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Case reports

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CASE 1

A 28-year-old woman was referred to an epilepsy and neuropsychiatry service following a disastrous attempt at treating her infertility by a local gynaecological unit.

At the age of 14 she had developed complex partial seizures. A single electroencephalograph (EEG) had shown epileptic activity focal to the right temporal lobe and she was placed on sodium valproate by a paediatrician. She continued to have several complex partial seizures a year despite this medication and gained a great deal of weight. Her periods became irregular and finally stopped at the age of 20. She was discharged from paediatric care at the age of 18, but was not referred for further secondary care, however, she was managed by her General Practitioner (GP) who continued her prescriptions.

At the age of 22 she married and attempted to conceive. She did not become pregnant and at the age 26 was seen by a gynaecologist for her infertility. Her amenorrhoea was investigated, she was shown to have the polycystic ovary syndrome and, without further consideration, treated with clomiphene to induce ovulation—the epilepsy, and the possible consequences of the medication she was taking, were ignored even though her seizure frequency dramatically increased during the three courses of clomiphene she had: during the courses of clomiphene she received artificial insemination from her husband.

To her delight she conceived: later screening, however, showed her to be carrying a child with a severe spina bifida (she had not been offered folic acid) and she and her husband reluctantly agreed to a termination of pregnancy at 20 weeks. She became very depressed and was referred to the neuropsychiatry clinic, more for her mental state than her epilepsy: she was having frequent seizures.

Her depression was talked through, but not treated with anti-depressants and she recovered. Her epilepsy was investigated: there was a clear right temporal focus on electroencephalography and right hippocampal sclerosis shown on magnetic resonance imaging (MRI). A right temporal lobectomy was suggested: whilst waiting for this operation, lamotrigine was substituted for valproate and she rapidly became seizure free. She quickly lost weight: both her sexual desire and her periods returned and a few months later she found herself unexpectedly pregnant. She had a subsequent normal delivery of a normal baby, and has had a further successful pregnancy since. She remains seizure free and has not had the operation.

When she became seizure free she had a transient severe affective psychosis with some paranoid ideation, which required brief chemotherapy. She had a brief recurrence of this illness for a short while after both confinements, but both episodes lifted spontaneously.

Comment

This case illustrates the need to manage people with epilepsy holistically and for other specialists not to neglect the patient's epilepsy (and the possible consequence of its treatment) whilst pursuing some other therapeutic goal. It also illustrates the need for better hand over care at the end of paediatric supervision.

We encourage our gynaecological colleagues, assessing women with epilepsy with infertility problems, to refer them across for re-assessment of their epilepsy and its treatment before starting therapy for the infertility. Our experience is that clomiphene can often increase seizure frequency (or re-activate quiescent epilepsy) and we warn our obstetric colleagues of the teratogenic potential of valproate (which they often seem unaware of).

Only further research will tell us if this woman's sudden reversion from the polycystic ovary syndrome into normal menstruation and fertility was due to the withdrawal of valproate, the effect of cloniphene,

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the control of her seizures, or the exhibition of lamotrigine (or all four) but, as mentioned in the review, we have some preliminary evidence that it may be a lamotrigine effect and, following a few other unexpectedly early pregnancies, routinely warn women switching from valproate to lamotrigine in our preconception clinic to stick to effective contraceptive practice, until the switch is fully complete, and ensure they are taking prophylactic folic acid[1].

CASE 2

A girl of 11 had two witnessed tonic–clonic seizures in her sleep: EEG examination showed a typical pattern of generalized epilepsy. She was put on sodium valproate, the dose was built up to one gram daily and she had no more seizures.

She started to menstruate at the age of 9, but had not established a regular menstrual cycle by the time she took valproate. She had one or two further periods thereafter but then had no more periods from the age of 13. She steadily gained weight during her adolescence, developed a degree of male pattern hirsutism, a gruff voice and clitoral enlargement.

At the age of 22 she was referred by her GP to a physician to determine whether she could withdraw from the valproate as she wished to have children. In his letter to the GP the physician stated that he 'had read somewhere' that valproate 'could cause polycystic ovaries', added in phenytoin to her valproate (presumably with the intention of later withdrawing the valproate) and investigated her amenorrhoea.

Follicle stimulating and luteinizing hormone levels were normal as was her prolactin level: but her testosterone level was very high, three times above the upper limit quoted by the laboratory. Abdominal ultrasound showed no ovarian abnormality but the examination was technically difficult to interpret due to her obesity: being a virgin she declined transvaginal ultrasound.

It was decided that she had the polycystic ovary syndrome, so the valproate was withdrawn, but her periods did not return. Nine months after withdrawal of the valproate she had a tonic–clonic seizure in the bathroom in the early morning and began to develop multiple myoclonic jerks later in the morning.

