Clinical commentary

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A case of recurrent status epilepticus and successful management with progesterone

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ABSTRACT – Catamenial epilepsy (CE) is a commonly observed phenomenon among women with epilepsy, the management of which is both hormonal and non-hormonal. Progesterone therapy has been tried in these patients, as the possible mechanism of CE is withdrawal of progesterone and a higher oestrogen/progesterone ratio in the perimenstrual and periovulatory periods. Here, we describe a 24-year-old lady with multiple seizure types since childhood, which were refractory to adequate antiepileptic drug therapy after menarche with catamenial clustering of seizures. She went on to have several episodes of non-convulsive status epilepticus also with similar periodicity, which would abate only with midazolam infusion, without the need for ventilatory support. She was tried on acetazolamide, progesterone vaginal pessaries, and maximum tolerated doses of antiepileptic medications, but finally responded to intramuscular and oral progesterone, and has been seizure-free for more than a year.

Key words: catamenial epilepsy, recurrent NCSE, progesterone therapy

The phenomenon of catamenial epilepsy has been known for several years, it was first defined by Herzog *et al*. (1997) as greater than average seizure frequency during perimenstrual or periovulatory periods in normal ovulatory cycles and during the luteal phase in anovulatory cycles. Periodic exacerbation of seizures was seen in 46.8% of the total number of cycles recorded in 79 women with epilepsy, and of these, over 70% were anovulatory cycles (Kim *et al*., 2010). There are three patterns of catamenial seizure clustering: C1 (Days -3 to 3) -the perimenstrual period when there is a sudden drop in serum progesterone levels; C2 (Days 10 to -13) -the periovulatory phase, during or just after the preovulatory surge in oestradiol; and C3 (Days 10 to -3) -the non-menstrual phase in non-ovulatory cycles; Day1 being the first day of menses. Herzog *et al*. (1997) noted that of 42.4% catamenial seizures, 35.7%, 28.5% and 41.4% could be classified as C1, C2

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and C3 patterns, respectively. Aetiopathogenesis of CE probably results from the potentiating effect of oestrogen on N-methyl-D-aspartate (NMDA) glutamate receptors in the hippocampus, and the enhancing effect of progesterone on conduction of the inhibitory gamma amino butyric acid (GABA) -A receptors (Majewska *et al.,* 1986; Woolley *et al*., 1997). Thus, treatment with progesterone in different formulations has been tried in patients with CE with varying results, most studies showing an improvement in seizure control. Based on the NIH progesterone study, a randomized controlled trial of progesterone therapy for CE, there was no significant improvement compared to placebo in subjects with patterns other than C1 level ≥3, *i.e*. three times more seizures in the perimenstrual period than at other times (Herzog *et al.,* 2012). Here, we describe a management dilemma in a young lady who presented with multiple episodes of non-convulsive status epilepticus (NCSE) related to her menstrual cycle, and their complete resolution on taking progesterone therapy.

Case study

A 24-year-old lady with childhood-onset epilepsy presented to us for the first time with unconsciousness for several hours after a few myoclonic jerks in both arms, uprolled eyeballs, and this was followed by a generalized tonic-clonic seizure (GTCS) lasting for about a minute. She had had several such episodes in the last two to three years and the unresponsiveness would last for many hours to even two days. She was on multiple antiepileptic drugs (AEDs), taken with good compliance. When examined, she had no focal deficit or signs of meningeal irritation. Her blood biochemistry and CT scan of the head were normal, but continuous EEG monitoring was suggestive of NCSE (*figure 1*), and she regained consciousness after intravenous midazolam 0.2 mg/kg bolus administration.

