svalheim *et al.,* 2003). In this study, WWE had lower FSH values with even lower score among WWE without medications in both pre-ovulatory and luteal phase similar to findings from a previous study by El- Khayat *et.al,* (2008). Possible explanation include; the negative effect of epilepsy on ovulation and menstruation, effect of carbamazepine, or seizure effect on the hypothalamus. Left temporallobe epilepsy has been shown to have an effect on FSH and this can explain lower levels in WWE. The concomitant increase in FSH level among WWE on carbamazepine raises the possibility of reduction or resolution of seizure events as the mechanism behind his change in FSH level. This may however be unlikely in this study as there was no change in seizure Control between FWE on medications and those not on medication. The relationship between menstrual parameters and AED in the study will suggest carbamazepine may act at this level. Carbamazepine has been shown to impact on FSH level, as it aids conversion of inactive to active metabolite(Bangar et al.2016, Svalheim *et al*., 2009, Verrotti *et al.,* 2011) The fact that an ovulatory condition like polycystic ovarian syndrome is less common with carbamazepine contrary to the use of other anti-epileptic drugs that reduces the FSH level also supports this notion (Bangar *et al*., 2016; Svalheim *et a l.,* 2009, Verrotti *et al.* 2011). It is therefore explainable that values of LH/FSH among WWE not on carbamazepine were greater than 1 in our study. Notably, Miia *et al*, (2006) demonstrated the differential effect of carbamazepine on LH, FSH prolactin, sex hormone binding globulin at two months and twelve months respectively. Further studies to ascertain the acute, chronic and cytochrome p450 activities of carbamazepine action on sex steroid and ovulation in FWE with focus pharmacogenomics is suggested. The fact that WWE had similar estradiol levels with controls in this study is surprising. With themetabolic effect of AEDs on estradiol, a lower estradiol is expected. Also, with a lower FSH level in WWE, a lower estradiol can be expected. However, we postulate that peripheral action of carbamazepine on FSH might be an explanation to higher estradiol than expected. This couple with increase estradiol receptor sensitivity in the brain of WWE (Verrotti *et al*., 2009,Viswanathan *et al.,* 2016, Mukherjee *et al.,* 2017) can both explain the lower FSH seen in WWE, change in menstrual characteristics and absence of clinically relevant sexual dysfunction earlier documented (Ogunjimi *et al.* 2018). Another explanation not explored in this study is the acute versus chronic seizure effect and pulsatility of gonadotropins. More clinical data are emerging that estrogen may have no pro-convulsant or even anticonvulsant effects, even though it is commonly accepted that estrogen affects neuronal excitability and thus may mediate pro-convulsant effects (Preux & Druet-Cabanac 2005). The pro-convulsant effect of estrogen has been linked to modulation of gene expression, direct interaction with neurotransmitter receptors and release and induction of brain derived

neurotrophic factor (BNDF) which potentiates excitatory glutaminergic pathway in the hippocampus and elevation in seizure frequency, particularly after estradiol surge during peri-ovulatory catamenial epilepsy (Scharfman & MacLusky 2006,Sohrabji *et al* 1995, Wang *et al.*, 2018). However, estrogen also closely relate to endogenous molecules like NPY with seizure protecting property. There is a sequential induction of BDNF and NPY to bring about transient rise and fall in seizures frequency (Scharfman & MacLusky 2006. Scharfman & MacLusky 2008). Again, as demonstrated in this study, WWE had a lower progesterone level in the luteal phase and by extension a higher E/P ratio. This is similar to what was reported by various authors (Velíšková et al 2010 Mukherjee *et al.,* 2017; Scharfman & MacLusky 2008). Interestingly, the peri-ovulatory pattern C1, of Catamenial epilepsy has been best explained by high E/P ratio (Harden & Pennell 2013, Herzog 2015, El Khayat *et al.,* 2008). However, while a high E/P ratio is seen in this study, none of the FEW reported features suggestive of catamenial epilepsy. This may give credence to other possible explanation which includes rise in glucocorticoid levels, LH-FSH surge, sequential induction of brain derived growth factor (BDNF) and neuro peptide Y (NPY). The overall effect of estrogen however depends on treatment duration, mode of administration, seizure type/model, estrogendose and hormonal status.

It should be stated that the levels of LH, FSH, progesterone and estrogen did not vary with epilepsy classification and were comparable in patients with idiopathic epilepsy and those with symptomatic epilepsy. However, testosterone level was lower among those with symptomatic epilepsy even though use of carbamazepine was similar between both groups. The lower levels of testosterone in the female with symptomatic epilepsy compare to those with idiopathic epilepsy, further reinforce our initial thought that a difference in etiology may be associated with an unexpected hormonal profile and therefore difference in clinical presentation.

Studies have suggested that epileptogenic focus has some association with hormonal profile. Epilepsy, especially those with involvement of limbic system might have ictal and post ictal effect on hypothalamo-pituitary-ovarian axis thus affecting the hormonal levels. Of importance however is that temporal lobe epilepsy in particular have adverse effect on testicular endocrine function and unilateral amygadala seizures activates the hypothalamus in a laterally asymmetric fashion resulting in different endocrine disorders(Taubøll et al 2015).The left temporal lobe epilepsy was associated with significantly higher pulse frequency of gonadotrophin release hormone secretion which is associated with higher testosterone and LH/FSH ratio(Herzog et al. 2003 Herzog 1993). On the contrary, right temporal lobe epilepsy leads to a reduced GnRH pulse frequency, higher frequency of hypothalamic amenorrhea, lower LH and estradiol (Herzog *et al.,* 2003). This may thus explain why both hypermenorrhea and hypomenorrhea are commoner in FWE compared with controls in this study and emphasizes the need for neuroimaging, the lack of which limits further analysis in this study. Also, evaluation of the inter-ictal and post-ictal secretion of luteinizing hormone in mesial temporal lobe epilepsy revealed that acute seizures induced timing irregularity in luteinizing hormone secretion, whereas chronic epilepsy was associated with changes in luteinizing hormone pulse frequency, amplitude, and mass(Luef 2010; Herzog 1993). Our study demonstrated a relatively higher E/P, lower FSH and lower progesterone in the luteal phase among WWE with a higher prevalence of menstrual abnormalities.

CONCLUSION

The use of carbamazepine however, had an effect on menstrual symptoms and improved FSH levels. Also, testosterone levels were lower in the female with symptomatic epilepsy when compared to those with idiopathic epilepsy. A difference in seizure etiology may explain the unexpected hormonal profile seen in our setting. Therefore, physician should not only consider effect and duration of AEDs usage but also the etiological impact, duration and lateralization of epilepsy, when managing females with epilepsy to optimize care and improve quality of life. The inability to properly localize epileptogenic focus is however a limitation in the study as variations in hormone level cannot be fully explaine.

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