CASE REPORT

Development of forced normalisation psychosis with ethosuximide

Sean Apap Mangion,¹ Fergus Rugg-Gunn²

¹Department of Telemetry, University College London, Institute of Neurology, London, UK

²Department of Neurology, National Hospital for Neurology and Neurosurgery, London, UK

Correspondence to
Dr Sean Apap Mangion,
seanapapmangion@gmail.com

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SUMMARY

A 50-year-old man with known multidrug resistant coexistent focal and generalised epilepsy was commenced on ethosuximide, with normalisation of his electroencephalogram and cessation of absence seizures. Within 3 weeks, he developed a rapidly worsening paranoid psychosis with visual and olfactory hallucinations. A month after the cessation of ethosuximide and concurrent treatment with olanzapine, his psychosis resolved and permitted reinitiation of ethosuximide at a lower dose without recurrence of psychotic symptoms.

BACKGROUND

Epilepsy is a complex neuropsychiatric condition, with population studies demonstrating prevalence of mental health disorders of 28.6% in children and between 19% and 52% in adults.^{1 2} Higher incidences of psychoses have been specifically demonstrated in patients with epilepsy (9%) compared with the general population (1%).³

Delirium presents in 7%–20% of patients that present to emergency departments,⁴ and while the causes are broad, the significance of epilepsy and epilepsy medication as part of the diagnostic picture is easily overlooked.

The relationship between seizures and psychotic episodes is complex, with a number of theories focusing on abnormal limbic activity^{5 6} and research suggesting a role for abnormal dopamine metabolism.⁷

Clinically, the induction of seizures has been demonstrated to improve psychotic symptoms. Historically, the chemical camphor (now commonly used in vapour steam products to relieve sinus congestion) was used to artificially induce seizures in the management of manic psychoses,⁸ and more recently in the form of electroconvulsive

therapy-induced seizures in non-depressive psychiatric illness.⁹

Forced normalisation can be viewed as the converse of these treatments, with the development of psychosis resulting from significant seizure reduction or electroencephalogram (EEG) normalisation, following treatment.¹⁰

CASE PRESENTATION

A 50-year-old man with no personal or family history of neurological or psychiatric illness first presented with absence seizures at the age of 7 years. Following successful treatment with ethosuximide (dose unknown), and improvement of his EEG, his epilepsy was quiescent until he suffered a generalised tonic-clonic seizure (GTCS) at age 16 years. Subsequently, he was treated with sodium valproate (maximum dose unknown) and phenytoin (550 mg/day). His epilepsy was once more well controlled for a further 2 years until the development of drop attacks. An EEG recording at the time demonstrated generalised spike and wave discharges.

Following this, the phenytoin was withdrawn and lamotrigine trialled; however, this proved ineffective and was subsequently replaced with a combination of topiramate (maximum dose unknown), phenytoin and valproate. Over the subsequent 15 years, trials to withdraw the phenytoin proved unsuccessful, and levetiracetam was added to his treatment. Repeat EEG demonstrated persisting generalised spike and polyspike-wave epileptiform discharges.

A year later, a vagus nerve stimulator was implanted, but without benefit. A year after this, phenytoin and then topiramate were withdrawn due to loss of efficacy.

Following the discontinuation of phenytoin and topiramate, he was started on zonisamide (maximum 200 mg twice daily) and perampanel

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Figure 1 Seizure development and antiepileptic drug summary prior to presentation. GTCS, generalised tonic-clonic seizure. ETX, ethosuximide. LAM, lamotrigine. LAC, lacosamide. LEV, levetiracetam. GTCS, generalised tonic-clonic seizure. PER, perampanel. PHY, phenytoin. TOP, topiramate. VAL, valproate. VNS, Vagal nerve stimulation, ZON, zonisamide.

Figure 2 Generalised, frontal-predominant spike and wave discharges during wakefulness.

(maximum dose unknown). The latter was stopped due to the development of significant irritability. Attempts were made to change zonisamide to lacosamide (maximum dose unknown) due to the development of word finding difficulties and a decline in his overall language performance; however, ultimately the zonisamide proved an ineffective antiepileptic drug (AED) and the change was reverted.

An MRI brain scan demonstrated equivocal increased signal intensity in the left temporal cortex, involving the temporo-mesial cortical structures through the amygdala and hippocampi, with possible volume loss affecting the insular structures, the hippocampi, precuneus and cerebellar hemispheres.

On admission, after the aforementioned history (figure 1), the patient reported ongoing absence seizures at a frequency of 2–3 per week, GTCS occurring twice per month and rare drop attacks (<1 per year). At this point, he was being treated with sodium valproate 900 mg BD, levetiracetam 1.5 g BD, zonisamide 150 mg BD and clobazam 10 mg as needed.

