CASE REPORT

Temporal lobe epilepsy exacerbation during pharmacological inhibition of endogenous neurosteroid synthesis

Matteo Pugnaghi, Giulia Monti, Giuseppe Biagini, Stefano Meletti

Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Modena, Italy

Correspondence to
Dr Stefano Meletti,
stefano.meletti@unimore.it

SUMMARY

We report the case of a woman who presented cryptogenic temporal lobe seizures from the age of 43 years. Antiepileptic drug (AED) treatment with carbamazepine was able to control seizures for 1 year, but seizures relapsed and an add-on treatment with lamotrigine was started without achieving seizures control. The patient's medical history was unremarkable except for a mild hirsutism for which she was taking finasteride since 45 years of age. In view of the possible relationship between finasteride, a known inhibitor of neurosteroids synthesis, and patient's seizures exacerbation, we stopped finasteride resulting in prompt recovery of seizures control. It is know that 5α-dihydrosteroids are precursors of powerful positive modulators of γ-aminobutyric acid-A inhibitory currents and exert antiseizure effects in animal epilepsy models. This case supports the hypothesis that endogenous neurosteroids can modulate seizure susceptibility and response to AEDs also in humans, suggesting their possible use as a new therapeutic option.

BACKGROUND

Finasteride is a synthetic 5α-reductase inhibitor, commonly used in men for the treatment of benign prostatic hyperplasia and baldness, and in women for hirsutism. These clinical uses are related to finasteride that has an ability to block the conversion of testosterone in its active form. In the brain, finasteride can interfere with endogenous neurosteroids synthesis by blocking the same enzymatic pathway.[1–3]

Neurosteroids are directly synthesised in the brain by transforming cholesterol to pregnenolone, a precursor of progesterone that is further converted into 5α,3α-tetrahydrosteroids (5α,3α-THSs).[1] In view of their ability to modulate neurotransmission, neurosteroids may influence the clinical course of epileptic disorders.[2] In this line, progesterone has been proposed as antiepileptic treatment in women with catamenial seizures.[3] The mechanism underlying this clinical effect is presumably based on the conversion of progesterone into 5α,3α-THSs, which are potent positive modulators of γ-aminobutyric acid type A ($GABA_A$) receptor-mediated transmission.[4]

The $GABA_A$ receptor-related anticonvulsant effects of 5α,3α-THSs are strongly supported by experimental evidence obtained from animal models.[5] Indeed, high-levels of 5α,3α-THSs appear to delay the establishment of chronic temporal lobe epilepsy (TLE) following pilocarpine-induced status epilepticus in rats. Conversely, the administration of finasteride anticipated the appearance of spontaneous recurrent seizures.[6 7] Notably, finasteride was also able to increase the seizure frequency in pilocarpine-treated rats presenting with recurrent spontaneous seizures.[2]

At present, although evidence for a role of 5α,3α-THSs in the treatment of human epilepsy was demonstrated in a patient taking exogenous progesterone to control catamenial temporal lobe seizures,[8] no other clinical data are currently available to support an involvement of neurosteroids in modulating seizure frequency in human TLE.

CASE PRESENTATION

A 57-year-old right-handed woman presented focal seizures from the age of 43 years. Seizures were initially characterised by autonomic and gustatory auras with a preferential occurrence during the menstrual cycle. Two years later autonomic and gustatory sensations were followed by oroalimentary automatisms, language dysfunction and rare loss of contact. At this time carbamazepine treatment up to 800 mg/day was initiated and seizures were controlled for more than 1 year, then a convulsive seizure occurred during the night. Although carbamazepine plasmatic levels were well within the therapeutic range, seizures relapsed with a frequency of 8–10 episodes/year. Thus, an add-on treatment with lamotrigine up to 300 mg/day was administered, but seizures were not controlled, and during three occasions they were complicated by fall to the ground. Patient's medical history was unremarkable except for a mild hirsutism that was treated with 5 mg/day of finasteride since 45 years of age. Based on previous evidence,[6–8] we hypothesised a possible relationship between finasteride and temporal lobe seizures exacerbation in our patient. Therefore, we stopped finasteride administration at the age of 50 years. Lamotrigine was then gradually reduced and subsequently stopped (52 years) and carbamazepine was decreased to 600 mg/day. At present the patient is still seizure-free with a terminal remission of 7 years after the discontinuation of finasteride.

INVESTIGATIONS

The interictal electroencephalogram (EEG) during finasteride treatment demonstrated left temporal θ activities and spikes during drowsiness and sleep. A high-resolution 3T brain MRI was normal; in particular no abnormalities were evident in the

To cite: Pugnaghi M, Monti G, Biagini G, *et al*. *BMJ Case Rep* Published online: [*please include* Day Month Year] doi:10.1136/bcr-2012-008204

temporal lobe. Routine clinical tests did not reveal any abnormality. The EEG performed after finasteride discontinuation was normal. Neuropsychological evaluation at 55 years of age showed a normal cognitive status. In particular no memory deficits, visual or verbal, were present.

