CASE REPORT

A young woman with seizures and psychosis

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SUMMARY

We present a case of a 24-year-old woman with abnormal behaviour of recent onset. She had been diagnosed previously with epilepsy and had been started on antiepileptic medication. Clinical examination confirmed features of psychosis including paranoid delusions and auditory hallucination. Neurological examination showed nystagmus and dysmetria. Further evaluation revealed the underlying cause for her symptoms. She responded promptly to appropriate therapy with complete resolution of psychosis.

BACKGROUND

An association between epilepsy and psychosis has been demonstrated in various studies,^{1 2} and it has been estimated that psychosis in the form of schizophrenia affects between 3% and 7% of all epileptic patients as compared with 1% of the general population.³ Several mechanisms exist to explain this association principally through a common aetiology such as systemic lupus erythematosus, involvement of the temporal lobe producing seizures and behavioural disturbance and structural abnormalities including intracranial haematomas and tumours.⁴ Interictal and postictal psychoses comprise a distinct group of disorders and are diagnosed by excluding all other causes.⁵

Psychotropic adverse effects of medication constitute another mechanism connecting epilepsy and psychosis. The capacity of various antiepileptic drugs to affect behavioural patterns is well known, to the extent that many of these drugs have been studied for possible use in psychiatric disorders.⁶

Phenytoin is a sodium channel blocker and has been extensively employed as an antiepileptic drug, especially in the management of generalised tonic-clonic seizures. Despite the development of newer drugs with better safety profiles the comparatively low cost of phenytoin has allowed it to retain its popularity in resource-limited settings. The relative lack of awareness with regard to the psychopharmacological effects of phenytoin among physicians working in these settings contrasts sharply with the general cognizance of such common medical adverse effects such as hepatotoxicity, cerebellar toxicity and teratogenicity. This case is being reported to address this lacuna and generate increased recognition of psychosis as a potential adverse effect of phenytoin.

CASE PRESENTATION

A 24-year-old housewife presented with abnormal behaviour for 2 weeks, consisting primarily of auditory hallucinations and non-bizarre paranoid delusions. She reported hearing voices telling that her

relatives were plotting against her and insisted that these people had attempted to harm her in various ways, although she would not elaborate their motives. Careful questioning of her family members revealed similar albeit milder symptoms for the past few months including excessive suspiciousness and occasional references to unnamed persons advising her, with progressive worsening in the 2 weeks prior to presentation. The patient also reported excessive fatigue and inability to perform routine household activities. She did not report any symptoms specific to cerebellar dysfunction such as giddiness, or swaying while walking. There were no other neurological symptoms. She denied any history of substance abuse.

Her medical history included a diagnosis of generalised tonic-clonic epilepsy, for which she was receiving maintenance therapy with phenytoin (300 mg orally once daily) since the past 11 months. She had suffered one episode of generalised convulsion after defaulting on phenytoin 10 months earlier; thereafter she resumed phenytoin therapy and did not suffer any further convulsions. Her family history was unremarkable.

Physical examination showed normal vital signs. Neurological evaluation revealed mild generalised hypotonia, grade I horizontal nystagmus on lateral gaze to either side, and bilateral dysmetria on finger nose testing, but no other focal neurological deficits. The patient was fully oriented with preserved registration and recall. Her Mini-Mental State Examination score was 30/30.

INVESTIGATIONS

Routine laboratory investigations including liver function tests were essentially normal. Serum phenytoin levels were grossly deranged (greater than 78.9 µg/mL).

DIFFERENTIAL DIAGNOSIS

Phenytoin toxicity with cerebellar dysfunction and drug-induced psychosis.

TREATMENT

Phenytoin was immediately discontinued, and the patient was initiated on levetiracetam (1 g intravenous loading dose followed by 500 mg orally twice daily) for her seizure disorder. Antipsychotic medication was not administered after consultation with psychiatrists.

