A case report on catamenial epilepsy*

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ABSTRACT

A case of a 17-year-old nulligravid with onset of seizure episodes since menarcheis reported. She was diagnosed with Seizure Disorder treated with Phenobarbital and was seizure free for 2 years. Two years prior to consult, seizure recurrences were noted to coincide with menstruation, hence, was diagnosed with Catamenial Epilepsy. Patient was shifted to Lamotrigine but seizure exacerbations were still observed, prompting referral to the Reproductive Medicine service for adjunctive hormonal therapy. Depot medroxyprogesterone acetate was added to the antiepileptic drug which provided seizure control. Adjunctive hormonal therapy proved to be helpful in the management of intractable seizures in this patient.

The report aims to give a better understanding of the neuroactive properties of estrogen and progesterone and its role in the development of Catamenial Epilepsy. Gender-related and psychosocial issues in the treatment of Epilepsy in the child-bearing years up to the menopause are also discussed.

Keywords: Catamenial epilepsy, seizure, antiepileptic drug, hormonal therapy

INTRODUCTION

Epilepsy is a disorder characterized by unpredictable seizure episodes and has long been associated with other medical conditions. Regularity of seizures that coincides with menstruation is a reason to explore the role of estrogen and progesterone in seizure development. Catamenial Epilepsy is derived from the Greek word *katamenios*, meaning monthly, first described by Charles Locock in 1857 as "hysterical epilepsy"[1]. It was described as regular seizure episodes confined to women connected with the menstruation. Verrotti et al. defined Catamenial Epilepsy as having at least 75% of the attacks during a 10-day period of the menstrual cycle beginning 4 days before menstruation and 6 days after its onset[2]. Navis and Harden specified that the term Catamenial Epilepsy does not refer to a specific Epilepsy syndrome, but rather to catamenial seizure exacerbations[3]. Catamenial Epilepsy is more common in women with focal Epilepsy than those with generalized Epilepsy, though any type of Epilepsy can have a catamenial exacerbation[2]. In women with Epilepsy during the reproductive years, a correlation has been observed between the cyclic monthly levels of estrogen and progesterone and seizure frequency[4].

Catamenial seizure exacerbations can affect 10% to 70% of reproductive age of women[2]. The wide range of incidence is due to the absence of a fixed definition of the disease entity. Diagnostic criteria are still vague since others argue that Catamenial Epilepsy can be diagnosed with occurrence of seizures around menstruation, while some consider such diagnosis with an increase in seizures in relation to the menstrual cycle. The percentage of increase in seizure episodes is also not well defined. Duncan et al. documented successive seizure episodes for 3 consecutive months in 40 women. Only 5 women out of 40 fulfilled the criteria of Catamenial Epilepsy of having at least 75% of seizures each month in the 10-day time frame[5]. There is no local report on Catamenial Epilepsy to date.

This paper aims to present a case of Catamenial Epilepsy and discuss its pathophysiology, diagnosis, management, and issues in Reproductive Medicine.

CASE REPORT

A 17-year-old nulligravid, single, Roman Catholic, from Quezon City, consulted due to recurrent generalized seizures. Onset of seizure wasatage 12, upon patient's menarche. The attacks were noted on day -5 to +8 of menstruation, with 1-4 episodes of jerking movements of both upper extremities, circumoral cyanosis and drooling of saliva lasting for 1 minutes. There was no loss of consciousness or anyprodromal signs and symptoms. Consult with the Pediatric-Neurology service of a government hospital was done 4 years prior to consult (PTC). Workup such as cranial magnetic resonance imaging (MRI) and electroencephalogram (EEG) were normal. (Figures 1 and 2). A diagnosis of Seizure disorder etiology to be determined was given.

