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Case report

Deep brain stimulation for levodopa-refractory benign tremulous parkinsonism

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ABSTRACT

Benign tremulous parkinsonism (BTP) is characterized by prominent resting tremor combined with action and postural components, and with only subtle rigidity and bradykinesia. This tremor is frequently disabling and poorly responsive to therapy with levodopa. Thus, BTP could be considered either as a distinct clinical disorder or a variant of PD. We present a case of a 57-year-old man who had a 3-year history of severe and functionally disabling resting tremor with action and postural features bilaterally but with left dominant hand predominance. There was only very mild rigidity and bradykinesia and no postural instability. His tremor was refractory to dopaminergic therapy, including carbidopa/levodopa. The dopamine transporter (DAT) imaging showed reduced tracer uptake in the putamen bilaterally, more so on the right side. He was treated with deep brain stimulation (DBS) targeting the right ventral intermediate nucleus of the thalamus. His tremor resolved immediately after procedure. The DAT imaging abnormalities indicate the presynaptic dopamine deficiency. In some autopsied BTP cases classic alpha-synuclein pathology of PD was observed. Thus, despite the lack of levodopa responsiveness BTP likely represents a variant of PD and not a distinct neurodegenerative disorder. DBS should be considered for patients with BTP PD variant despite their poor responsiveness to levodopa treatment.

1. Introduction

Benign tremulous parkinsonism (BTP) is characterized by severe resting tremor that is usually asymmetric and predominantly affects the upper extremities [1]. Action tremor with postural and kinetic components is usually present as well. The tremor is often problematic because it is refractory to dopaminergic therapy. Other cardinal parkinsonian signs such as rigidity, bradykinesia, and postural instability are usually mild. These symptoms either do not progress or progress very slowly over the time [1]. It is common for patients with BTP to

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have a positive family history of Parkinson's disease (PD) or tremors [1,2]. In some cases BTP can resemble essential tremor (ET) due to significant action and postural features.

Josephs et al. argued that BTP may be a distinct disorder similar to but distinguishable from PD [1]. Others suggest that BTP is a variant of classic PD [3,4]. Here we present a case of BTP with levodopa-refractory resting tremor in which the tremor was completely resolved after deep brain stimulation (DBS).

2. Case report

A 57-year-old, left-handed American man presented with a 3-year history of hand tremor. He had severe and persistent resting tremor with postural and kinetic components that affected mostly his left hand (Video 1). He had only mild tremor in his right hand when operating a computer mouse. He was able to cope with basic daily living activities but with significant compromise. Drinking and writing were difficult. His tremor forced him to proceed with earlier retirement from his work as travel agent. He also had mild, bilateral upper extremity rigidity and reduced arm swing, with left side predominance.

His past medical history was unremarkable; in particular he denied a history of head trauma, encephalitis, and exposure to industrial toxins or psychotropic medications. However, his father, two paternal aunts and his maternal grandfather had PD. His father had akinetic-rigid type of PD without any tremor. Additionally, his mother, maternal grandmother, and sister had ET. None of them were examined by us for the independent verification of their diagnosis. Pedigree is depicted in Fig. 1A. He did not carry the most common autosomal dominant PD gene mutation, LRRK2 p.Gly2019Ser.

The results of his brain MRI were normal. Dopamine transporter (DAT) imaging showed reduced tracer uptake in the putamen bilaterally, but the right side displayed less uptake (Fig. 1B). He was treated with various combinations of trihexyphenidyl, primidone, amantadine, pramipexole, propranolol, and carbidopa/levodopa (250 mg three times daily) alone or with entacapone, with very minimal or no benefit.

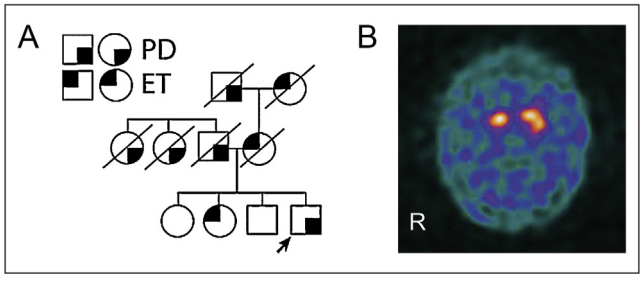

Fig. 1 – Pedigree and dopamine transporter imaging. The proband's father, two paternal aunts, and the proband's maternal grandfather had Parkinson's disease. The proband's mother, maternal grandmother, and sister had essential tremor. Standard pedigree symbols are used; arrow, the proband; circles, female; squares, male; slush through symbols, diseased individuals; ET, essential tremor; PD, Parkinson's disease (A). Dopamine transporter imaging shows decreased tracer uptake in the putamen bilaterally, and this was more prominent on the right side (B).

We diagnosed him as having BTP since his phenotype fulfilled the characteristic features of BTP description except for disease duration; the duration of his illness was only 3 years as opposed to classic descriptions that is usually at least 8 years [1]. Although there were no significant changes to his UPDRS part III score between the worst-off and the best-on (score = 13; documented at his mid-dose state 3 h after the last dose anti-parkinsonian medication), and there was no difference in the Total Tremor Rating Score (25; items 15–21 = 12) with or without anti-parkinsonian medication on two separate examination days prior to surgery, we offered the patient surgical treatment with DBS because his tremor continuously and markedly impeded his daily activities. He was implanted with DBS targeting the right ventral intermediate nucleus of the thalamus. After the procedure his left hand tremor had completed subsided (Video 2). Ten months after DBS, his left-hand tremor did not reemerge, but he still had a slight tremor in his right hand, very mild rigidity, and reduced arm swing predominantly on his left side. There were no adverse events. To cope with these residual symptoms, the patient continued to take the pramipexole and amantadine.

3. Discussion

A core feature of BTP is resting hand tremor. Our patient's most prominent symptom was resting tremor, which was substantially more severe than mild action (postural and kinetic) tremor. Although an alternative diagnosis of ET could be considered, the presence of presynaptic neuronal dysfunction as evidenced by his DAT scan, suggests that the underlying etiology is parkinsonism rather than ET. One case series found that 17 out of 26 BTP cases (65%) had reduced striatal tracer uptake on DAT imaging [3] (Table 1). In our case, other mild parkinsonian signs such as asymmetric rigidity and bradykinesia further supported the diagnosis of parkinsonism. In another case series, nearly three quarters (16/21) of the cases that had a clinical diagnosis of BTP were autopsy-proven PD [4]. In addition, some BTP cases have had mutations in PD-associated genes, such as *LRRK2* and *parkin* [3–5]. These radiologic, pathological, and genetic observations support the notion that BTP can be a variant of PD. However, BTP cases without Lewy body pathology have also been reported [4,6], suggesting that BTP may be a heterogeneous condition.

Our patient's symptoms were unresponsive to levodopa. In classic PD, tremor is usually very responsive to this therapy. In general, PD patients with poor or no responsiveness to levodopa are considered to be poor candidates for DBS surgery [7]. Nevertheless, we offer our patient a DBS procedure designed to combat his tremor and had an excellent outcome. In one case series of 15 BTP cases treated with DBS, all improved with a long-lasting beneficial effects for the median of 4 years after the procedure [2]. This beneficial response was observed for shorter period (one month to three years) in 3 only cases [1]. However, none of these DBS cases had DAT testing performed. There has been only one reported case of BTP in whom DAT imaging showed bilaterally reduced tracer uptake