Video telemetry demonstrated a clearly abnormal interictal EEG, with (1) spike and slow wave activity, (2) polyspike discharges and (3) polyspike and slow wave activity in a generalised pattern with frontal predominance (figure 2). However, focal discharges in sleep were seen over the right hemisphere, both frontally and temporoparietally. Rarely generalised discharges were preceded by right frontal discharges (figure 3).

The evidence of additional ongoing generalised epileptiform discharges prompted a retrieval of ethosuximide which was gradually increased to 750 mg per day. Subsequent ambulatory EEGs demonstrated a marked improvement of the neurophysiological picture with no clearly defined epileptiform activity during wakefulness, and only very occasional brief bursts of generalised, anterior polyspikes or spike/polyspikes and slow waves, occasionally more marked on the right side during sleep. Simultaneously, his seizure control improved substantially, with no further absence seizures and the patient reported an improvement in cognitive function.

Figure 3 Right-sided frontal and temporoparietal discharges during sleep.

Over the subsequent 3 weeks, the patient developed a gradually worsening, predominantly persecutory, paranoid psychosis, associated with olfactory and visual hallucinations, with preserved arousal, orientation and awareness.

TREATMENT

His ethosuximide was withdrawn and olanzapine was commenced and increased to 50 mg once a day. An EEG taken at this time was still largely normalised during wakefulness, with persistent occasional spikes/polyspikes and waves as described above.

Over the next month, his psychosis resolved as his absence seizures returned to pre-ethosuximide frequency of several events per day, in addition to one GTCS per week. A repeat ambulatory EEG demonstrated a clear deterioration but a similar background to recordings taken prior to initiation of ethosuximide, being a little slow with generalised bursts

Table 1 Previously reported forced normalisation phenomena

Antiepileptic drug	Case/paper
Ethosuximide	Yamamoto <i>et al</i> ¹⁶ Wolf <i>et al</i> ¹³
Lacosamide	Abou Khaled <i>et al</i> ¹⁷
Lamotrigine	Clemens ¹⁸
Levetiracetam	Loganathan <i>et al</i> ¹⁹
Phenobarbitone	Gobbi <i>et al</i> ²⁰
Vigabatrin	Weber <i>et al</i> ²¹
Zonisamide	Hirose <i>et al</i> ²²
Vagal nerve stimulation	Blumer <i>et al</i> ¹⁵

of spikes and polyspikes, more often occurring in sleep and sometimes having a right-sided emphasis.

OUTCOME AND FOLLOW-UP

On repeat admission, ethosuximide was cautiously reintroduced up to a reduced maximum daily dose of 500 mg. By the time of writing, over 3 months since the reintroduction of ethosuximide, he has not had a recurrence of his psychotic symptoms. His absence seizures have however not improved significantly on this occasion.

DISCUSSION

The patient described fulfilled all the essential diagnostic criteria and one supportive criterion as laid out by Krishnamoorthy and Trimble in 1999, namely the presence of an established diagnosis of epilepsy, and the development of a rapid-onset behavioural disturbance with a significant improvement of awake EEG recordings within 4 weeks of starting new medication.¹¹ The fact that cessation of ethosuximide resulted in a recurrence of the EEG abnormality, seizures and resolution of psychiatric symptoms further supports the diagnosis of forced normalisation—however, the addition of olanzapine and its role in dopamine metabolism, which may be important in FN psychosis is a potential confounder. Furthermore, the patient was successfully treated with ethosuximide for approximately 10 years as a child without the development of psychotic symptoms. Changes in brain structure and neurotransmitter expression,¹² and long-standing poorly controlled epilepsy, may significantly alter the neurotransmitter architecture compared with childhood.

Previous literature has suggested a particular predilection for FN in patients with absence epilepsy,¹³ and though it would be tempting to theorise on the mechanism of action of ethosuximide (largely believed to be a T-type calcium channel inhibitor¹⁴) and how it may bring about FN, the phenomenon has been described following the use of numerous AEDs (table 1), and has also been described following use of a vagal nerve stimulator, although with an apparent tendency towards more aggressive psychotic features.¹⁵

Though cases of FN with ethosuximide have been described previously, this is the first instance, to the authors' knowledge, that revisiting a previously effective AED has resulted

in the development of FN, suggesting the potential impact of neurotransmitter pathway changes which result from long-standing poorly controlled epilepsy.

Contributors SAM collected the patient data, performed the data review and composed the primary case report. FR-G provided the case, oversaw the case report write-up, and subsequently updated and corrected the drafts presented and offered expert advice.

Competing interests None declared.

Patient consent Obtained.

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Learning points

- Psychosis is more prevalent among patients with epilepsy compared with the general population.
- Forced normalisation is a cause of psychiatric disturbance in patients with epilepsy, particularly in the context of the recent introduction of an antiepileptic medication.
- Development of forced normalisation does not rule out a further trial of medication at a lower dose.

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