CASE 1: EPILEPSY AND PREGNANCY

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Case 1:
A 19 year-old woman had two witnessed generalized tonic clonic seizures which occurred two weeks apart. She recalls having some brief jerks in her arms sometimes early in the morning after wakening for several years. Her EEG shows generalized spike-wave discharges. What is your advice and potential plans for the patient?

Discussion:
Based on her semiology and EEG, this patient likely has Juvenile Myoclonic Epilepsy. Certain antiepileptic drugs (AEDs) work poorly for generalized epilepsy (e.g., carbamazepine). Of effective AEDs for this type of epilepsy, valproate has been shown to have better effectiveness than lamotrigine and topiramate,[1] in which those patients remaining on valproate was 8% more than lamotrigine and 16% more than topiramate. In another study, valproate and levetiracetam had similar effectiveness in generalized epilepsy.[2] If this patient was male, valproate would be a good first choice, but since she is a woman of childbearing age, the issue of teratogenesis must be considered.

A summary of major studies on fetal antiepileptic drugs (AED) teratogentic risks is available from recent publications.[3-8] Fetal valproate exposure carries a marked risk for both anatomical and behavioral teratogenic abnormalities compared to other AEDs. Valproate's risk for major malformations is 5-11%; the risk of cognitive deficits is 8-11 points compared to three other commonly used AEDs;[9] the risk of autism is increased.[10] These effects are dose dependent, but a safe dose is not defined.

Some AEDs have intermediate risk for malformations including phenobarbital and topiramate.[11] A few AEDs (e.g., carbamazepine, lamotrigine and levetiracetam) possess low risks. When large sample sizes are available, even carbamazepine and lamotrigine have shown dose-dependent effects on malformations.[12] Sample sizes for levetiracetam and many other AEDs are not adequate to assess dose-dependent effects. Furthermore, apart from valproate and a few other AEDs, our knowledge of the teratogenic risks remains inadequate for most AEDs, especially in regards to cognitive/behavioral effects.[5]

Similar to alcohol, several AEDs have been shown to produce widespread neuronal apoptosis in immature animal brains including phenytoin, vigabatrin, valproate, clonazepam, diazepam, and phenobarbital.[13,14] The effect can occur with single dose exposure, is dose-dependent, and occurs at therapeutically relevant blood levels.[15] Further, when two of these AEDs are given at below threshold dosages the full apoptotic response is triggered, suggesting a synergistic effect. Valproate's increased risk may be because it induces apoptosis below its typical therapeutic range unlike the other tested AEDs.[14] In contrast, carbamazepine, lamotrigine, levetiracetam, or topiramate in monotherapy at therapeutic dosages do not produce neuronal apoptosis. However, when these AEDs (except for levetiracetam) are added to an AED that produces apoptosis in monotherapy, they increase the apoptotic effect, which may suggest polytherapy risk.[16,17] These observations in animals raise serious concern that certain AEDs, which are commonly used in women of childbearing potential, could produce similar adverse effects in children exposed in utero or in the neonatal period.

Although we have substantially more data than 20 years ago to direct care in WWE, evidence remains inadequate to maximize maternal and child outcomes across all AEDs. [3,5,18-19] Additional studies are needed to examine the effects of other AEDs in animal models and in humans.

Although valproate has excellent efficacy for this type of epilepsy, it poses substantial risks for future pregnancies including congenital malformations, cognitive impairments, and autism in her children. Options include: levetiracetam, lamotrigine, and possibly zonisamide, lacosamide, topiramate, perampanel, or low dose valproate. The best data for low pregnancy risks are for levetiracetam and lamotrigine. The highest risks are for valproate with intermediate risks for topiramate. The risks remain unknown for zonisamide, lacosamide, and perampanel.

In addition to the above issues, the discussion with this patient should encourage use of preconceptual folic acid 1-4 mg daily to reduce risks of malformations and possibly improve cognitive outcomes. The importance of not stopping AED if she becomes pregnant should be stressed. Inform the patient to contact her neurologist and obstetrician as soon as she knows she is pregnant. Because her pregnancy may change her metabolism and the level of her AED, and the levels may need to be monitored to adjust dose to avoid seizures. Other pregnancy issues to discuss include sleep management, and risks of OB complications, breakthrough seizures, depression, and breastfeeding.[8] Note that when take AEDs during pregnancy, there appears to be no additional risk of continuing AEDs while breastfeeding.[20] The physician should seek to achieve seizure control using monotherapy if possible and at the lowest dose possible. Finally, make sure the patient understands the risks, but balance the discussion with the fact that the large majority of women with epilepsy have normal pregnancies outcomes even though they have increased risk.

Salient Points for Consideration in this Case:

1. The decision for choice of AED includes consideration of efficacy as well as side effects. For a woman of childbearing potential, this decision needs to include teratogenic risks prior to pregnancy, i.e., at the time when the drug is first prescribed, since almost half of pregnancies are not planned.
2. Although valproate has excellent efficacy for this type of epilepsy, it poses substantial risks for future pregnancies including congenital malformations, cognitive impairments, and autism in her children. Options include: levetiracetam, lamotrigine, and possibly zonisamide, lacosamide, topiramate, perampanel, or low dose valproate.
3. Aim for seizure freedom prior to pregnancy, try to use monotherapy if possible, and use lowest dose possible to control seizures.
4. Encourage preconceptual folic acid 1-4 mg daily.
5. Inform her to contact her neurologist as soon as she knows she is pregnant, because her pregnancy may change the level of her AED and levels may need to be monitored to adjust dose to avoid seizures.
6. Other pregnancy issues to discuss include sleep management, and risks of OB complications, breakthrough seizures, depression, and breastfeeding.

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