Epilepsy in Women

27

Katherine Noe

Case Presentation

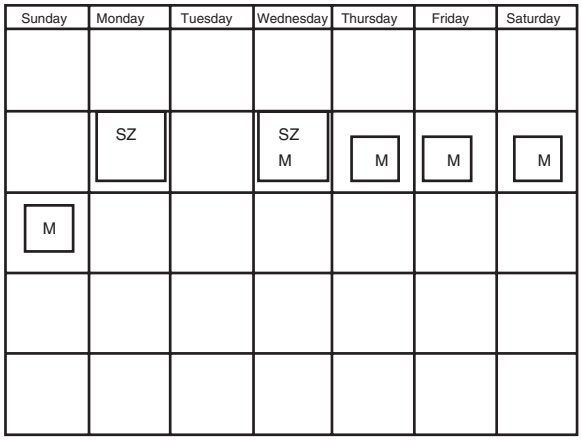
A 32-year-old woman wants to explore additional options for management of drug-resistant focal epilepsy. Her stereotypic seizure begins with a paroxysmal feeling of anxiety and rising epigastric sensation followed by a stare and unresponsiveness and repetitive lip-smacking. Despite trials of multiple antiseizure drugs over the last 15 years, she continues to have focal impaired awareness seizures on average every month. She was previously evaluated for epilepsy surgery but was found to be a poor candidate due to seizures of independent bi-temporal onset and normal MRI brain. She is currently treated with lamotrigine, carbamazepine, and vagus nerve stimulator. She is otherwise healthy and takes no medications other than her those for epilepsy. She brings a diary in which she has charted her seizures and her menstrual periods (Fig. 27.1). She has observed that her seizures usually occur with menses and would like to know if stopping her periods would help control her epilepsy.

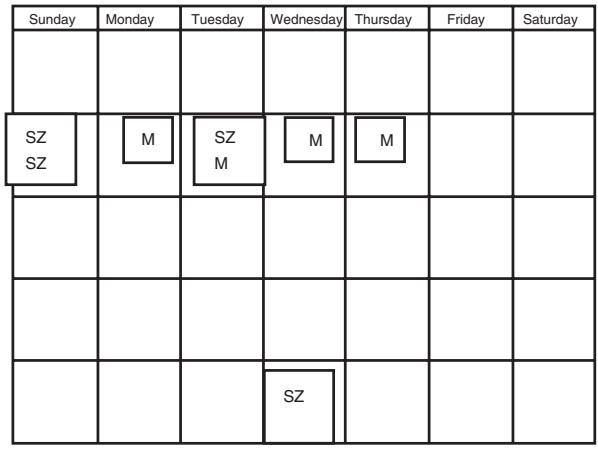
Questions

1. Does the diary contain information valuable to the management of this patient?
2. Could hormonal therapy be used to help control seizures in this patient?
3. Does the diagnosis of catamenial epilepsy expand options for treatment with conventional antiseizure drugs?

K. Noe (✉)
Mayo Clinic Arizona, Phoenix, AZ, USA
e-mail: Noe.katherine@mayo.edu

W. O. Tatum et al. (eds.), *Epilepsy Case Studies*,
https://doi.org/10.1007/978-3-030-59078-9_27





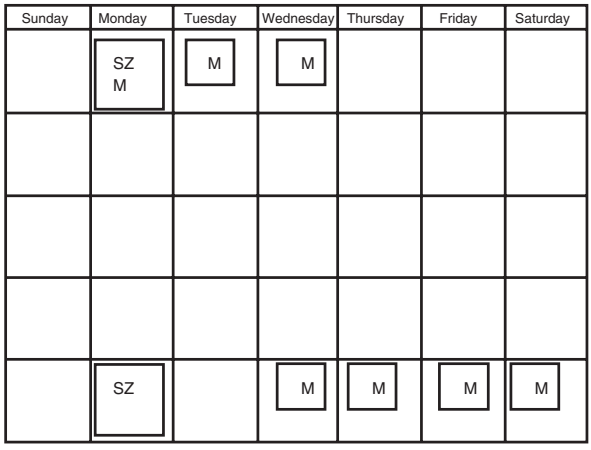


Fig. 27.1 Seizure calendars for 3 months demonstrating a catamenial pattern of breakthrough seizures in relationship to the menstrual cycle. *SZ* seizure, *M* menses

4. Are there other treatments (non-hormonal, not standard antiepileptic drugs) that could be used to treat catamenial epilepsy?
5. In the future as this patient enters perimenopause and menopause, is it likely that her seizure activity will change?