OUTCOME AND FOLLOW-UP

The patient improved rapidly after discontinuation of phenytoin, with complete resolution of her psychotic symptoms and cerebellar signs over the next 4 days. She remains asymptomatic and seizure

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free on follow-up of 6 months after cessation of phenytoin therapy.

DISCUSSION

A diagnosis of certain adverse drug reaction was carried out in this case by the causality assessment criteria of the WHO Collaborating Centre for International Drug Monitoring, the Uppsala Monitoring Centre (WHO-UMC).⁷

The psychopharmacological effects of phenytoin encompasses a broad spectrum ranging from decreased cognition, sedation and psychomotor retardation to antidepressant and antimanic activity and mood stabilisation.⁶ Awareness of these properties has expectedly led to off-label use of phenytoin in an adjunctive role for a wide variety of psychiatric disorders including acute mania, in combination with haloperidol, and bipolar disorder, post-traumatic stress disorder and intermittent explosive disorder as a single agent.⁸ These indications are based predominantly on case reports, small open-label series and poorly designed controlled studies, and have not been confirmed by larger adequately powered trials.⁶ Thus phenytoin is not currently indicated for any psychiatric condition.

The wide and somewhat unpredictable range of these psychopharmacological actions has also hindered attempts to develop phenytoin into a psychotropic drug. Prolonged phenytoin overdose for instance has been associated with chronic encephalopathy with cerebellar degeneration, while acute toxicity can produce delirium and even seizures.⁶

Conversely, phenytoin remains highly effective as an anticonvulsant and is widely employed in resource-constrained settings as an economical alternative to newer antiepileptics. A direct consequence of this preference for phenytoin is an increased likelihood of inadvertently encountering its psychotropic effects. The fact that there is no available data on the incidence of such effects within the Indian subcontinent only serves to raise the possibility that phenytoin-induced psychosis is not being adequately recognised by physicians.

The association of phenytoin with interictal psychosis was demonstrated in a study by Kanemoto *et al*,⁵ involving 132 patients with epilepsy and psychosis.⁹ In this study, antiepileptics were implicated in 45 patients with new onset psychosis, 20 of who had received phenytoin. A strong correlation was demonstrated between the initiation or augmentation of phenytoin therapy and onset of psychotic episodes. These findings were echoed in a study by Noguchi *et al*.¹⁰

Pertinently, only 6 of the 45 patients described by Kanemoto *et al*⁵ subsequently developed chronic psychoses as compared with 18 of 54 epileptic patients with unprovoked psychosis. This finding would suggest that prompt cessation of the culprit anticonvulsant can produce durable reversal of psychosis and obviate the need for additional antipsychotic therapy, underlining the importance of early recognition by the treating physician.

It should also be noted that psychopharmacological activity is an integral property of virtually every antiepileptic, possibly through actions on neural pathways common to seizure and psychosis.⁶ Unfortunately without a clear understanding of these mechanisms, it is impossible to predict the cross-reaction between one class of antiepileptic and another. Therefore

substitution of one anticonvulsant with another should be accompanied by careful monitoring for alleviation of psychotic symptoms and trial of a third alternative if appropriate.

By the very nature of its subjective and often subtle symptoms, psychopathology is frequently unrecognised and untreated in persons with epilepsy.¹¹ Nonetheless such symptoms can produce substantial distress in the patient and their family members and can be potentially fatal when associated with undiagnosed suicidal ideation.¹ Maintenance of a high index of suspicion and judicious use of alternative anticonvulsant therapy in suitable candidates would appear to be beneficial in such situations.

Learning points

- ▶ Psychosis can develop in patients with epilepsy through a variety of mechanisms, including drug toxicity.
- ▶ Typical features of drug toxicity, such as cerebellar dysfunction in this instance, can be subtle and should be carefully looked for.
- ▶ Assaying of antiepileptic drug levels is confirmatory of toxicity, and should be performed in all epileptic patients presenting with psychosis.

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Competing interests None.

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