She was referred for re-investigation of her epilepsy and a diagnosis of juvenile myoclonic epilepsy was made. She was also photosensitive. Phenytoin was withdrawn and lamotrigine substituted, the dose being slowly escalated until all traces of photosensitivity had gone: she had no more seizures or myoclonic jerks.

Re-investigation of her amenorrhoea showed a high testosterone level as before: MRI scanning of her ovaries revealed ovaries slightly smaller than normal, with multiple small atretic cysts (not a typical picture of polycystic ovaries). A search was then made for other causes of her high testosterone level and MRI of the abdomen revealed an androgen secreting tumour of the left adrenal gland.

Comment

This case illustrates the importance of arriving at correct syndromic classification before deciding on withdrawal of medication. The girl had been having morning jerks for some time before her first two tonic–clonic seizures but their diagnostic importance was ignored. Juvenile myoclonic epilepsy will return even after many years of full control of seizures if medication is then withdrawn.

It should have been recognized that there are other causes for a high testosterone level than the polycystic ovary syndrome and that the clinical history was one of progressive virilization: the girl should have been assessed first by an endocrinologist. The choice of phenytoin as a substitute for valproate was an irrational one and the clinician who decided on this was almost certainly unaware of the complex interaction between the two drugs, which can lead to serious if inadvertent phenytoin intoxication[2]. He should also have known that withdrawal seizures can occur many months after withdrawal of valproate. In other words he was acting outside his knowledge base and should have sought the advice of colleagues. Following successful treatment the girl is losing her virilization, is menstruating and is seizure free: but is not yet pregnant.

CASE 3

A woman of 32 presented in the triage clinic of an epilepsy service having had two witnessed tonic–clonic seizures whilst at work the previous week. There was a clear witness description of the events and the nurse running the clinic was satisfied that they were epileptic in nature and arranged the necessary investigations. There was no previous history of epilepsy. She correctly enquired if the woman had had any warning that the seizures might be coming but was told there had been no warning: they had come out of the blue.

Her only other health problem was her irregular menstruation, so irregular that she had not had a period for the previous 18 months. She was known to have the polycystic ovary syndrome and had been told that she would need hormone treatment (clomiphene) when she wished to become pregnant. She accepted this as both her mother and her sister had the same problem. Her mother had just developed type II diabetes.

A couple of weeks later the consultant and nurse were reviewing the patient in the clinic: EEG examination had shown a clear cut epileptic focus in the left temporal area, but head MRI scanning was normal. On further questioning about any sequalae after the two seizures she blushed, looked at the (male) doctor with some alarm, turned to the (female) nurse and said 'well, you know, I've not had one of my female funnies since I had the fits'.

It transpired that since the age of 14, she had been having regular occurrences of warm sexual feelings starting in her vagina and spreading to her abdomen. They were intense and accompanied by 'pleasant thoughts'. They only lasted a few seconds: those who knew her well might notice them, she thought, because she flushed and became pre-occupied (but did not lose awareness). She enjoyed them, particularly if they occurred when she was bored, and had never considered them to be abnormal: she thought all women had them, but just did not talk about them. They had been intermittent all her life, without obvious pattern, but had been particularly frequent in the month or two before her seizures and had disappeared after them.

Investigations also showed the typical hormonal parameters of the polycystic ovary syndrome, with raised testosterone and luteinizing hormone levels. Pelvic MRI scanning showed bilateral enlarged ovaries with multiple enlarged cysts. She was not having treatment for the syndrome.

Lamotrigine was introduced in monotherapy and the dose slowly escalated (to a 150 mg total daily dose) until 'the female funnies' which had returned (and were obviously simple partial seizures) disappeared again: she has been totally seizure free for over a year. Two months after starting lamotrigine (at a dose of 50 mg per day) she started to menstruate, and is now menstruating regularly. A repeat of her hormone assessment (at the right time of the cycle—day four of menstruation) showed a normal testosterone and luteinizing hormone level: repeat MRI scanning of her ovaries a year after menstruation restarted now showed normal sized ovaries and normal sized cysts. She is not yet trying to get pregnant, but is using reliable non-hormonal contraception.

Comment

Sexual feelings are a not uncommon aura in women with epilepsy[3], but are often not disclosed to male doctors, or not recognized for what they are or not enquired about. They may, of course, be equally common in men, but since men's spontaneous sexual feelings bounce about like yo-yos all day long anyway, they may just not be recognized as abnormal!

The apparent cessation of this woman's familial polycystic ovary syndrome following the exhibition of lamotrigine is interesting: but might equally well be due to the cessation of left temporal lobe epileptic activity which has also been shown to contribute to the exacerbation of the polycystic ovary syndrome in women with epilepsy[4].

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Self-assessment questions

Question 1.

Which of the following statements are true?

(a) At the end of reproductive life, when the oocyte mass is exhausted, the quiescent ovary becomes an ‘indifferent gonad’.

(b) Luteinizing hormone release at midcycle increases testosterone production in the ovary.

(c) High follicle stimulating hormone levels decrease oestrogen levels.

