

## Women and Epilepsy: Sudanese experience

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### Abstract

Epilepsy is equally prevalent in men and women. However, for women there are unique concerns related to hormone effects on seizures and the effects of seizures and antiepileptic drugs (AEDs) on reproductive health. Some AEDs reduce the efficacy of oral contraceptive agents, increasing the probability of unplanned pregnancies. Seizure frequency may change during pregnancy, seizures may cause pregnancy complications, and the treatment of a woman with epilepsy must consider all these issues.

**Objective:** To study the clinical presentation of epilepsy among adult Sudanese females and to verify aspects of epilepsy specific to women.

**Methods:** This is a cross sectional descriptive non intervention clinical based study; it was carried out in Elshaab Teaching Hospital and El-shiekh Mohamed Kheir charity clinic, from February-2008 to June-2008. 630 female patients with epilepsy were included in the study.

**Results:** The study showed that 72% of the patients had generalized epilepsy and 28% had partial epilepsy, primary epilepsy is more common than secondary epilepsy, 54% of our patients had warning symptoms and 39.7% had triggering factors, irregular menstrual cycle was observed in 28%, 22% of our patients had catamenial seizures, 7.1% had increased frequency of seizures during pregnancy. Obstetric complications were common among our studied group. The incidence of infertility increased among our studied group.

**Conclusion:** Women had differences in presentation and control of epilepsy that must be understood and considered when treating women with epilepsy.

**Key Word:** Sudanese Women, Epilepsy

### INTRODUCTION

Epilepsy is a condition characterized by repeated seizures due to a disorder of the brain cells. In many respects epilepsy in women is a little different from epilepsy in men; the investigations, diagnosis, and many aspects of treatment are

identical. The menstrual cycle is fundamentally a neurological event. Normal reproductive function requires an interaction between hypothalamic, pituitary and ovarian hormones. The sex steroid hormones; estrogen and progesterone have a direct effect on cortical excitability. A balance between estrogen and progesterone effect is

required for a normal menstrual cycle and fertility. Abnormalities of sex steroid hormones may adversely affect cortical excitability in persons who have epilepsy. [1-2]

Contraceptives have not been associated with exacerbation of epilepsy. The effectiveness of hormonal contraceptives can however, be reduced by enzyme inducing AED (carbamazepine, phenytoin, phenobarbital, felbamate, topiramate). Hormonal contraceptives come in three formulations: oral (*estrogen-progesterone combinations, or progesterone only*); subcutaneous, (*levonorgestrel*) or intrauterine, (*progestasert*) implants; and injectable (*Depo-Provera*). All three forms can be adversely impacted by enzyme inducing AED. [3-4]

Fertility may be as low as two-thirds of that expected in the general population. [5-6]

One-quarter to one-third of women with epilepsy will have an increase in seizure frequency during pregnancy especially in the third trimester. Obstetric complications associated with epilepsy include:

1. Increased risk of vaginal bleeding
2. Anaemia
3. Hyperemesis gravidum
4. Abrupto placenta
5. Eclampsia
6. Premature labour
7. Spontaneous abortion
8. Stillbirth and perinatal death
9. Children of women with drug treated epilepsy had lower birth weight, length, and head circumference than children of women without epilepsy.

The infants of epileptic mothers are at greater risk to a variety of adverse pregnancy outcomes. These include fetal death, congenital malformations, neonatal haemorrhage, low birth weight, developmental delay, feeding difficulties, and childhood epilepsy. There is agreement that children exposed to polytherapy are at increased risk of malformation. [7-8]

## OBJECTIVES

To study the clinical presentation of epilepsy among adult Sudanese females seen in Elshaab

Teaching Hospital and El-shiekh Mohamed Kheir charity clinic, and to verify aspects of epilepsy specific to women e.g.

1. Menstrual cycle associated with epilepsy.
2. Infertility.
3. Complications associated with pregnancy.
4. Complications occurring during and after delivery.
5. Neonatal congenital abnormalities.

## METHODOLOGY

This is a cross sectional descriptive non intervention clinical based study design; it was carried out from February-2008 to October-2009.

