Menopause and Epilepsy

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Case 1
- 45 year old woman with history of complex partial seizures.
- Seizures since age 20.
- Febrile seizures as a baby.
- The seizures involve an aura in the form of an abnormal smell followed by confusion.
- Was having seizures initially in clusters during her menstrual periods.
- Has been seizure free on keppra for about 5 years.
- Recently started having multiple seizures a week.
- Has been compliant with her medications.
- Not sick in any other way.
- Has been having irregular periods with missed periods every few months.

Case 2
- 55 year old woman.
- History of seizures since age 20.
- The seizures involve a "de ja vu" feeling followed by confusion and at times convulsion.
- Was having multiple seizures a month especially during her menstrual period.
- Tried multiple medications and was having them at least once or twice a month despite medications.
- Stopped having her menstrual periods.
- After the menstrual periods stopped, she did not have any seizures.
- Has stayed seizure free now for about 5 years.

Case 3
- 55 year old woman.
- History of seizures since early 20s.
- Seizures involved a feeling of intense nausea and an epigastric rising sensation followed by confusion.
- Was having them with her menstrual periods for a number of years.
- Attained menopause at age 50.
- Seizures stopped after menopause.
- Has stayed seizure free now for about 5 years.
- Got started on hormone replacement therapy for "thinning bones" about 2 months ago.
- Had 2 of her typical seizures last week.

Case 4
- 20 year old lady.
- Started having seizures at age 15.
- The seizures are all convulsions.
- No aura.
- Has random jerking of her extremities in the early am.
- On keppra and topamax.
- Seizures pretty much under control except has them 1-2 a month - these happen 2 days before her menstrual periods, during her menstrual periods or for 2 days after.
- Her neurologist suggested Onfi to be taken 2 days prior to her periods, during periods and for 2 days after.
- Has stayed seizure free on this regimen for 5 years.

Hormones and Epilepsy in Women
- The relationship between menstrual cycle and epilepsy in women has been known (Herzog et al., 1997) - Catamenial epilepsy.
- Most common seizures increase just before or during the menstrual periods.
- This is the period when estrogen levels are high.
- Small trials had suggested that progesterone may reduce seizures (Watson et al., 1998; Herzog et al., 1997).
- Progesterone, is converted to allopregnanolone which is a seizure inhibitor.
- A large randomized study however (Herzog et al., 2012) did not show any benefit of treating with progesterone.
Epilepsy and Menopause

- Epilepsy has been known to be hormone sensitive for a long time.
- Women with epilepsy in the peri-menopausal and post-menopausal age groups have many questions regarding this.

Definitions

- Peri-menopause: Period of menstrual irregularity with increasing episodes of amenorrhea culminating in menopause.
- Menopause: Cessation of menstrual periods for 12 consecutive months with no obvious cause (WHO research on Menopause)
- The transition occurs usually over 4 years or so.
- The peri-menopausal period is associated with more extreme fluctuations in estrogen and progesterone compared to during reproductive years.

Hormones and epilepsy

- Regions of the limbic cortex and amygdala (Which is the focus of temporal lobe epilepsy) have significant reciprocal connections with the hypothalamus and can modulate hormone production.
- Many anti-seizure medications like phenytoin, carbamazepine, oxcarbazepine can lower sex hormones and valproic acid can increase testosterone.

Seizure frequency and menstrual cycle

- There is a relationship of seizure frequency and menstrual periods in some women.
- Seizures in this group can increase the week before the menstrual periods and at onset of menstrual bleeding (Herzog et al., 1997)
- This is called catamenial epilepsy.
- Estrogens increase seizures and progesterone decreases seizures (Scharfman &MacLusly, 2006)

Seizure changes related to menopause

- It has been shown that women who have catamenial epilepsy tend to have more seizures in the peri-menopausal period (Harden et al., 1999).
- The study also showed that women with catamenial epilepsy tend to have less seizures post-menopause.
- During peri-menopause, estrogen levels remain the same or rise but progesterone levels decrease leading to anovulatory cycles.
- Estrogens have been shown to increase seizures and progesterone to reduce seizures. This explains the increase in seizures during peri-menopause in patients who are hormone sensitive.

Menopause onset

- There is a risk of experiencing peri-menopausal symptoms earlier than typical in women with epilepsy (Kline et al., 2001)
- They have a risk of developing premature ovarian failure.
- It has been reported that the severity of epilepsy correlates with early menopause, (Harden et al., 2003)
- Women with rare seizures did not develop early menopause but women with frequent seizures developed early menopause.
- This study showed no correlation between early menopause and any specific anti-seizure medication. Thought to be a consequence of epilepsy itself.
Menopause and post-menopause

- Patients with history of catamenial epilepsy reported a decrease in seizures at menopause (Harden et al., 1999).
- This is possibly related to the decrease in hormonal triggers.

Hormone Replacement Therapy

- Hormone replacement therapy during and after menopause can be associated with increase in seizures.
- This was dose related.
- Patients on lamotrigine had a decrease in lamotrigine levels as expected and may have contributed to the increase in seizures but this happened in patients not on lamotrigine as well.

HRT in menopausal women with epilepsy

Hormone Replacement Therapy in general is not recommended in post-menopausal women with Epilepsy.

If absolutely needed, For the progestin component, prometrium with 17 beta estradiol may be used – but the risks of increased seizures have to be explained.

Anti-epileptic drug dosing in the elderly

- In general, the elderly need a lower dose of anti-epileptic medications. (Not much data on gender differences).
- This is because of:
  - A decrease in the elimination rate by the kidneys.
  - Reduced drug metabolism rate.
  - Decrease in serum albumin which is a protein leading to less binding of the drug and more available active free drug.
  - Slower gastric emptying time.

Bone health

- This is of special relevance to women especially after menopause.
- There is a 2-6 fold increase in fractures in patients with epilepsy on anti-seizure medications (Mattson et al., 2004).
- The risk of fractures is higher among women than among men (Pack et al., 2008).

Bone Health

- The increased fractures in women is related to decreased bone density and quality.
- This is mostly related to enzyme inducing anti-seizure medications.
- The enzyme inducers include phenytoin, carbamazepine, oxcarbazepine, phenobarbital.
Bone Health

- The main mechanism of decreased bone density is supposed to be related to increased metabolism of Vitamin D.
- Valproic acid is confusing – it is an enzyme inhibitor but is known to reduce bone density.
- This basically means that we understand less than we think we do.

In one study, lamotrigine was seen to cause less reduction in bone density.

In postmenopausal women on prolonged exposure to anti-seizure medications screening should be performed regularly for bone density.

Vitamin D

- In one study, comparing low dose 400 IU a day to high dose 4000 IU a day of vitamin D, the high dose showed more improvements in bone density.

In post-menopausal women, with low bone density, bone density reducing anti-seizure medications are best avoided and medications like lamotrigine probably preferred.

In women with catamenial epilepsy, peri-menopause can increase seizures and menopause can decrease seizures.

Hormone replacement therapy in post-menopausal women with epilepsy can trigger seizures.

The anti-epileptic medications should be used in very low doses and increased very slowly in the elderly.

Special attention needs to be paid to bone density in this population of women on anti-seizure medications.

Conclusion

- Increased vigilance in women with catamenial epilepsy entering peri-menopause.
- Absolute compliance with medications.
- Frequent blood level monitoring of medications especially lamotrigine.

THANKS FOR YOUR ATTENTION