Her medical history included a full-term normal vaginal delivery with no history suggestive of birth asphyxia, but there was a slight delay in achievement of motor and language milestones. Her first seizure was a GTCS associated with fever at age 1 and a half years, and another after a gap of five months, when she was prescribed phenobarbitone. At the age of 2 and a half years, she started having multiple daily episodes of GTCS and atonic seizures that finally stopped on successive addition of carbamazepine, valproate and vigabatrin. AEDs were gradually tapered off with no recurrence for nine years when, a few months after menarche at age 16 years, she had two episodes of GTCS and was started on valproate again. For the next four years, she had clusters of two to four GTCS, atypical absences, and atonic seizures, once every three to five months, and other AEDs were added, one by one. Then, at 20 years of age, these clusters were followed or interspersed by periods of altered sensorium of very long duration, as described above. In subsequent episodes, the semiology was similar and intravenous midazolam 0.2mg/kg bolus was followed by valproate or levetiracetam, but she would only respond to continuous midazolam infusion at 0.2 mg/kg/hour (15 mg/hour) given for about an hour, starting at 0.05 mg/kg/hour, with hourly uptitration. Her blood oxygen saturation monitored by pulse-oximeter and periodic arterial blood gas analysis never went below 90%, therefore she was managed under close supervision, without mechanical ventilation, in every episode.

Between these episodes, MRI of the brain was performed and found to be normal, EEG exhibited normal background with generalized interictal epileptiform discharges, and assessment of her intelligence quotient showed a score of 79 (mild disability). Her menstrual and seizure calendar showed that these episodes occurred in the perimenstrual and periovulatory phases, and a diagnosis of recurrent catamenial status epilepticus was made. *Figure 2* depicts the pattern of NCSE in this patient.

Around the time she started having these episodes of status epilepticus, she was also diagnosed with polycystic ovary syndrome (PCOS), and had used progesterone vaginal pessaries between Days 18 and 28 for six months, with no effect on seizure frequency, periodicity or severity. Tablet acetazolamide, 250 mg four times a day, was given starting on Day 3 and tapered off at 125 mg per day after Day 6, besides maximum tolerated doses of levetiracetam, valproate, topiramate, zonisamide, and clobazam. However, she continued to have episodes of the same kind almost every month. Therefore, intramuscular injection of depot medroxyprogesterone (150 mg) was administered twice at an interval of three months, which led to seizure control for the next six months. She has now been on norethisterone, 5 mg twice a day, for the last six months and has had no further episodes of NCSE or even a single seizure, though she does have some spotting off and on and has gained about 10 kg of weight.

Discussion

The risk of recurrent status epilepticus is greatest in those with progressive disease. In a prospective study of 95 children between one and 18 years, 67% recurrent SE was reported in subjects with progressive neurological illness. A population-based study, noted 100% risk of recurrence in this group of patients (Shinnar *et al*., 1992; Hesdorffer *et al.,* 2007). Our patient did not have any progressive disease, had episodes of NCSE and

