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Valproate induced parkinsonism

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ABSTRACT This short report describes a case of drug induced parkinsonism associated with the use of sodium valproate therapy as a mood stabiliser. The clinical utility of FP-CIT SPECT scanning in the differential diagnosis of parkinsonism and tremor disorders is briefly reviewed. The importance of early recognition of valproate-induced parkinsonism is emphasised since this clinical syndrome is largely reversible after drug withdrawal.

KEYWORDS Cognitive impairment, FP-CIT SPECT scanning, parkinsonism, sodium valproate, tremor

LIST OF ABBREVIATIONS Computerised tomography scan (CT scan), gamma aminobutyric acid (GABA), mini mental state examination (MMSE), Parkinson's disease (PD)

DECLARATION OF INTERESTS Dr Macphee has acted as a consultant to GE Healthcare, makers of DaTSCAN.

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CASE REPORT

A 73-year-old man presented with a three month history of deteriorating mobility and increasing falls. His family also reported that he had difficulty in rising from a chair, tremor in his hands when writing and mild intermittent confusion. There was no significant past history apart from a bipolar disorder. He had been commenced on sodium valproate 500 mg three times daily as a mood stabiliser in the preceding six months.

Clinical examination demonstrated an abbreviated mental test score of 9fi out of 10 and an MMSE of 29 out of 30. There was a broad based shuffling gait with difficulty in turns. The pull test was negative. There was bilateral hyper-reflexia with crossed adductor responses but flexor plantar responses. There was bilateral postural and kinetic tremor of the outstretched hands but no resting component. There was mild bradykinesia noted in the left hand and some lack of arm swing on the left. There were no limb cerebellar signs and external ocular movements were normal. There was no evidence of orthostatic hypotension. Speech was of normal volume but with mild dysarthria. Facial expression appeared normal. A computerised tomography scan of brain showed mild atrophy but no other focal abnormality.

The clinical presentation of postural tremor, mild cognitive impairment and predominant lower body parkinsonism initially suggested vascular parkinsonism as the working diagnosis. However, the absence on CT scan of strategic lesions associated with parkinsonism such as basal ganglia infarcts raised the possibility of another aetiology. An FP-CIT SPECT scan was performed which showed normal striatal uptake of radioligand (Figure 1) excluding idiopathic Parkinson's disease. This supported a diagnosis of sodium valproate induced parkinsonism.[1, 2] Following discussion with his psychiatrist, sodium valproate was withdrawn and all symptoms had resolved within three months, apart from persistence of a mild postural tremor.

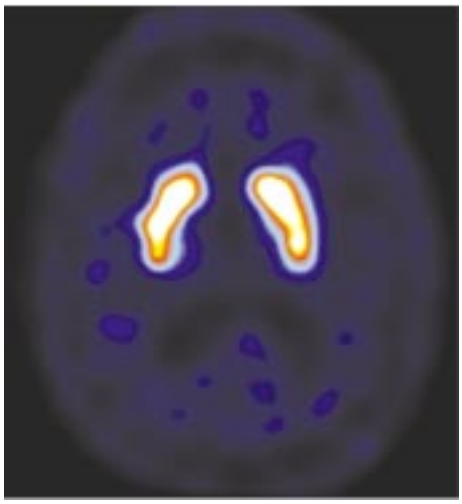

FIGURE 1 FP-CIT SPECT scan showing normal pattern of uptake in both caudate and putamen bilaterally