**Study area:** The study was carried out in:

1- *Elshaab Teaching Hospital which is a tertiary hospital, which receives patients from all parts of the country, located in the centre of El-Khartoum town. There are two neurological units with 43 beds and two neurosurgical units with 50 beds, there are three intensive care units, two neurology referred clinics and three neurosurgery referred clinics each week.*

2- *El-Shiekh Mohamed Kheir Charity clinic: which is a charity clinic located in El-fetehab region south of Omdurman city in which volunteer neurologists tend to treat people from the local area and different parts of the Sudan.*

**Study population:** Adult Sudanese women with epilepsy.

**Sample size:** 630 female patients with epilepsy over 14 year's of age were included in the study. All patients gave their verbal consent to participate in the study; ethical approval was obtained from the local ethical committee.

**Data collection:** Data was collected by direct contact with patients using data collection sheets composed of personal data and detailed history. The history included symptoms, onset, presence of warning symptoms, triggering factors, family history, frequency of attacks, menstrual cycle pattern, and frequency of seizures during pregnancy, history of obstetric complications, the type of epilepsy, imaging studies and drug treatment was obtained from each patient.

**Sampling technique:** None probability sampling was undertaken; all female patients fulfilling the criteria of selection (females above 14 years of age with epilepsy) and who accept to participate in the study were enrolled in the study.

**Methods of data analysis:** All collected data was finally entered using statistical package program for social science (SPSS) to analyze the data.

#### Limitations of the study:

1. Short duration of the study.
2. Drugs' levels sample especially during third trimester of pregnancy was not taken.
3. Hormone level (*estrogen, progesterone*) were not taken especially at mid-cycle to determine non-ovulatory cycles.
4. Many patients failed to remember previous events. These factors affect detection of complications and correlation between complications and side effects of the drugs and correlation between hormonal levels and occurrence of fits.

## RESULTS

Almost 630 adult Sudanese female patients with epilepsy were enrolled in the study. Their age ranged between 14 and 65 years with a mean age of 30 years. Generalized epilepsy was detected in 72% of our patients; simple partial epilepsy in 11% and 17% had complex partial epilepsy. Almost 41% of our patients had their onset of epilepsy at an age younger than 10 years, 25% of the patients reported their onset to be between the age 10 to 19 years, 22% between 20 to 29 years, 8% of patients at age 30 to 39 years old and 3% at an age greater than 50 years. Regarding causes of epilepsy 410 (65%) had primary epilepsy and 220 (35%) had secondary epilepsy. On asking our patients 29 (46%) reported that they didn't have any warning symptoms while 340 (54%) had warning symptoms. From 180 patients with partial epilepsy, 120 (67%) were experiencing warning symptoms in contrast to 220 patients out of 450 patients with generalized epilepsy (49%) had warning symptoms. The presence of triggering factors was reported in 250 patients (39.7%). Out of 180 patients with partial epilepsy 140 (77.8%) reported having triggering factors compared to 240 out of 450 patients (53.3%) with generalized

seizures having triggering factors. When patients were asked about family history of epilepsy 480 (76%) denied the existence of family history, 70 (11%) had history of epilepsy in first degree relatives and 80 (13%) had history of epilepsy in second degree relatives. The control of epilepsy varies between patients from no attacks for more than two years (controlled) to more than once per day. It did appear that (4.8%) of the patients were controlled without antiepileptic therapy, 410 patients (65%) on monotherapy and 190 patients (30.2%) on polytherapy.

Out of 630 female patients with epilepsy 60 had reached menopause; so they were not asked about regularity of their cycle, from the remaining 570 patients 410 (72%) women had a regular cycle and 160 (28%) had an irregular cycle. The 630 patients were asked if they noticed any relation between the attacks of seizure and their cycle, even those who were post menopause were asked to remember from their pre-menopause time. 490 patients (78%) reported no relation, 140 (22%) reported increased frequency of fits either before onset of bleeding (10 patients) or at onset of bleeding (130 patients), some of them reported that they had fits only at time of the period. Out of 630 patient 440 (69.8%) were not married, 190 (30.2%) were married. (140 had children and 50 patients didn't have children). Out of 190 married patients 175 denied having using contraceptives. Contraceptives have not been associated with exacerbation of epilepsy among those who used to take the pills. Regarding type of delivery; out of the 140 patients who had children 110 (78.5%) had a history of a normal delivery, while 30 patients (21.5%) had a caesarean section. Out of the 140 patients who had children 120 had history of obstetric complications. Regarding change of control of epilepsy during pregnancy; 30.1% of our patients reported increased frequency of fits during pregnancy.