Pharmacotherapy in the form of Phenobarbital 90 mg/tab twice a day was given providinga 2-year seizure

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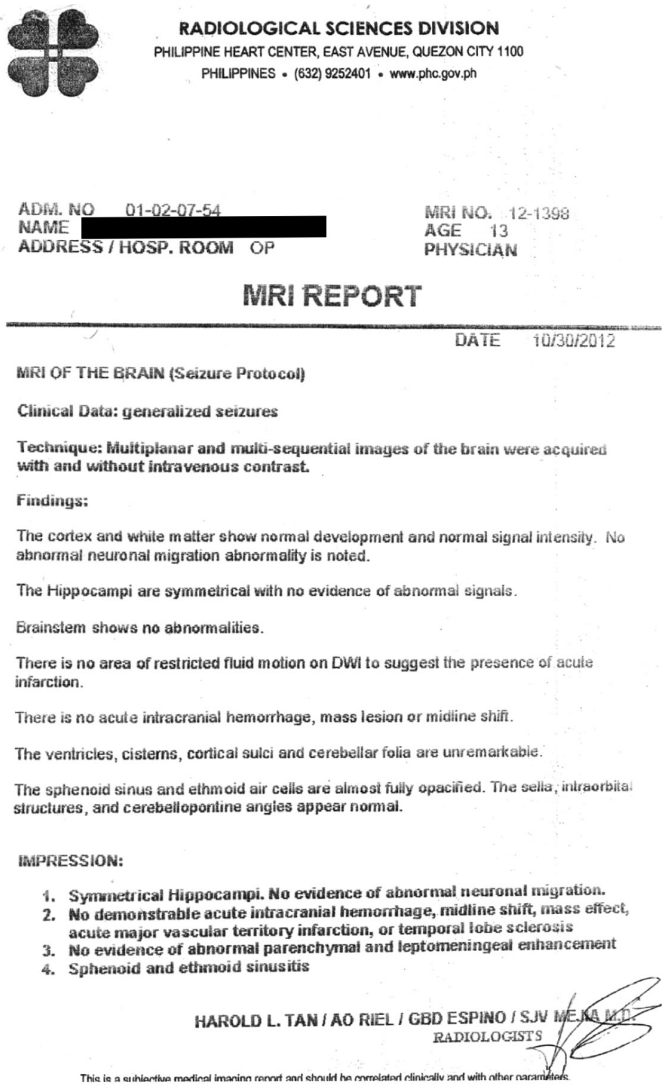

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ADM. NO 01-02-07-54 MRI NO. 12-1398
NAME [redacted] AGE 13
ADDRESS / HOSP. ROOM OP PHYSICIAN

MRI REPORT

DATE 10/30/2012

MRI OF THE BRAIN (Seizure Protocol)

Clinical Data: generalized seizures

Technique: Multiplanar and multi-sequential images of the brain were acquired with and without intravenous contrast.

Findings:

The cortex and white matter show normal development and normal signal intensity. No abnormal neuronal migration abnormality is noted.

The Hippocampi are symmetrical with no evidence of abnormal signals.

Brainstem shows no abnormalities.

There is no area of restricted fluid motion on DWI to suggest the presence of acute infarction.

There is no acute intracranial hemorrhage, mass lesion or midline shift.

The ventricles, cisterns, cortical sulci and cerebellar folia are unremarkable.

The sphenoid sinus and ethmoid air cells are almost fully opacified. The sella, intraorbital structures, and cerebellopontine angles appear normal.

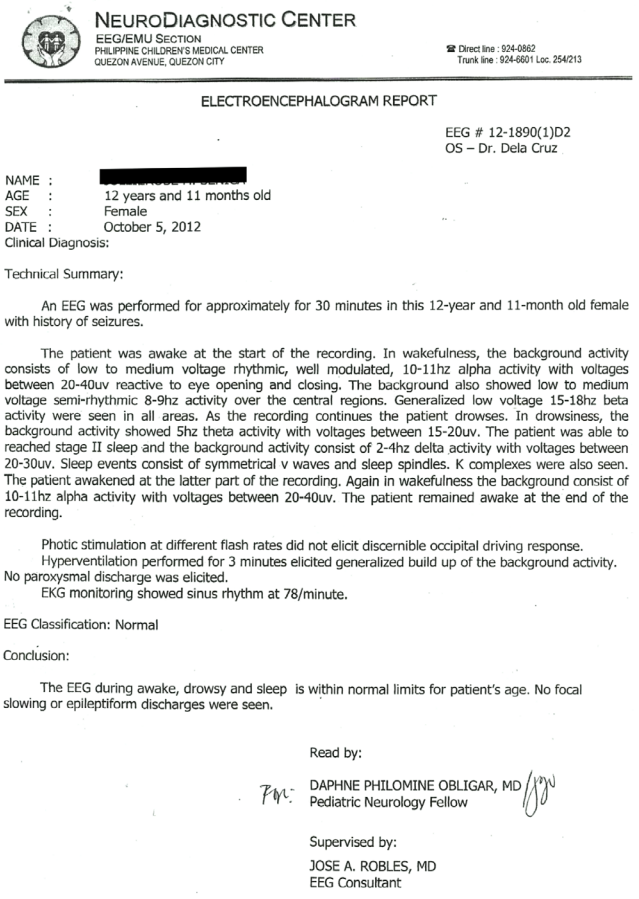
IMPRESSION:

1. Symmetrical Hippocampi. No evidence of abnormal neuronal migration.
2. No demonstrable acute intracranial hemorrhage, midline shift, mass effect, acute major vascular territory infarction, or temporal lobe sclerosis
3. No evidence of abnormal parenchymal and leptomeningeal enhancement
4. Sphenoid and ethmoid sinusitis

HAROLD L. TAN / AO RIEL / GBD ESPINO / SJV MEJIA M.D.
RADIOLOGISTS

This is a subjective medical imaging report and should be correlated clinically and with other parameters.

Figure 1. Cranial magnetic resonance imaging report of index patient done last October 12, 2012



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ELECTROENCEPHALOGRAM REPORT

EEG # 12-1890(1)D2
OS – Dr. Dela Cruz

NAME : [redacted]
AGE : 12 years and 11 months old
SEX : Female
DATE : October 5, 2012
Clinical Diagnosis:

Technical Summary:

An EEG was performed for approximately for 30 minutes in this 12-year and 11-month old female with history of seizures.

The patient was awake at the start of the recording. In wakefulness, the background activity consists of low to medium voltage rhythmic, well modulated, 10-11hz alpha activity with voltages between 20-40uv reactive to eye opening and closing. The background also showed low to medium voltage semi-rhythmic 8-9hz activity over the central regions. Generalized low voltage 15-18hz beta activity were seen in all areas. As the recording continues the patient drowses. In drowsiness, the background activity showed 5hz theta activity with voltages between 15-20uv. The patient was able to reached stage II sleep and the background activity consist of 2-4hz delta activity with voltages between 20-30uv. Sleep events consist of symmetrical v waves and sleep spindles. K complexes were also seen. The patient awakened at the latter part of the recording. Again in wakefulness the background consist of 10-11hz alpha activity with voltages between 20-40uv. The patient remained awake at the end of the recording.

Photic stimulation at different flash rates did not elicit discernible occipital driving response.
Hyperventilation performed for 3 minutes elicited generalized build up of the background activity. No paroxysmal discharge was elicited.
EKG monitoring showed sinus rhythm at 78/minute.

EEG Classification: Normal

Conclusion:

The EEG during awake, drowsy and sleep is within normal limits for patient's age. No focal slowing or epileptiform discharges were seen.

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Supervised by:

JOSE A. ROBLES, MD
EEG Consultant

Figure 2. Electroencephalogram of the index patient last October 5, 2012

free interval. However, she was noted to be impatient, irritable, and exhibited excessive attention-seeking behavior. Aggressive behavior in school was reported where she would inflict physical injury to classmates for no reason. A psychiatric consult was done and was prescribed with Olanzapine 5 mg/tab 1 tab once a day and Na Valproate + Valproic Acid 500 mg/tab once a day. Psychiatric assessment was Behavioral Changes due to another Medical Condition (Seizure Disorder). School psychiatrist advised discontinuation of Phenobarbital and suggested to take a break from school. Olanzapine was shifted to Clozapine 100mg/tab ½ tab at bedtime. Pediatric neurologist was informed of the behavioral changes and said that it was an expected side effect of patient's medications. She was forced to stop school for two years due to unpredictable behavior and poor concentration. She also suffered from low self-esteem and social withdrawal due to discrimination during seizure attacks in public.