DISCUSSION

FP-CIT SPECT scanning utilises a new readily available iodine 123 based product (Ioflupane, also known as DaTSCAN) for SPECT imaging of presynaptic dopamine transporters. This technique can assess the integrity of the dopaminergic nigrostriatal system. A semiquantative

assessment can be made by calculating the ratio of uptake in striatum to mean uptake in the occipital area but a simple visual inspection method has a high sensitivity and specificity for the diagnosis of presynaptic parkinsonism.[3] Clinical utility has been confirmed on follow-up studies of two to four years duration.[4,5] Normal scans are seen in control subjects, essential tremor and non presynaptic parkinsonism such as drug induced causes which affect postsynaptic receptors.[3,4] These show the striatum (caudate nucleus and putamen) in a well defined crescentic pattern. In the presence of nigrostriatal degeneration such as PD, there is a progressive reduction in uptake with increasing disease severity. In PD there is a distinctive pattern of transporter loss which has been likened to a 'retreating comma' with the tail image of the putamen receding before the caudate head (Figure 2). Bilateral abnormality may be seen in patients with unilateral symptoms of PD suggesting this imaging can demonstrate pre-clinical disease.

Sodium valproate is an anti-epileptic drug also used in the treatment of mood disorders. Tremor is a well recognised side effect but recent reports have confirmed a reversible syndrome of parkinsonism with a degree of cognitive impairment.[1,2] The mechanism of action of the drug in mood disorders and epilepsy is thought to be complex. Sodium valproate increases neuronal concentrations of GABA but the relevance of this finding to clinical efficacy is unclear. Preclinical research implicates effects on ion channels, monoamines, corticotropic releasing factor and intracellular signalling proteins in the

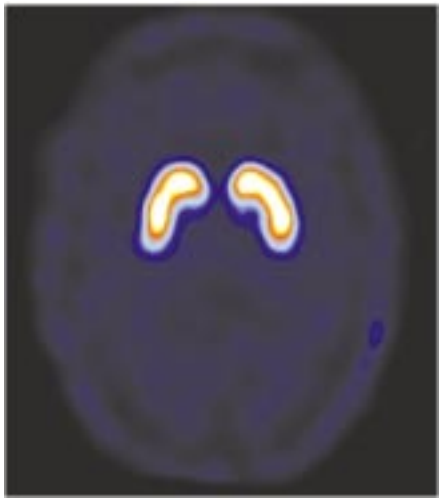

FIGURE 2A Normal tracer uptake.

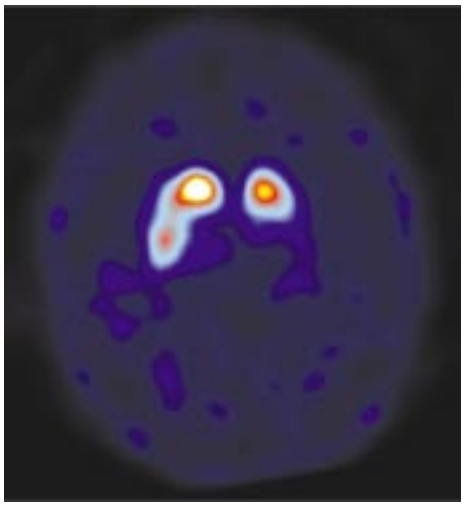

FIGURE 2B Abnormal image grade 1: asymmetric uptake with normal or near normal uptake in one hemisphere and reduction in contralateral putamen.

FIGURE 2C Abnormal image grade 2: marked bilateral reduction in putamen uptake with tracer confined to the caudate nuclei.

FIGURE 2D Abnormal image grade 3: virtual absence of uptake bilaterally.

FIGURE 2 Example of FP-CIT SPECT scan in normal and PD cases of increasing severity.

pharmacological action of the drug.[6] A plausible mechanism for sodium valproate induced parkinsonism may be dysfunction in the mitochondrial respiratory chain. Abnormalities of anti-mitochondrial complex I have been reported in some cases of PD and sodium valproate is known to affect complex I activity *in vitro*.[1] The parkinsonian and cognitive syndrome is largely reversible on sodium valproate withdrawal and this emphasises the importance of early recognition. A normal FP-CIT SPECT scan supports a diagnosis of drug-induced parkinsonism whereas an abnormal scan suggests underlying PD or other presynaptic degeneration such as multiple system atrophy or progressive supranuclear palsy.

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