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**Multiple system atrophy due to prolonged valproic acid treatment**

Studies reported in the literature indicate a wide range of movement disorders associated with anti-epileptic treatment (Easterford *et al.*., 2004). Valproic acid is a well-known cause of reversible neurotoxicity characterized by symptoms resembling idiopathic Parkinson’s disease (PD) and cognitive impairment (Armon *et al.*., 1996; Onofrj *et al.*., 1998).

Here we describe the case of a woman on prolonged valproic acid treatment, who has developed a neurodegenerative condition mimicking multiple system atrophy (MSA). The patient gave written informed consent to publication of this letter reporting her case.

A 61-year-old woman taking valproic acid since the age of 14 for generalized idiopathic epilepsy was admitted to the Neurology Unit, University of Brescia, Italy. Over the past 20 years, she has been seizure-free on valproic acid (400 mg total integrated dose (t.i.d.)). Her family history was unremarkable for neurodegenerative conditions.

In the past 10 years, however, she has progressively developed extrapyramidal syndrome, characterized by moderate bradykinesia, increased tone along with bilateral cogwheel sign, mild upper limb resting and postural tremor, and brisk reflexes (Unified Parkinson Disease Rating scale, UPDRS-III = 20). Moreover, cerebellar symptoms – i.e. truncal ataxia – and pyramidal signs – i.e. bilateral extensor planter responses – were present. Neuropsychological assessment excluded cognitive impairment.

Routine laboratory exams were within normal range, valproic acid levels were 121 µg/mL (normal range: 40–100). Electroencephalogram (EEG) recordings demonstrated bilateral slowing over the frontal and temporal derivations. Magnetic resonance imaging (MRI) of the brain showed the presence of cerebral...
cortical-subcortical and cerebellar atrophy, with secondary enlargement of both lateral and third ventricles. Intriguingly, MRI also demonstrated the presence of hypointensity of the tails of both putamen on T2 weight-sequence, one of the neuroimaging features associated with atypical Parkinsonism. Thus, the diagnosis of MSA-like was made according to current available criteria (Consensus Committee of the American Autonomic Society and the Academy of Neurology, 1996).

At that time, the hypothesis of MSA-like induced by valproic acid was raised. To investigate this hypothesis, the treatment with valproic acid was progressively stopped, which resulted in clear improvement over the following few months. Three months after withdrawal, extrapyramidal symptoms ameliorated, with only subtle upper limb postural tremor persisting. Cogwheel rigidity as well as bradykinesia were no longer present (UPDRS-III = 2), and gait disturbances and ataxia improved as well. The patient has never taken L-dopa treatment.

The benefit observed following pharmacological withdrawal supported the relationship between prolonged valproic acid treatment and the onset of MSA-like symptoms.

Reversible neurological deficits due to valproic acid have been previously described. Most of the reports referred to PD, and only one case of MSA secondary to valproate therapy has been suggested (Armon et al., 1996; Onofrj et al., 1998; Shill and Fife, 2000; Easterford et al., 2004). The development of extrapyramidal syndrome induced by valproate is further emphasized by observation of an improvement in symptoms after discontinuation of treatment in most of the cases. All the previous reports except one, however, were not corroborated by cerebral structural neuroimaging abnormalities (Guerrini et al., 1998). In the case presented here, we report neuroimaging findings previously associated with atypical Parkinsonism and MSA, suggesting that longer chronic valproate therapy may cause structural changes in the brain.

The underlying pathogenesis involved in the development of this reversible neurological syndrome is still unknown. Valproate raises levels of brain gamma-aminobutyric acid (GABA), suppresses the sodium channel of rapidly firing neurons, thus influencing dopamine pathways, leading to the inhibition of mitochondrial fatty acid oxidation.

The reported associated neurological symptoms develop insidiously and resolve quite quickly following withdrawal. Whether these findings result from neurotransmitter changes or mitochondrial dysfunction remains a matter of speculation.

In our case, the causal role of valproate seems to be likely as the patient was taking no other medication, and after several years of progressive impairment, she made a rapid and dramatic recovery when valproate was discontinued.
It is unlikely that classical MSA due to neurodegenerative condition would spontaneously remit.

This observation suggests that valproic acid withdrawal should be taken into account in patients presenting extrapyramidal features, balancing risks and benefits. Further, the clinical evidence of the relationship between valproic acid treatment and MSA features opens a new clue for further investigation of the disease pathogenesis. The mechanism of action and the related changes due to prolonged valproate use should be evaluated to better understand the underpinnings of neurodegenerative extrapyramidal diseases such as MSA.

References


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The unspoken secret: sexual violence in World War II

War is a complex, enduring trauma composed of variable forms of extreme stress, such as violence, fear of death, displacement, loss of family members, abuse and starvation (Berman, 2001). More than 90% of war victims are civilians (UNICEF, 2006). Children and women are extremely vulnerable to traumatic experiences in times of war and the risk continues even in post-war-situations (Shanks and Schull, 2000). As far as former war-children are concerned, a high