Two years PTC, seizures recurred and observed to be coinciding with menstruation. She consulted at the Pediatric-Neurology service of this institutionand was given the diagnosis of Catamenial Epilepsy. Phenobarbital was tapered and was shifted to Lamotrigine. Despite dose adjustments of Lamotrigine, persistence of seizure attacks prompted referral to the Reproductive Medicine service for adjunctive hormonal therapy. Depot medroxyprogesterone acetate (DMPA) was started in conjunction with Lamotrigine and patient has been seizure free up to present.

Past medical and family history were non-contributory. Menarche was at age 12, each period lasting for 5-6 days in a 28-day cycle consuming 3 pads per day with reported seizures and hypogastric pain on days -5 to +8. She has no sexual intercourse. Currently, she is a 9th grade student at a Special Education (SPED) school and claims to be well adjusted in school with no mood fluctuations nor depressive episodes. Current medications are Lamotrigine 50mg/tab twice a day, Clozapine 100mg/tablet ½ tablet at bedtime, Sodium Valproate + Valproic acid 500 mg/tablet twice a day, and DMPA 150 mg intramuscularly every 3 months.

On physical examination, she is classified as Tanner

stage IV for breast and pubic hair. Rectal examination showed good sphincteric tone, cervix was firm, long, with a normal-sized corpus and no adnexal mass palpated.

Neurologic examination revealed normal cortical function. No cranial nerve lesions with intact sense of smell, pupils are 2-3 millimeter, equally reactive to light, primary gaze midline, full extraocular movements, intact and symmetrical sensation on bilateral cranial nerves V1-V3. No facial asymmetry, able to do facial muscle movements, intact gross hearing, intact gag reflex, uvula at the midline, equal palatal elevation, good shoulder shrug, good sternocleidomastoid tone and strength, and able to protrude tongue without any deviation. Motor examination shows 5/5 muscle strength on all extremities with no atrophy. No sensory deficit noted. Patient is normoreflexic with no noted pathologic reflex. She has a supple neck, no nystagmusnor tremors, dysdiadochokinesia, able to do finger to nose test, without gait disturbances.

Diagnosis given was G0, Catamenial Epilepsy.

CASE DISCUSSION

Seizures may be attributed to vascular disorders, infections, trauma, autoimmune, metabolic or toxic causes, neoplastic, structural or congenital disorders[6]. The regularity of the patient's seizure attacks coinciding with the menstrual period makes Catamenial Epilepsy a likely diagnosis. It is diagnosed clinically and is the primary consideration in this patient. Vascular, structural disorder and neoplasm as the cause of seizure in this patient were ruled out due to normal imaging studies. Metabolic disorders such as hypoglycemia, hypocalcemia, hypomagnesemia, and hypo/hypernatremia were ruled out with negative findings on blood chemistries. No history of trauma and infections elicited. Autoimmune disorders usually present with other clinical symptoms, not seen in the index patient.

Patient's onset of seizure and its exacerbations occur around the time of menstruation. Such seizure pattern clearly attributes the attacks to the cyclic variation and neuroactive properties of endogenous steroid hormone, hence was diagnosed with Catamenial Epilepsy. More than 75% of the attacks during a 10-day period of the menstrual cycle was observed in the index patient which qualifies her for the diagnosis of Catamenial Epilepsy as defined by Verotti et al.[2] Estrogen and progesterone are steroid hormones which have a role in neuronal development and plasticity due to their capacity to regulate synthesis, release, and transport of neurotransmitters[7]. The estrogen progesterone ratio (EP ratio) has a positive correlation to one's susceptibility to seizure occurrence throughout a normal menstrual cycle. High EP ratio leads to clustering of seizures, since estrogen is a pro-convulsant by increasing neuronal excitability while progesterone is an anticonvulsant by enhancing GABA-mediated inhibition[7]. The three main pathophysiological determinants of Catamenial Epilepsy involve the neuroactive properties of reproductive steroids, the variation of neuroactive steroid levels across the menstrual cycle, and the susceptibility of the epileptic substrate to neuroactive steroid effects[8].