(d) Increased insulin levels increase androgen production in the ovary.

(e) Atretic ovarian follicles become ovulatory follicles through the action of tumour necrosis factor (TNF).

Question 2.

Which of the following statements are true?

(a) Resection of the ovaries leads to resolution of the symptoms of the polycystic ovary syndrome.

(b) Women who have more than 10 cysts in their ovaries on ultrasound examination have the polycystic ovary syndrome.

(c) Girls with type I diabetes are likely to have the polycystic ovary syndrome.

(d) Women with epilepsy have an altered LH pulse frequency.

(e) Women with left temporal lobe epilepsy are more likely to have polycystic ovaries.

Question 3.

Which of the following statements are true?

(a) Women with epilepsy are more likely to have anovulatory cycles.

(b) Anovulatory cycles lead to a reduction in seizure frequency in women due to increased progesterone levels.

(c) There is a probable association between the polycystic ovary syndrome and insulin resistance.

(d) Women taking sodium valproate have a greater prevalence of polycystic ovaries.

(e) The polycystic ovary syndrome can occur before puberty.

Question 4.

Infants born to women receiving antiepileptic drugs have:

(a) no additional risk of being born with an anomaly or a malformation.

(b) at least double the risk of being born with an anomaly or a malformation.

(c) at least triple the risk of being born with an anomaly or a malformation.

(d) at least quadruple the risk of being born with an anomaly or a malformation.

Question 5.

Which of the following statements are true?

(a) By the time a woman with epilepsy presents in pregnancy it is too late to change AED therapy.

(b) All anti-epileptic drugs are equally teratogenic in pregnancy.

(c) Children born to mothers taking sodium valproate during pregnancy have a higher risk of needing help at school.

(d) The risk of spina bifida associated with sodium valproate therapy can be reduced by decreasing the dose of sodium valproate or changing to Epilim Chrono.

(e) All women with epilepsy should take high dose folic acid for a month before and 3 months after conception.

Question 6.

Which of the following statements are true?

(a) Treatment of choice for women with primary generalized epilepsy is sodium valproate.

(b) All women with epilepsy should have preconception counselling.

(c) All women with epilepsy need Vitamin K prophylaxis in the last month of pregnancy.

(d) Breast feeding is contra-indicated for women on anti-epileptic drugs.

(e) Anti-epileptic drug levels should be measured during pregnancy.

Answers

1. (a) is false: the indifferent gonad is the undifferentiated gonadal tissue found in the very early embryo.
   (b) is true.
   (c) is false: it is the other way round.
   (d) is true.
   (e) is false: TNF causes apoptosis of the follicle.

2. (a) is true: but hardly an appropriate treatment. Resection of a wedge of ovarian tissue or of one ovary will reduce androgen production from the ovary and may restore ovulation, at least for a while, and may temporarily restore fertility.
   (b) is false: they have polyfollicular ovaries (European definition).
   (c) is false: it is type II diabetes.
   (d) is true (probably).
   (e) is true: in the sense there is published evidence for this, but probably an artefact of small numbers: women with generalized epilepsy also have them.

3. (a) is true.
   (b) is false: they lead to an increased number of seizures due to unopposed action of oestrogen.
   (c) is true.
   (d) is false.
   (e) is false: polyfollicular ovaries can be detected before puberty. The polycystic ovary syndrome may appear quite early on in puberty but not before it.

4. (a) is false.
   (b) is true.
   (c) is false.
   (d) is false.

5. (a) Is true: by day 56 after conception the foetus is fully formed.
   (b) Is false. Valproate is significantly more teratogenic than carbamazepine in the UK pregnancy database. Some drugs (lamotrigine, gabapentin, tiagabine and levetiracetam) do not appear to be teratogenic in animal studies. We are still awaiting human data.
   (c) Is true.
   (d) Is true. The teratogenicity of sodium valproate is dose dependent and relates to peak dose concentrations which can be reduced by use of a Chrono preparation.
   (e) Is true. The increased incidence of spina bifida associated with sodium valproate and carbamazepine therapy. Folic acid has not been shown to definitely decrease this risk. There are suggestions that women with epilepsy have a slightly increased risk of spina bifida than the general population.

6. (a) Is false. Sodium valproate is significantly more teratogenic than carbamazepine. Currently lamotrigine is tending to be used in women of childbearing age.
   (b) Is true.
   (c) Is false. Only those on enzyme inducing drugs need Vitamin K prophylaxis.
   (d) This is false—although all anti-epileptic drugs are excreted in breast milk in varying concentrations according to the drug. It is rare for the baby to experience side effects. Occasionally this can happen with phenobarbitone, benzodiazepines and lamotrigine and lamotrigine, especially in the very premature.
   (e) Is false. Total AED concentrations are misleading. If monitoring of blood levels is desired, free levels need to be measured. However, it is better to treat the patient clinically, i.e. if seizures increase the dose of anti-epileptic drug is increased.