Neurosciences Quiz

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A young woman with recurring seizures

Case Presentation

A 17-year-old girl had a generalized tonic-clonic seizure (GTCS) shortly after waking up in the morning in August 2008. While waiting for a specialist visit, she had a second GTCS 3 weeks later. Family history was negative. She reported in the previous year occasional jerky movements when brushing her teeth. Neurological examination and MRI were normal and an interictal EEG showed brief bursts of generalized, bisynchronous 3.5 Hz spike or polyspike and wave discharges with predominance over the anterior regions. A diagnosis of juvenile myoclonic epilepsy (JME) was made, and she was started on lamotrigine, titrated up to 200 mg/day.

In May 2010 she reported to her neurologist for her yearly visit. She had remained free from seizures since starting lamotrigine, she was feeling well, and she had no side effects. She also mentioned that she was going to start a combination oral contraceptive after consultation with her family doctor. Her neurologist requested an EEG, and blood chemistry/hematology tests, which were normal. She was asked to return for a follow-up review in 12 months. After 4 months, however, she called her neurologist saying that she was depressed and her family doctor had prescribed her citalopram (maintenance dose 40 mg/day), and she wanted to check that this would not interfere with her epilepsy. Her neurologist did not object.

Today, 8 weeks later, she calls again, and she reports having had a recurrence of 2 GTCS, 2 hours apart in the morning. She denies non-compliance, but she reports having been up late the night before, although this had happened on other occasions over the years without adverse consequences.

Questions

1. Was lamotrigine an appropriate choice for first-line treatment in this patient?

2. Could additional laboratory tests have helped clinical management?

3. Could lamotrigine have reduced the blood levels of contraceptive steroids?

4. What is the most likely cause for the recurrence of her seizures?

5. What is the most appropriate management now?

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Answers & Discussion

1. The drug with the best documented efficacy in JME is valproic acid, which is, however, a problematic choice in a woman of childbearing potential because of its adverse effects on embryonic development.[1] Lamotrigine is less likely to adversely affect the offspring, although its use in pregnancy can be complicated by prominent pharmacokinetic changes.[1] Lamotrigine is also less efficacious than valproic acid in JME,[2] and sometimes it may even exacerbate seizures, particularly myoclonic jerks, in patients with idiopathic generalized epilepsy.[3] However, some patients with JME do well on lamotrigine, and lamotrigine is a reasonable option for some women with JME, after careful discussion of the risk/benefit ratio.[4] Levetiracetam is another option, but there is as yet insufficient information on the risks associated with its use during pregnancy.[4]

2. It would have been desirable to measure serum lamotrigine levels before starting the contraceptive pill, and during intake of the contraceptive. This would have allowed identifying the fall in serum lamotrigine levels, which most probably occurred after starting the pill. Monitoring serum lamotrigine levels would also have allowed making timely adjustments in lamotrigine dose, in order to restore serum levels similar to those found before the interaction occurred.

3. A well conducted study in 22 healthy women (16 evaluable) found that lamotrigine at a dose of 300 mg/day reduced the area under the serum concentration curve (AUC) of levonorgestrel by around 20% on average.[5] The follicle-stimulating hormone and luteinizing hormone levels were significantly increased in the presence of lamotrigine, but there was no evidence of ovulation in this small group of women. The clinical significance of this interaction is uncertain, and it is unknown whether a similar fall in progestogen levels occur with a lower lamotrigine dose. However, the possibility that lamotrigine reduces the efficacy of the combined contraceptive pill cannot be excluded.

4. The most likely cause for seizure recurrence is an oral contraceptive-induced reduction in serum lamotrigine levels, resulting in reduced anticonvulsant effect. The decrease in serum lamotrigine caused by the combined contraceptive pill is marked (around 50% on average or even more, with considerable interindividual variation[5-8]) and there have been reports of this interaction resulting in re-emergence of seizures.[6] Interestingly the reduction in serum lamotrigine is greatest during the last week of the 3-week pill taking cycle, and a rebound increase in serum lamotrigine occurs during the week in which the pill is not taken.[9] The decrease in serum lamotrigine is due to stimulation of glucuronide conjugation of lamotrigine by the estrogen component of the contraceptive.[10] This stimulatory effect is antagonized by valproic acid. Therefore, in women taking lamotrigine together with valproic acid, oral contraceptives no longer appear to significantly influence lamotrigine levels.[11] Other factors may have contributed to the recurrence of seizures in this woman, including sleep deprivation, and a reduction in seizure threshold caused by the estrogen component of the pill. However, there is no clear evidence that combined steroid contraceptives can precipitate seizures.[12] It is also unlikely that seizure susceptibility was increased by citalopram, because this compound and other selective serotonin reuptake inhibitors (SSRIs) when used at therapeutic doses have been found generally to be safe in patients with epilepsy.[13,14]

5. The need to continue use of the contraceptive pill should be evaluated, particularly in view of the possibility that the pill might have precipitated the development of her depression.[15] If continuation of the pill is deemed to be indicated, then the dosage of lamotrigine should be increased gradually, probably up to 400 mg/day. Additional adjustments in lamotrigine dose may be indicated based on clinical response. Lamotrigine levels should also be measured to provide a reference to guide dose adjustments in the future (for example, to prevent toxicity should the contraceptive pill be stopped).[7]

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