



Acute chorea caused by valproate in an elderly

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Abstract

We present the case of an elderly woman chronically treated with valproate as migraine prophylaxis. She developed acute chorea secondary to valproate dose increase. Choreiform movements ceased following valproate discontinuation. Chorea is a rare and dose dependent side effect of valproate.

Introduction

Various different drugs have been reported to cause chorea. Most frequent and best known is the chorea secondary to treatment with levodopa and dopamine agonists in Parkinson patients. Chorea induced by anticonvulsants is rare and has been most frequently described with the use of phenytoin (Jain, 2001). Valproate causing chorea seems to be exceedingly rare (Lancman, 1994; Gunal 2002; Srinivasan, 2010).

Case report

An 80-year-old woman presented with acute onset of forcible choreiform movements of the 4 limbs and face. The movement disorder had begun the night before admission. Her medical history included a transient ischaemic attack with aphasia 6 years before and migraine with aura. Although a new diagnosis of migraine with aura is unusual in the elderly, her description of 4 stereotypical attacks with an expanding circular scotoma, followed by a speech disturbance and paresthesias in the right hemicorpus and contralateral headache were quite suggestive of this diagnosis. Furthermore, the excellent response to treatment with valproate supported this hypothesis. She was taking clopidogrel 75 mg/d, simvastatin 40 mg/d and valproate extended release (ER) 600 mg twice daily (as migraine prophylaxis). She didn't take any other drugs which could have caused

a movement disorder. According to her medical record she was supposed to take valproate ER 300 mg twice daily since 4 years. The recent dose increase of valproate was instated by her general practitioner because of a 'low' blood level of 48 $\mu\text{g/ml}$ a few weeks before. Valproate blood level on admission was 89 $\mu\text{g/ml}$. Routine haematologic and biochemical blood examinations, including tests of thyroid function, antinuclear antibodies and antiphospholipid antibodies were all normal or negative. Because valproate, and especially the recent and substantial blood level increase, seemed the most obvious cause of the chorea, treatment with valproate was discontinued immediately. She was treated with haloperidol 1 mg orally during 10 days. EEG on admission day showed a normal background activity which was interrupted by occurrence of frontal intermittent rhythmic delta activity. Brain MRI showed global atrophy and arteriosclerotic leukoencephalopathy but no acute ischaemic (on diffusion weighted images) nor haemorrhagic lesions. Chorea extinguished gradually over the next few days. During observation a diagnosis of mild cognitive impairment was made. On a follow-up consultation 6 months later, we learned that no movement problems had recurred and clinical examination confirmed the absence of any kind of movement disorder.

Discussion

Valproate is a broad spectrum antiepileptic drug, also commonly used in a variety of nonepileptic disorders. Its mechanism of action is blocking of voltage-gated sodium and calcium channels, increasing the activity of the inhibitory gamma-aminobutyric acid (GABA)-ergic system and decreasing the activity of the excitatory glutamatergic system (Panayiotopoulos, 2005). Valproate can cause various different neurological side effects (Table 1);

Table 1

Possible neurological side effects of valproate (Jain, 2001)

Induction or enhancement of physiological tremor
Encephalopathy (with or without hyperammonemia)
Induction or aggravation of parkinsonism
Psychosis
Reversible dementia (sometimes with pseudoatrophy of the brain)
Paradoxical induction or aggravation of seizures
Asterixis
Chorea
Nystagmus
Tinnitus
Vivid dreams and nightmares

tremor and encephalopathy are the most frequent (Jain, 2001).

Very few cases of valproate-induced chorea were reported. The first, and most frequently cited article about this topic, is the one by Lancman *et al.* They described 3 patients with severe brain damage and epilepsy who developed chorea after several years of valproate use. Episodes of chorea were closely related to the expected peak levels of valproate. Two of their patients were taking phenytoin as well. In both of those cases chorea didn't improve after discontinuation of phenytoin; in 1 case it stopped shortly following discontinuation of valproate and in the other case chorea improved after divalproex sodium sprinkles were used instead of regular valproate. In their patient treated with valproate monotherapy, chorea also ceased with substitution of valproate by divalproex sodium sprinkles. Their most important conclusions were that valproate-associated chorea can occur after long term treatment and that chorea seems dose-related (peak level). Phenytoin and underlying brain damage are possible risk factors in developing valproate-related chorea (Lancman, 1994). Gunal *et al.* reported a patient with posttraumatic epilepsy who developed generalized choreiform movements during the second month of treatment with 1500 mg/d of valproate. Chorea disappeared after cessation of valproate treatment (Gunal, 2002). Srinivasan and Lok described a gentleman with a history of a right frontal haemorrhage,

residual left hemiparesis and lesional epilepsy for which he was treated with valproate 1400 mg/d. This patient developed left-sided hemichorea because he unknowingly overdosed his valproate, taking 1900 mg/d instead of 1400 mg/d. Valproate blood level during chorea was 182 $\mu\text{g/ml}$ whereas prior blood level was 90 $\mu\text{g/ml}$. Valproate was stopped and chorea had resolved 3 days later (Srinivasan, 2010).

Suggested pathophysiology is that valproate in high blood levels inactivates glutamate acid decarboxylase (GAD), whose role is in increasing GABA levels and thereby exerts differing effects on the predominant GABA pathways of the basal ganglia-thalamocortical circuits, leading to motor cortex activation rather than the expected inhibition (Srinivasan, 2010).

To our knowledge, our patient represents the first case with valproate-induced chorea without epilepsy. Consistent with previous reports, chorea seemed to be dose-related and our patient also had some kind of cerebral damage with vascular leukoariosis, atrophy and mild cognitive impairment.

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