Herzog et al. presented statistical evidence which is in current use showing at least 3 distinct patterns of seizure exacerbation in relation to the menstrual cycle: (1) perimenstrual (2) periovulatory in normal cycles and (3) luteal in patients within adequate luteal phase cycles (Figure 3).[9]

Catamenial type 1 (C1 pattern) is the most common type, wherein seizures occur perimenstrually from Days -3 to 3 due to the withdrawal of the anticonvulsant effects of progesterone accompanied by decrease in allopregnanolone, a potent positive allosteric modulator of $GABA_A$ receptor. In Catamenial type 2 (C2 pattern), seizures occur between Day 10 to -13 due to the pro-convulsant effect of the estradiol surge. In Catamenial type 3 (C3 pattern) seizures occur during the entire luteal phase in an anovulatory cycle, from Day 10 of one cycle to Day 3 of the following cycle. There is inadequate progesterone secretion in the luteal phase of anovulatory cycles as compared to ovulatory cycles, hence one is more susceptible to seizure attacks.[9] The decline in EPratio

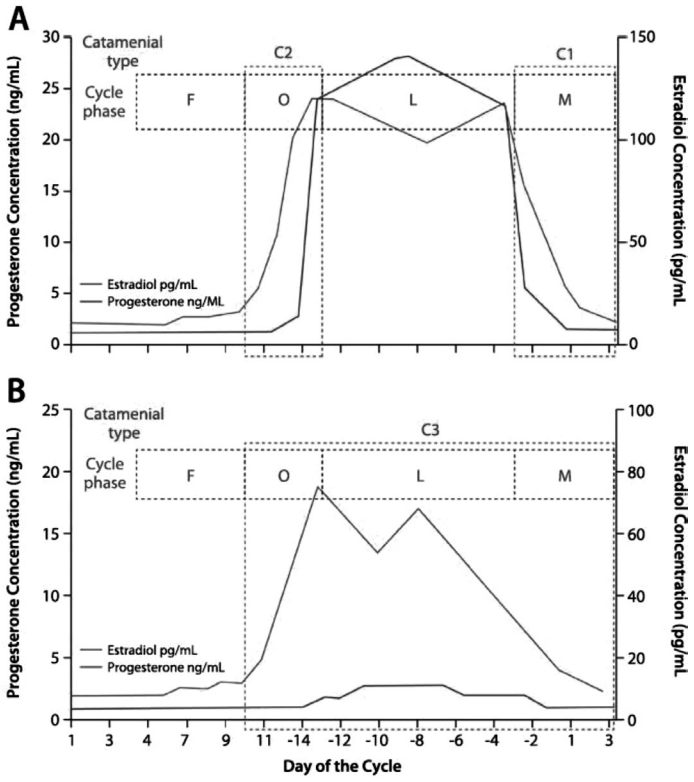
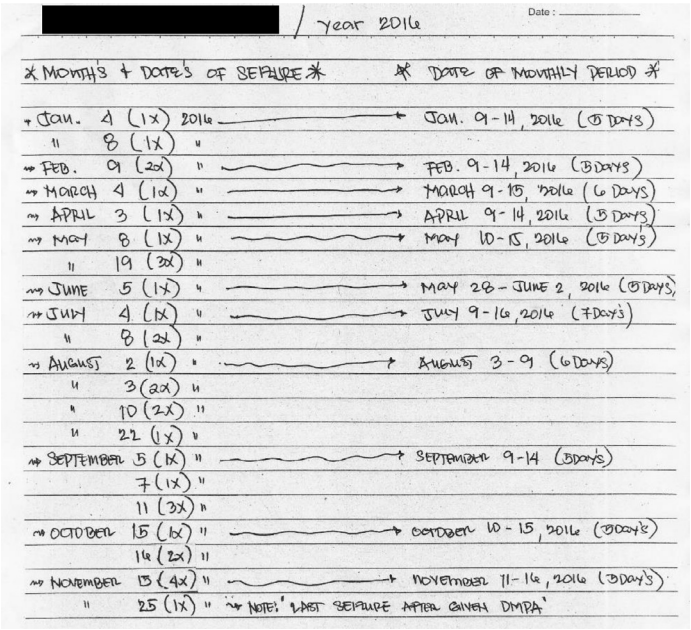


Figure 3. Types of Catamenial seizure. (A) C1 and C2 pattern of catamenial seizure (B) C3 pattern of catamenial seizure. (Herzog et al., 1997)

during the midluteal phase makes it the period where seizure is least likely to occur.