DISCUSSION

We present a case of late-onset cryptogenic TLE with marked seizures' exacerbation occurring after the initiation of treatment with finasteride, a drug known to inhibit the endogenous synthesis of 5α,3α-THSs, that is used as a therapy of prostatic hyperplasia or for dermatological purposes.[1–3 6] Steroids not only act as remote endocrine messengers, but are also synthesised by neurons and glial cells in the brain where they modify the activity of neural networks.[1] Finasteride, by blocking 5α,3α-THSs synthesis, causes a marked increase in seizure susceptibility, as consistently shown in animal models.[2 3 6 7] Beside the patient reported here, only another case characterised by seizure exacerbation during finasteride treatment has been described.[8] In particular, Herzog and Frye[8] reported a patient affected by catamenial epilepsy whose seizures, previously well controlled by progesterone administration, were exacerbated by finasteride. It was proposed that finasteride abolished the therapeutic effect of progesterone interfering with its conversion into 5α,3α-THSs. Conversely, in the present case finasteride probably interfered with the antiseizure properties of *endogenous* 5α,3α-THSs produced in the brain, as described by Lawrence *et al*,[2] in the pilocarpine TLE model. This overall evidence supports the hypothesis that endogenous 5α,3α-THSs could regulate seizures' susceptibility in patients affected by TLE and also could modulate the efficacy of concomitant AED treatments.

We cannot exclude with certainty that the seizures' exacerbation and remission in our patient have occurred by chance, but there is strong evidence in favour of a causal relationship with finasteride intake. In fact, the patient has not been taking other drugs during the period of seizures' exacerbation, she was not affected by any intercurrent disease and she did not undergo any type of medical procedure. Moreover, there was a close temporal relationship between finasteride withdrawal and seizures' complete disappearance with a long subsequent follow-up (7 years), without seizures' recurrence. Sometimes seizures can have a relapsing–remitting time course despite any changes in the patient's antiepileptic treatment.[9] However, in the present case seizures' recurrence does not suggest a relapsing–remitting course, but rather a drug-responsive trend with only one period of seizure exacerbation followed by a very prolonged terminal remission. Finally, finasteride has a mechanism of action that can justify a clinical effect on the seizures' occurrence, as clearly demonstrated in animal models[2 3 6 7] and strongly suggested in a previously reported human case report.[8]

In the present case finasteride could have caused seizures' exacerbation by inhibiting the antiepileptogenic effect of endogenous neurosteroids, which is because of a positive modulation of $GABA_A$ receptor-mediated neurotransmission. Moreover, we can speculate that the epileptogenic tissue itself could produce endogenous anticonvulsive compounds (such as allopregnanolone and tetrahydrodeoxycorticosterone) that can have a synergistic effect with different AED to promote seizure control. Consequently, a decreased availability of these compounds may result in a loss of effectiveness of multiple AED treatments. This is an important topic since a significant percentage of epilepsy patients (about 20–30%) show a poor response to AED treatments.

With our hypothesis, clinical trials have been carried out consistently demonstrating positive although still preliminary effects for ganaxolone, an analogue of the 5α,3α-THS allopregnanolone, in drug-resistant epileptic patients.[10] Moreover, it has been demonstrated in animal models that 5α,3α-THSs can act as regulators of epileptogenesis.[6 7] Thus, the possibility that exogenously administered 5α,3α-THSs or their synthetic analogues could have clinical utility in the prevention of epileptogenesis can be taken into account, particularly in the setting of status epilepticus or in other situations where there is a risk for the development of epilepsy, such as in traumatic brain injury.[11]

Learning points

- Neurosteroids are a family of compounds that can modulate neuronal excitability and seizures in animal models and probably also in humans.
- We describe a case of seizures' exacerbation in a patient with temporal lobe epilepsy under finasteride treatment, controlled with its withdrawal.
- Finasteride, a drug commonly used for prostatic hyperplasia and dermatological problems, can block neurosteroids' synthesis causing an increase in seizure susceptibility.
- Physicians should be aware of this pharmacological effect and of the resulting clinical consequences.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Belelli D, Lambert JJ. Neurosteroid: endogenous regulators of the GABA A receptor. *Nat Neurosci* 2005;6:565–75.
2 Lawrence C, Martin BS, Sun C, *et al*. Endogenous neurosteroid synthesis modulates seizure frequency. *Ann Neurol* 2010;67:689–93.
3 Reddy DS. The role of neurosteroids in the pathophysiology and treatment of catamenial epilepsy. *Epilepsy Res* 2009;85:1–30.
4 Maguire JL, Stell BM, Rafizadeh M, *et al*. Ovarian cycle-linked changes in GABA A receptors mediating tonic inhibition alter seizure susceptibility and anxiety. *Nat Neurosci* 2005;8:797–804.
5 Gangisetty O, Reddy DS. Neurosteroid withdrawal regulates GABA-A receptor α4-subunit expression and seizure susceptibility by activation of progesterone receptor-independent early growth response factor-3 pathway. *Neuroscience* 2010;170:865–80.
6 Biagini G, Baldelli E, Longo D, *et al*. Endogenous neurosteroids modulate epileptogenesis in a model of temporal lobe epilepsy. *Exp Neurol* 2006;201:519–24.
7 Reddy DS, Ramanathan G. Finasteride inhibits the disease-modifying activity of progesterone in the hippocampus kindling model of epileptogenesis. *Epilepsy Behav* 2012;25:92–7.
8 Herzog AG, Frye CA. Seizure exacerbation associated with inhibition of progesterone metabolism. *Ann Neurol* 2003;53:390–1.
9 Sillampaa and Schmidt. Natural history of treated childhood-onset epilepsy: prospective, long-term population-based study. *Brain* 2006;129:617–24.
10 Nohria V, Giller E. Ganaxolone. *Neurotherapeutics* 2007;4:102–5.
11 Biagini G, Panuccio G, Avoli M. Neurosteroids and epilepsy. *Curr Opin Neurol* 2010;23:170–6.