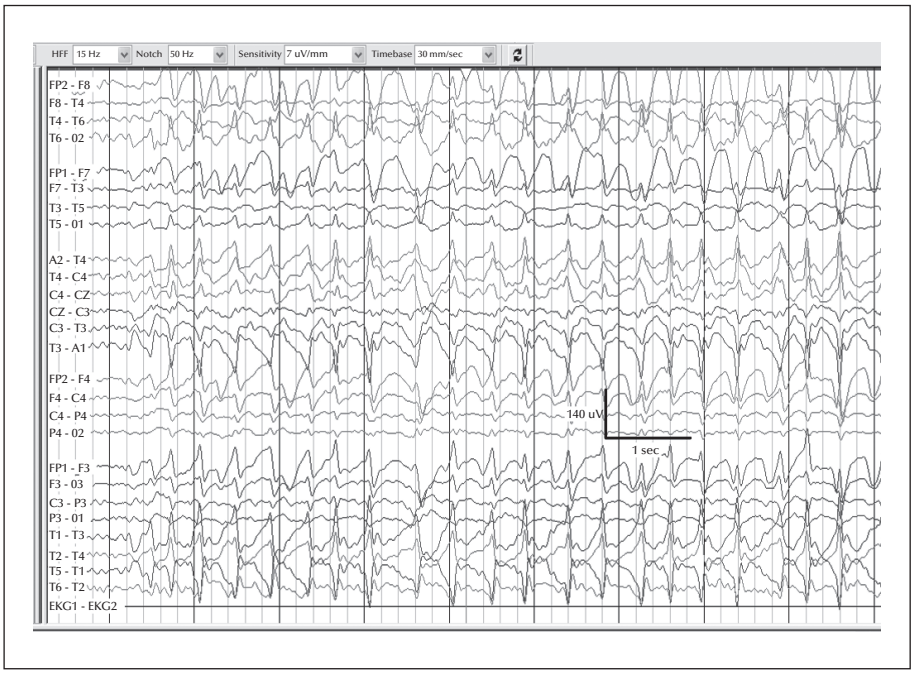

Figure 1. EEG of patient showing generalized epileptiform discharges during periods of unresponsiveness.

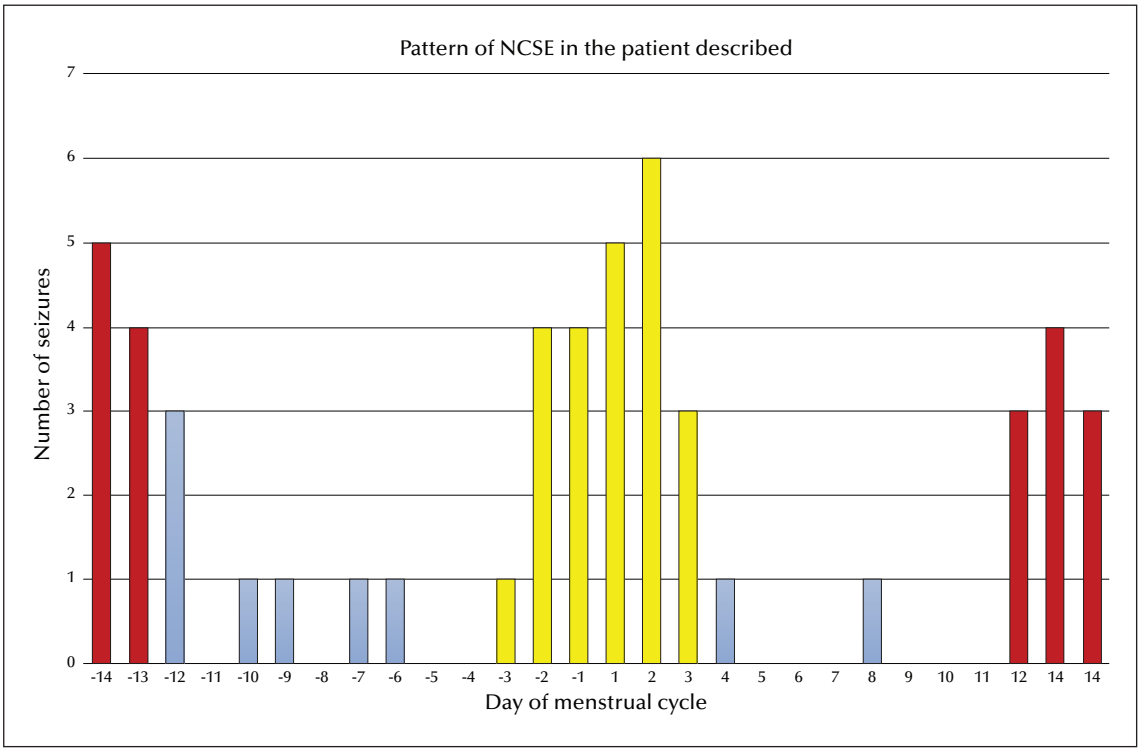

Figure 2. Pattern of NCSE in the patient described.
Yellow bars: Days -3 to 3 perimenstrual phase; Red bars: Days 10 to -13 periovulatory phase.

clusters of GTCS almost every month for almost two years, and would recover with intravenous infusion of midazolam, without ever needing general anaesthetic agents or ventilatory support. Another case report of episodes of multiple seizures and encephalopathy related to menses was due to toxic shock syndrome (Sibon, 2004).