The three patterns of Catamenial Epilepsy can be distinguished by (1) charting menses and seizures and (2) obtaining a mid-luteal phase serum progesterone to differentiate normal from an inadequate luteal phase cycle (<5 ng/ml).[10] Seizures in the index patient were observed to occur from day -5 to +8 of the menstrual cycle and does not strictly fall under any of the abovementioned patterns (Figure 4). She still qualifies as a case of Catamenial Epilepsy since more than 75% seizures occurred during the 10-day period of the menstrual cycle beginning 4 days before menstruation and 6 days after its onset.

Antiepileptic drugs (AEDs) are the mainstay treatment of Catamenial Epilepsy.[11] Seizures are caused by paroxysmal discharges from neurons arising due to excessive excitation or loss of inhibition which needed to be controlled to prevent neuronal damage that can have an adverse effect on cognition, development, and reproductive function. Phenobarbital, an allosteric modulator of $GABA_A$ receptor, was the initial drug given to the patient. However, there are no direct studies of effectiveness of this drug in Catamenial Epilepsy. Phenobarbital is limited by its enzyme-inducing activity, interaction with sex steroid hormone and undesirable side effects such as behavioral changes which was exhibited by the patient. She was shifted to Lamotrigine, a phenyltriazine antiepileptic which inhibits release of excitatory glutamate and voltage-sensitive sodium channel stabilizing neuronal membrane. Gilad et al. prospectively studied women with Catamenial Epilepsy who were treated with Lamotrigine for 3 months and concluded that Lamotrigine is efficacious


[redacted] / Year 2016 Date :

* MONTH'S & DATE'S OF SEIZURE * * DATE OF MONTHLY PERIOD *

- JAN. 4 (1x) 2016 → JAN. 9-14, 2016 (5 DAYS)
- " 8 (1x) "
- FEB. 9 (2x) " → FEB. 9-14, 2016 (5 DAYS)
- MARCH 4 (1x) " → MARCH 9-15, 2016 (6 DAYS)
- APRIL 3 (1x) " → APRIL 9-14, 2016 (5 DAYS)
- MAY 8 (1x) " → MAY 10-15, 2016 (5 DAYS)
- " 19 (3x) "
- JUNE 5 (1x) " → MAY 28 - JUNE 2, 2016 (5 DAYS)
- JULY 4 (1x) " → JULY 9-16, 2016 (7 DAYS)
- " 8 (2x) "
- AUGUST 2 (1x) " → AUGUST 3-9 (6 DAYS)
- " 3 (2x) "
- " 10 (2x) "
- " 22 (1x) "
- SEPTEMBER 5 (1x) " → SEPTEMBER 9-14 (5 DAYS)
- 7 (1x) "
- 11 (3x) "
- OCTOBER 15 (1x) " → OCTOBER 10-15, 2016 (5 DAYS)
- 16 (2x) "
- NOVEMBER 13 (4x) " → NOVEMBER 11-16, 2016 (5 DAYS)
- " 25 (1x) " NOTE: 'LAST SEIZURE AFTER GIVEN DMPA'

Figure 4. Seizure diary of the index patient for 2016

in 66% of women, with disappearance of seizures or 50% reduction in the number of seizures.[12] Lamotrigine also increases progesterone levels however its mechanism of action is unknown.[11] A tri-directional interaction between Epilepsy, AEDs and sex steroid hormones exist. AEDs and Epilepsy itself can adversely disturb the hypothalamic-pituitary ovarian axis and affect sexual and reproductive functioning causing disorders such as hyperandrogenism, menstrual disorders, ovarian failure, polycystic ovary syndrome, hyperinsulinemia, and weight gain. On the other hand, the decrease in both estrogen and progesterone pre-menstrually activates enzymes that metabolize AEDs in the liver causing breakthrough seizure.[11]

