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Recurrent catamenial status epilepticus: Is it rare or an under recognized phenomenon in women with epilepsy?

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Citation
Case Report

Recurrent catamenial status epilepticus: Is it rare or an under recognized phenomenon in women with epilepsy?

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1. Introduction

The term ‘catamenial epilepsy’ is used to refer a condition in which the seizures are clustered around specific periods of the menstrual cycle and the purest form is rare. The authors here refer to ‘catamenial epilepsy’ as the occurrence of a cluster of seizures or exacerbation of seizures in relation to the menstrual cycle in women with epilepsy. Three types of catamenial seizure pattern have been described in women with epilepsy [1]: perimenstrual (C1, the most common type), periovulatory (C2), and inadequate luteal-phase (C3). C1 and C3 are associated with a decrease in progesterone levels and C2 with a rise in estrogen. Neuroactive properties of reproductive hormones (neurosteroids) and their fluctuations in the menstrual cycle are thought to be the cause of catamenial seizure exacerbations. Epilepsy with catamenial exacerbation is common and described in one-third of patients with drug-resistant focal epilepsy [1]. The incidence of catamenial status epilepticus (SE) is unknown and is rarely reported [2]. We report two patients who presented with recurrent episodes of catamenial status epilepticus to our epilepsy monitoring unit over the last two years (2/376; 0.5% of all patients monitored including presurgical work-up and invasive EEG monitoring).

2. Case report

2.1. Case 1

A 33-year-old right-handed female with a family history of genetic generalized epilepsy (GGE) developed seizures from the age of 28 years. After seizure freedom for one year, she re-presented with episodes of SE. In the preceding six months, each episode consisted of recurrent periods of unresponsiveness and up to six convulsive seizures occurring on day 1 of her menstrual cycle. She was refractory to three anti-seizure drugs. Routine EEGs and brain imaging were normal. Due to the multiple admissions, video-EEG (vEEG) was performed for further diagnostic clarification. Interictal background EEG showed frequent bursts of generalized spike-and-wave activity lasting up to 20 s in duration. With anti-seizure drug reduction, her typical clusters of seizures occurred 10 days prior to her anticipated menstruation. EEG showed almost continuous generalized spike-and-wave activity lasting up to 40 s with corresponding behavioural arrests, excessive blinking and facial twitching and brief inter burst intervals of 1–7 s. These periods of absence SE were interrupted by generalized tonic-clonic (GTC) seizures throughout the day (Fig. 1).

She became seizure free on a new combination of anti-seizure drugs including zonisamide, lacosamide and regular clobazam and is well at six months follow-up.

2.2. Case 2

A 22-year-old right-handed female with cystic fibrosis developed focal epilepsy at the age of seven years. She became seizure free on carbamazepine monotherapy until 21 years of age when she re-presented with convulsive seizures. There was a very strong peri-menstrual distribution (C1) for the seizures but the menstrual cycles were irregular. Typical seizures were preceded by a non-specific aura followed by clusters of focal to bilateral tonic-clonic seizures, aphasia and post ictal right hemiparesis. She had several episodes of SE and was admitted to ICU at least on four occasions complicated by respiratory failure. Extensive metabolic and autoimmune work-up, MRI brain and inter-ictal PET imaging were normal. Multiple anti-seizure drugs and hormonal treatment including mirena coil insertion were unsuccessful. Due to recurrent SE, vEEG was performed for further diagnostic clarification. Six electrographic seizures associated with right upper limb stiffening.

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rightward head deviation and focal to bilateral tonic clonic seizures were captured confirming left frontal lobe epilepsy. She was commenced on Triptorelin due to very strong catamenial pattern for seizures leading to multiple admissions to ICU. Triptorelin is a synthetic long acting agonist of gonadotropin releasing hormone (GnRH) and is a potent inhibitor of testosterone (in men) and oestrogen (in women). Triptorelin caused medical oophorectomy in our patient and became seizure free at her last follow-up (at one year) and did not require further hospitalization.

3. Discussion

We report two challenging cases (one with GGE and other with focal non-lesional frontal lobe epilepsy) presenting with recurrent episodes of catamenial status epilepticus. There is growing evidence that the alteration of neuronal excitability by oestrogen and progesterone (the endogenous neurosteroids) are responsible for catamenial seizure exacerbations. Estrogen is a pro-convulsant and exerts its effect through several mechanisms including effect on N-methyl D-aspartate receptors in hippocampal pyramidal cells (CA1). Progesterone’s anti-seizure effect is mediated through its metabolite, allopregnanolone which enhances the GABA-ergic effect and decreases glutamate responsiveness.

In patients with catamenial exacerbation of seizures, both non-hormonal and hormonal treatment in addition to regular anti-seizure drugs have been used with varying results. Non-hormonal treatment includes acetazolamide (given daily or perimenstrually) and pulsed benzodiazepines. Clobazam found to have benefit in randomised controlled trials and is used intermittently when seizures are anticipated. Hormonal treatment includes natural progesterone supplementation, synthetic progesterone (oral agents are used cyclically or continuously and medroxyprogesterone acetate is given as intramuscular injections which suppress the ovulation) and menstrual suppressive therapies (GnRH analogues such as Triptorelin and Goserelin) but carrying a risk of bone density loss in the latter two options.

Treatment with non-hormonal agents (clobazam) was unsuccessful in the first patient. Although we planned to commence hormonal treatment, she became seizure free on a new combination of anti-seizure drugs and regular clobazam. In our second patient, clobazam, hormonal treatment with oral contraceptive pills (progesterone) and mirena coil (levonorgestrel-releasing intrauterine system) were ineffective. Triptorelin was commenced which caused amenorrhoea suppressing hormonal fluctuations, thereby stopping seizures and recurrent episodes of SE. Previously, Triptorelin was found to be effective in a small study and three of ten patients were reported to be seizure free and four reported seizure reduction (up to 50%) within 1–2 months of initiation of treatment [3]. The safety regarding the use of Triptorelin is unknown in this cohort of patients and may cause osteoporosis and cardiovascular disease on long term. Allopregnanolone, a metabolite of progesterone shown to have broad-spectrum effect in animal models enhancing both synaptic and as well as extrasynaptic inhibition by modulating GABA-A receptors, was also reported to be used in rare cases of super-refractory SE including in children [4] and may have a role in the treatment of refractory catamenial SE.

4. Conclusion

Catamenial SE is rare but may occur in pre-menopausal women presenting with recurrent episodes of unresponsiveness, seizure clusters or SE in both generalized and focal epilepsy. Our case report highlights the need for documenting the menstrual cycles, identifying a pattern and perimenstrual video-EEG for diagnosis. Although the treatment of refractory catamenial SE can be challenging, the options for treatment are expanding and may include hormonal treatment tailored to the needs of individual patient in addition to optimising anti-seizure drugs.
References