Discussion

1. The diary (Fig. 27.1) documents a pattern of consistent seizure exacerbation related to the menstrual cycle known as catamenial epilepsy. 30–40% of women with drug-resistant focal epilepsy have catamenial epilepsy when strictly defined as a doubling of seizure frequency during a specific phase of the menstrual cycle relative to other phases [1–5]. Three patterns of catamenial epilepsy have been defined: perimenstrual, periovulatory, and anovulatory [1, 2]. The most common, as demonstrated in this patient's diary, is the perimenstrual pattern with increased seizures in the days immediately before or after the onset of menses. The influence of the menstrual cycle on seizure threshold is attributed to the proconvulsant effects of estrogen via enhancement of neuronal sensitivity to glutamate and to the anticonvulsant effect of progesterone mediated primarily through central nervous system gamma-aminobutyric acid (GABA) receptors. Seizures are more likely to occur at any time in the cycle where estrogen levels are high relative to progesterone or when progesterone levels are rapidly declining such as occurs around menses.
2. First-line treatment for women with catamenial epilepsy should be standard antiseizure drugs prescribed with a conventional dosing regimen. However, when standard treatment is ineffective, such as in this case, it may be reasonable to consider alternative options including hormonal manipulation [2, 4, 5]. It is important to note that the clinical evidence supporting the effectiveness of such treatment is limited. The underlying rationale would be to try to maintain a relatively high and/or stable level of progesterone to estrogen, this attempting to decrease the likelihood of seizure. A standard oral contraceptive might have some efficacy for women with periovulatory seizures, but as these also work with withdrawal of estrogen and progesterone on the 4th week to induce withdrawal bleeding, they are not an appropriate treatment for the perimenstrual pattern. Extended cycle monophasic oral contraceptive pills, avoiding the standard 7 days of placebo tablets, could be an option for perimenstrual seizures. Another alternative is supplemental progesterone, either with sustained release injection therapy (Depo-Provera) or as an oral therapy. Supplemental progesterone provided as a three-times-daily lozenge was shown in a small open-label study to be effective in reducing both focal and secondarily generalized seizures in women with catamenial epilepsy; however, a subsequent randomized placebo-controlled trial showed no benefit [5]. As with any medical therapy, it is important to carefully consider the risks and benefits of hormonal therapy before proceeding. Furthermore, consider that the effectiveness of hormonal contraceptives is

decreased by antiseizure drugs that induce the cytochrome P 450 system, including carbamazepine.

3. Some women may choose to increase the dose of their conventional antiseizure drug intermittently over the course of the month to provide extra coverage during the menstrual phase of risk. For example, for woman with a perimenstrual pattern of seizure exacerbation, seizure medication could be increased in the days prior and during menses. For this strategy to be effective, it is critical to carefully consider the pharmacokinetic profile of the antiseizure drug to be sure that meaningful elevation in serum drug levels can be achieved with short-term changes in dosing. For some women benzodiazepines are also utilized in this way, although side effects including sedation can be limiting. Intermittent drug supplementation will also only be an effective treatment for women whose menstrual cycles are very regular and who are willing to consistently track, and plan 1 supplemental treatments must be started and stopped.
4. Acetazolamide, a carbonic anhydrase inhibitor, is another option that can be considered as adjunctive treatment for catamenial epilepsy that is refractory to standard antiepileptic drug therapy. Anecdotally, this drug has been used as both a daily and cyclical treatment starting 5–7 days prior to expected onset of menses in women with a perimenstrual pattern of seizure exacerbation [3]. Evidence for use is limited. However, in a small retrospective study, use of either continuous or intermittent acetazolamide resulted in a 50% or greater reduction in seizure frequency in 40% of subjects. Tolerance to this medication with loss of impact against seizure can develop with both short- and long-term use.
5. Menopause is defined as cessation of menstrual periods for more than 1 year. This is preceded by perimenopause, several years during which the menstrual cycle becomes increasingly irregular and fertility decreases reflecting fluctuations in the secretion of estrogen and progesterone. During perimenopause there is also an increase in anovulatory cycles. Many women with catamenial epilepsy will report worsen seizure control during perimenopause. Although cessation of a very in production of estrogen and progesterone might be expected to improve epilepsy post-menopause, changes in seizure control during this phase of life are unpredictable.

Pearls

1. Catamenial exacerbation of seizures, a pattern of reproducible seizure exacerbation related to a specific phase of the menstrual cycle, is common among women with epilepsy.
2. Seizures may be more likely to occur when estrogen levels are high relative to progesterone or when progesterone levels are rapidly dropping.
3. Catamenial seizures refractory to conventional antiseizure drugs may be treated adjunctively with cyclical supplementation of standard seizure medications, hormonal therapies, or acetazolamide though the clinical evidence for efficacy of all these therapies is limited.

4. Women with catamenial epilepsy may experience increased seizure frequency during perimenopause.
5. From menarche through menopause, gender-specific management is required and involves careful selection of antiseizure medication to provide optimal treatment to women with epilepsy.

References

1. Herzog AG, Harden CL, Liporace J, et al. Frequency of catamenial seizure exacerbation in women with localization-related epilepsy. Ann Neurol. 2004;56(3):431–4.
2. Hezog AG. Catamenial epilepsy: update on prevalence, pathophysiology and treatment from the findings of the NIH progesterone treatment trial. Seizure. 2015;28:18–25.
3. Lim LL, Foldvary N, Mascha E, Lee J. Acetazolamide in women with catamenial epilepsy. Epilepsia. 2001;42(6):746–9.
4. Herzog AG. Progesterone therapy in women with complex partial and secondary generalized seizures. Neurology. 1995;45:1660–2.
5. Herzog AG, Fowler KM, Smithson SD, et al. Progesterone vs. placebo therapy for women with epilepsy: a randomized clinical trial. Neurology. 2012;78(24):1959–66.