Partial seizures are the most commonly occurring seizures in catamenial epilepsy, but secondary and primary generalized seizures, even absences and myoclonic jerks, can be seen frequently. In the NIH progesterone study, seizures of left temporal origin have been found to show maximum catamenial clustering (Herzog *et al*., 2012). The case we have described had atonic seizures, atypical absences, and GTCS, and all three were seen to occur in a cyclic manner.

Both hormonal and non-hormonal forms of treatment, the latter being cyclic acetazolamide and benzodiazepines, have been tried in patients with CE. Cyclical progesterone was used in a study by Herzog in which improvement in seizure frequency was seen in 18 of the 25 women; 11 patients with perimenstrual seizures were given progesterone on Days 23-25 of the menstrual cycle, the rest with seizures in the second half of the cycle, on Days 15-25. Frequency of GTCS declined by 58% and partial seizures by 54% (Herzog, 1995). When these 18 patients were followed for three years, three did not have any seizures; seizure frequency reduced by 75-99% in three and by 50-75% in eight others (Herzog, 1999). A decline in frequency of generalized seizures was also found in 18 of 36 women who had exacerbations in the entire second half of the menstrual cycle; primary generalized by 20-96%, secondary generalized by 38-85%, myoclonic jerks by 46% in one, and complex partial seizures by 38-87% in 15 women in a trial which used oral progesterone on Days 16-25. This study also demonstrated significantly low serum progesterone levels on Days 22, 25 and 27 in women with CE compared to healthy controls (Motta *et al*., 2013).

Using progesterone containing vaginal suppositories, Herzog achieved a decline in seizure frequency by 69% in six patients (including two women not on AEDs) out of eight with complex partial seizures and serum progesterone levels in the mid-luteal phase below 7.95 mmol/l, adjusting the doses to obtain normal levels of 15.9-79.5 mmol/l (Herzog, 1986). Our patient though, did not respond to progesterone pessaries, probably because adequate serum levels may not have been achieved with this formulation. Her mid-luteal serum progesterone levels were never checked.

Mattson *et al*. administered 120-150 mg medroxyprogesterone intramuscularly in the depot form at 6-12-week intervals to six women with clusters of complex partial seizures for 3-24 months (12 months on average) with a decline in the frequency of complex partial seizures (Mattson *et al*., 1984).

Our patient had seizures in both periovulatory and perimenstrual periods and she has had no seizures after being started on systemic, continuous progesterone therapy. The fact that her seizures, even in the periovulatory phase, responded to progesterone administration may be explained by findings reported in some recent studies; Tuveri *et al*. found that serum concentrations of anticonvulsant neurosteroid tetrahydro-deoxycorticosterone (THDOC) were significantly lower in women with CE than in controls throughout the menstrual cycle (Tuveri *et al*., 2008). Further, cortical excitability assessed by motor threshold measurement by transcranial magnetic stimulation was found to be higher in the follicular phase in healthy controls, whereas among CE patients, cortical excitability was higher in the entire luteal phase in those with a C3 pattern only. Our patient, being a case of PCOS, may also have had some anovulatory cycles (Badawy *et al*., 2013).

In conclusion, the possibility of CE must be thoroughly explored and a trial of progesterone therapy should be given to all women with drug-refractory seizures with catamenial clustering. □

Disclosures.
None of the authors have any conflict of interest to disclose.

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TEST YOURSELF

(1) What are the patterns of catamenial epilepsy?

(2) What is the possible pathophysiology?

(3) What are the various therapeutic options?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".