## DISCUSSION:

The study showed that generalized epilepsy (including all types of generalized epilepsy) represents 72% of all cases while partial epilepsy represents 28% of the cases, this is not similar to what was reported by the UK National General Practice Study of Epilepsy (two thirds focal epilepsy and one third generalized epilepsy).<sup>[1]</sup>

But it approximates what was reported by WHO report about epilepsy in African region (where the majority of the cases are tonic clonic epilepsy). [2] The discrimination from the findings of the UK National General Practice Study of Epilepsy, may be due to the fact that grand mal epilepsy is dramatic in its presentation so that affected people are interested to seek medical treatment, unlike partial seizures which may go unnoticed especially in the developing countries, and this may be the same reason for its compatibility with the WHO report about epilepsy in the African region. It was observed that 66% of our patients had their onset of epilepsy at an age from 1 to 20 years (41% at age 1 - 9 and 25% at age 10 - 20); this is matched with what was mentioned in the literature. [3] It was found that 65% of our patients were with no identifiable cause and the remaining 35% with secondary epilepsy, this is similar to what was reported by the UK National General Practice Study of Epilepsy that the majority (60%) of people with newly diagnosed or suspected epileptic seizures had epilepsy with no identifiable etiology. [4] The study showed that (46%) of our patients had warning symptoms which is similar to the findings of the Hungarian study (50%), the most frequently reported symptoms included: abnormal sensation, which is felt but can not be identified clearly by the patients, headache, tinnitus, drowsiness, abdominal pain and palpitation were compatible with what was reported by other researchers. [5] It was noticed that the frequency of warning symptoms was more common among patients with partial epilepsy than those with generalized epilepsy which was compatible with what was mentioned by other researchers. [6] The identification and documentation of warning symptoms is important for patients as it may form some sort of forecasting coming attack and taking precautions to avoid dangerous and embarrassing situations. Presence of some factors that may precipitate or trigger seizure activity was observed by (39.7%) of our; this approximates the figures of the national centre of epilepsy in Norway (35%), but it was less than the figures of king's college hospital study (90%). [7-8] The main seizure precipitants reported was emotion, tiredness, fever, colic's and noise; many of these factors were similar to what was mentioned in the literature. [8-9] many patients reported more than one precipitating factor. Triggering factors were much more reported by

patients with partial seizures than generalized seizures (84% of the patients with partial seizure versus 53% of patients with generalized seizures); this variation is higher than what was mentioned in the literature and it has no explanation. [5-10]

It did appear that (28%) of our pre-menopause women had irregular cycle, which is less than the findings of the Norwegian study (48%) and approximate the figures of the control group in the study (30.7%). The study showed that (22%) of our patients reported increased frequency of seizures with menstruation. [11-21] the discrimination may be resulting from different definitions fore catamenial seizures, in this study for practical problems catamenial seizures have been defined as seizures occurring exclusively or primarily during the premenstrual period; as it may be easier for patients to remember. If we want to use a broader definition this may require to use the method proposed by Herzog AG, by asking the patients to chart their seizure occurrence and onset of menstruation on a calendar for one cycle during which they had a midluteal blood sample taken for serum progesterone determination on day 22, and close monitoring. This may allow determining the pattern of epilepsy occurring at time of ovulation. [15-16-17-18]

Catamenial epilepsy refers to the association of seizure to the menstrual cycle; the true frequency of menstrual exacerbations of seizures (catamenial epilepsy) is unclear. Women with catamenial epilepsy are notoriously difficult to control with AEDs. [1] Menstrual dysfunction and reproductive endocrine disorders are seen with increased frequency, compared with general population figures. Estimates vary because of different definitions of menstrual disorders. Best estimates suggest that one of every three women with epilepsy may be affected compared with one of seven in the general population. These disorders have been postulated to be secondary to the effects of seizures on prolactin, gonadotropin, and sex steroid hormone levels, although AEDs and psychosocial and socioeconomic factors may have a contributing role.

