Valproate-Associated Parkinsonism: A Critical Review of the Literature

Florian Brugger, Kailash P Bhatia & Frank M C Besag

Valproate was first approved as an antiepileptic drug in 1962 and has since also become established as a mood stabiliser and as prophylaxis for migraine. In 1979, Lautin published the first description of a valproate-associated extrapyramidal syndrome. Many cases of valproate-associated parkinsonism have subsequently been published, but uncertainties remain concerning its prevalence, risk factors and prognosis. The aim of this paper is to provide a critical review of the existing literature on valproate-associated parkinsonism and to discuss possible mechanisms. Literature databases were searched systematically: we identified a total of 116 patients with valproate-associated parkinsonism published in case reports, case series and systematic analyses. Prevalence rates ranged widely, between 1.4 and 75% of patients taking valproate. There was great heterogeneity with regard to clinical presentation, age of onset, valproate dose, concomitant conditions and imaging findings. In all patients apart from three, valproate plasma concentrations were within or even below the recommended reference range when the parkinsonism occurred. Parkinsonism was reversible in the majority of patients, although recovery was often prolonged and sometimes incomplete. A dopaminergic deficit was confirmed in three of six patients investigated with dopamine transporter imaging. Seven of 14 patients who were treated with dopaminergic medication had a good response. The quality of the evidence was assessed and probability of causation was examined using the Naranjo score, which ranged from 0 to 7 (median: 5.0). Several pathophysiological mechanisms, including altered gene expression and neurotransmitter signalling, enhanced neurodegeneration or unmasking subclinical dopaminergic degeneration, could theoretically lead to valproate-associated parkinsonism. Further studies are warranted to elucidate this entity and its underlying pathophysiology.