Despite dose adjustments the patient continued to experience seizure attacks, therefore adjunctive hormonal therapy was started in the form of DMPA. It suppresses ovulation by inhibiting secretion of gonadotropins from the pituitary gland and is currently being studied in the treatment of Catamenial Epilepsy. Mattson et al. used DMPA as an adjunct treatment to antiepileptic medication and reported a 39% decrease in seizures per month[13]. Levonorgestrel intrauterine device appears to be effective as an alternative with the advantage of having no drug interactions.[14] Progesterone has a more definite role in preventing seizure than estrogen. It exerts a direct membrane-mediated inhibitory effect by potentiating $GABA_A$-mediated chloride conductance.[11] Progesterone also acts by decreasing estrogen receptor numbers antagonizing estrogen effects. Chronic progesterone decreases the number of hippocampal CA1 dendritic spines and excitatory synapses faster than the simple withdrawal of estrogen.[11] However, progestin-only pills (POP) have been found to be ineffective when used in combination with enzyme-inducing AEDs due to increased hepatic clearance thus decreasing bioavailability of POP. Subdermal progestin implants are also not recommended due to high failure rates.[14] The index patient became seizure-free when DMPA treatment was started, however, long term administration is not advised because of associated bone mineral density loss, amenorrhea and delayed return of ovulation. A study by Clark et al. comparing bone mineral density of women aged 18-35 on DMPA reported that DMPA-related bone mineral density loss is significant and occurs mostly in patients given DMPA for 2 years.[15]

Treatment should take into consideration the catamenial pattern type, age, regularity of menstruation, response to initial medication and financial resources. Navis and Harden proposed an algorithm for women with suspected Catamenial Epilepsy (Figure 5) wherein oral natural progesterone is given during luteal phase in C1 types.[3] Nonhormonal drugs such as acetazolamide,a carbonic anhydrase inhibitor, clobazem or other

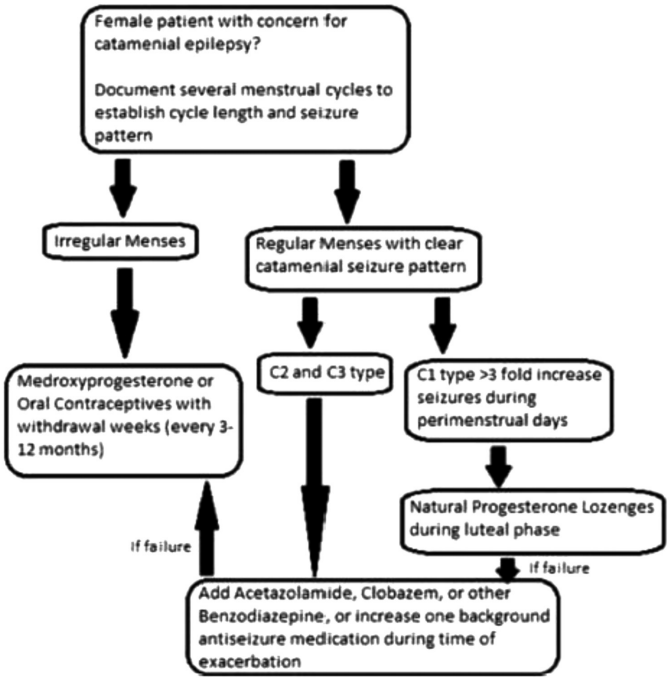


Figure 5. Algorithm for treatment if female patients with suspected catamenial epilepsy (Navis A, Harden C, 2016)

benzodiazepines are suggested medications in C2 and C3 types. Those with irregular menses are prescribed Medroxyprogesterone acetate or oral contraceptives with withdrawal weeks every 3-12 months.[3]