Contraceptives have not been associated with exacerbation of epilepsy. AEDs may lower

concentrations of estrogens by 40 to 50 %. They also increase sex hormone binding globulin (SHBG) which increases the binding of progesterone and reducing the unbound fraction. The result is that hormonal contraception is less reliable with enzyme inducing AED. Oral contraceptives should have at least 50ug. Of estrogen, (Which means taking two pills and woman should advise to report any breakthrough bleeding). If this occurs the dose of estrogen should be increased to 75 or 100 µg. The more rapid clearance of the estrogens when used in conjunction with an enzyme inducing AED will reduce the likelihood of unwanted side effects from higher dose tablets. Absence of breakthrough bleeding does not necessarily mean that the contraception is effective. If maximum protection against pregnancy is desired barrier methods (for example, condom or diaphragm), should be used in addition to the oral contraceptive pill, Alternatively non-enzyme inducing AED may need to be considered (valproate, lamotrigine, gabapentine or zonisamide). The oral progestogen-only contraceptive pill should not be used in women taking enzyme-inducing AEDs because effective levels of progestogen cannot be guaranteed. However, the progestogen depot injection medroxyprogesterone acetate (Depo-Provera) does not undergo first pass metabolism and is a very useful contraceptive in these circumstances.

A considerable number of our studied group had no children despite non contraceptives use; According to the World Health Organization, incidence of infertility is about 10 % worldwide. Epidemiological studies have demonstrated that women with epilepsy have only 1/4 to 1/3 as many children as women in the general population (Bilo et al. 1988, Isojarvi et al. 1993). Fertility was lower among women with treated epilepsy, with an overall rate of 47.1 live births per 1000 women aged 15-44 per year, compared with a national rate of 62.6 in the same age-group. Obstetric complications may be implicated in reduced fertility for women with epilepsy. [19-20-23] although it is difficult to refer this high incidence to epilepsy alone, other causes of secondary infertility should be excluded. The existence or absence of infertility should be confirmed by referral to gynecologist and the examination of the husband too, besides the psychological and social counseling.

The percent of cesarean section in this study is more than what was reported by other researchers e.g. the Iceland study, where the percentage is was found to be (31%). [24, 25-34] But one big limitation of our study is that the figures did not represent the number of deliveries but the number of females having history of cesarean section. Beside that the small sample size can not provide good estimates. To evaluate the significance of obstetric complications we need to have larger sample size and to have a control group with which the findings will be compared. The literature was variable about the obstetric complications associated with epilepsy, one of the study found that the risk of obstetric complications is comparable to background population ,while another study found that epileptic groups have increased risk of complications associated with pregnancy . [32, 33, 34] it is obvious that the group of the study has very high rate of obstetric complications (86%), the rate of preterm delivery was very high (57%), if compared to the figures of the UK. [26, 28, 35, 36] The risk of congenital malformations is relatively rare therefore its estimation requires large sample size, in this study we reported high rate of congenital malformation (7.14%). If we use this figure it is very high. Like what was observed by other researchers it was found that 30.1% of our patients reported increased frequency of fits during pregnancy. [27, 29, 32, 37] this increase is unrelated to seizure type, duration of epilepsy, or seizure frequency in a previous pregnancy. The exact mechanism is not known but it may be due to the fact that third trimester is associated with high level of hormones, hypomagnesaemia, fluid retention and low level of anti epileptic drugs; which may be due to fluid retention, impaired absorption, and enhanced clearance. About 1% of women with epilepsy will have a seizure during labor. Stress, low levels of AEDs, sleep deprivation, and hyperventilation may all contribute to lowering seizure threshold. [29]

## CONCLUSION

Generalized epilepsy and primary epilepsy were more common than partial epilepsy and secondary epilepsy respectively.

2-Almost 67% of the patients had their onset of epilepsy before age of 20 years.

3-Warning symptoms were observed in 54% of the patients.

4- Seizure precipitating factors were found in 39.7% of the patients.

5-Menstrual cycle disturbances and association of fits with the menstrual cycle were frequently reported in our studied group.6-The frequencies of Obstetric complications including; eclampsia, preterm delivery, cesarean section were high in this study.

## RECOMMENDATIONS

1- There is a pressing need for a well-designed studies addressing every health issue for WWE reviewed, especially in light of the availability of several new AEDs. Critical areas for future study may include; reproductive physiology, pharmacokinetics, and long term outcome studies.

2-Physician education surrounding management issues for WWE is required at all levels of training and practice, and evidence-based practice parameters provide a potentially valuable tool in this education process.

3- In order to enable informed decision and choice, and to reduce misunderstandings women with epilepsy and their partners, as appropriate must be given accurate information and counseling about contraception, conception, pregnancy, caring of child and breastfeeding .

4- There is urgent need to develop pregnancy registries, as continued enrollment of women with epilepsy in prospective pregnancy registries can serve as an "early warning system" by looking for either clusters of specific abnormalities or rates of malformation in excess of expected.

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