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Letter

Valproate delays diagnosis of anti-NMDA-receptor-encephalitis in a patient with psychiatric presentation

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To the Editor

Psychiatric presentations of anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis (anti-NMDARe) can lead to diagnosis delay and ineffective treatment.

The use of antiepileptics is inconsistently reported, although acute mania and mixed-mood state can be observed (Warren et al., 2018). However, the antiepileptic valproate is a first-line treatment to manage these symptoms. It is therefore important to report its effects on secondary psychiatric symptoms.

For this purpose, we present the case of a 26-year-old woman, whose diagnosis of anti-NMDARe was delayed by valproate.

She was hospitalized for a first fast-onset manic episode. Cranial computed tomography and usual blood tests were normal.

She failed to achieve clinical response with several antipsychotics at usual doses. Severe side effects including extra-pyramidal syndrome led to antipsychotic discontinuation.

Recovery was obtained after 10 days with valproate 2000 mg/day. It is worth noting that she reported later that she experienced brutal spatial disorientation few days before the hospitalization and had a total amnesia afterwards.

Several weeks later, she described minor acute episodes of dyspraxia and minor subjective memory impairment but did not experience any psychiatric symptoms for the next year.

As she planned her pregnancy, valproate was reduced. A major depressive episode occurred at 250 mg/day, which worsened to catatonia, with stupor, agitation not influenced by external stimuli, negativism, mutism and catalepsy.

Examination found pyramidal syndrome with exaggerated deep tendon reflexes and bilateral Hoffman's reflex. Basic blood tests and brain magnetic resonance imaging were normal. Electroencephalography showed generalized slowing. Fluorine-18-fluorodeoxyglucose positron emission tomography was consistent with encephalitis showing striatal hypermetabolism and bilateral internal temporal cortex hypometabolism. Anti-NMDAR antibodies were positive in cerebrospinal fluid.

Retrospectively, unusual high level of side effects with antipsychotics, dyspraxia, memory impairment and spatial disorientation, are arguments in favor of an undiagnosed anti-NMDARe (Warren et al., 2018). We thought valproate delayed this diagnosis.

NMDAR mediates excitatory neurotransmission involved in synaptic plasticity and excitotoxicity. Anti-NMDAR antibodies decrease surface NMDAR cluster density and synaptic localization, leading to disinhibition of glutamatergic neurons and to a hyperglutamatergic state (Manto et al., 2010).

Chronic administration of valproate attenuates NMDAR-evoked depolarization, increases gamma-amino-butyric acid (GABA) synthesis and potentiates GABAergic inhibitory transmission. This leads to increased inhibition of glutamatergic neurons (Lagace et al., 2004). This explains interesting therapeutic and neuroprotective properties in anti-NMDARe which could delay the diagnosis.

This case demonstrates that valproate alleviates secondary psychiatric symptoms and slows down clinical evolution of anti-NMDARe, which leads to misdiagnosing it as bipolar disorder.

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