Epilepsy is more complicated in females than in males since estrogen and progesterone affect seizure thresholds due to the close interaction between regions of the brain that generate seizures and regions that control hormonal activity. Patient awareness is imperative on how the disease and its treatment can affect sexual development, menstrual cycles, contraception, sexual dysfunction, such as infertility, impaired libido, and reproduction.[16] The index patient presented with seizure upon menarche making her anxious during menstruation. Social withdrawal and isolation are commonly reported among people with Epilepsy as was seen in this case. She verbalized her concern over discrimination received every time a seizure occurs in a public. Part of the social withdrawal and isolation can be due to parents' over-protectiveness wherein children's activities are closely monitored and restricted, rendering the child more socially inept, more dependent and attached. Patients also adopt a more passive role in family interactions and are less involved in family decision-making.[16] The index patient has regular consultations with a psychiatrist who provides behavioral therapy and makes the patient better understand the effect of the disease process.

Decreased fertility has been reported in women with Epilepsy which can be related to anovulatory cycles and/or hyperandrogenism upon initiation of anti-epileptic drugs.[16] Seizure attacks can damage the preoptic area of the hypothalamus where gonadotropin-releasing hormone (GnRH) is produced. Hattemer et al. discussed how temporal lobe Epilepsy lateralization is associated with reproductive dysfunction.[17] It was noted that left temporal lobe discharges were associated with polycystic ovary syndrome, and right-sided discharges with hypothalamic hypogonadism.[17]

Should the patient desire to become pregnant, preconception counseling should be offered. Teratogenic risks of AEDs must be balanced alongside risks of poor seizure control. The lowest effective dose should be used and monotherapy is advised. Malformation rates with Lamotrigine exposure ranges from 0-4.4%, Phenobarbital 2.9 to 10.4%, and Valproic Acid 5.7-16.8%.[14] It is expected that patients with perimenstrual catamenial epilepsy have reduced seizure frequency throughout the pregnancy due to the absence of cyclical hormone variations and the increase in circulating progesterone levels.[18]

Women with Epilepsy may be at risk for early onset of menopause.[16] Those with catamenial seizure should be monitored until their perimenopausal years since as high as 40% of women report worsening of seizures, while 27% improve, and a third had no observed change.[8] This is due to an initial steady increase in estrogen levels during the peri-menopausal transition. In other women, estrogen levels can remain stable, or become erratic with surges until estrogen levels diminish in the menopause. Hormone replacement therapy is significantly associated with an increase in seizure frequency during menopause, which is more likely in women with a history of Catamenial Epilepsy.[16] Osteoporosis and increased risk for fractures during menopause should be discussed with patients on long term DMPA since it is implicated in promoting accelerated vitamin D metabolism and bone loss. Adequate calcium supplementation and yearly bone scans are advised.

Long term plan for the patient includes maintaining her on AED and hormonal therapy with monthly visits to Neurology and Reproductive Medicine until control of seizure is achieved. Medications are tapered until a 10-year seizure free period is attained. Thereafter, AEDs may be discontinued. Regular psychiatric consult is advised.

SUMMARY

A case of a female adolescent who upon menarche experienced seizure attacks with exacerbations on day -5 to +8 of menstruation is reported. A diagnosis of Catamenial Epilepsy was given after ruling out other causes. Antiepileptic drugs and adjunctive hormonal therapy was necessary to control catamenial seizure

exacerbations. Gender- related and psychosocial issues in the treatment of Epilepsy in the child-bearing years up to the menopause are discussed.

RECOMMENDATIONS

1. Formulation of a standard definition of Catamenial Epilepsy will aid in its diagnosis and management.
2. Research on neuroactive properties of reproductive steroids will improve management of intractable catamenial seizure exacerbation to enable health care professionals provide correct treatmentand support services.
3. Females with a first seizure attack coinciding with menarche and subsequent menstrual periods should be referred to the Reproductive Medicine service.
4. Being a life-long disease, astrong neurologist-gynecologist-patient relationship is important to ensure open communication andclose monitoring up to the menopausal years.
5. Women with epilepsy of childbearing age and desirous of pregnancy should be counseled regarding fertility issues.
6. Campaigns to increase public awareness and understanding of Catamenial Epilepsy, and all types of Epilepsy is imperative to facilitate acceptance of patients for them to live productive lives. ■

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