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Benign tremulous parkinsonism of the young-consider Parkin

A B S T R A C T

Benign tremulous parkinsonism is generally considered a disease of the elderly, characterised by dominance of tremor over other motor manifestations, and by slower disease progression. Herein, we draw attention to a different clinical syndrome, *benign tremulous parkinsonism of the young,* which we have observed in Parkin disease.

Benign tremulous parkinsonism is classically considered a disease of the elderly, characterized clinically by dominance of tremor over other motor features (often for many years) and exhibiting slower clinical and neuropathological disease progression [1]. We wish to draw attention to an analogous clinical entity, which we term *Benign Tremulous Parkinsonism of the Young*. We have observed this clinical phenotype in patients carrying mutations in the Parkin gene.

The clinical syndromes of 3 of these patients are detailed in Table 1 and as supplementary material 1 and 2. All met criteria for juvenile parkinsonism, with onset before the age of 20 years. Rest tremor, frequently involving the legs, and in some worsening with posture and/or action was the dominant and sole motor manifestation for many years, with bradykinesia and/or rigidity appearing after an average of 16 years (range 7–25). Other features of Parkin disease such as foot dystonia, anxiety and hyper-reflexia were common findings. We observed that anticholinergic medications frequently produced dramatic and sustained improvements in tremor. Patient 1 reported 60% subjective improvement in tremor following treatment with benzhexol 6mg daily. Patient 2 began treatment with benzhexol 18mg daily at age 22 years-this produced a 70% subjective tremor improvement and enabled him to return to work as an electrician. Patient 3 takes trihexyphenidyl 6mg daily and notes marked worsening of tremor if he misses a dose. Despite a disease duration of over 40 years, he requires no levodopa and regularly plays competitive squash.

Parkin gene mutations are the most common cause of recessively inherited juvenile and young-onset parkinsonism [2]. The Parkin clinical syndrome, though heterogeneous, is relatively well defined, and includes many of the features seen in our patients. The classic phenotype is one of young onset (< 40 years) Parkinsonism, which follows a slow and relatively benign course [3]. Sleep benefit may be observed [3]. Leg tremor is a common finding, and patients frequently exhibit dystonia (often involving the foot) [3]. Limb hyper-reflexia may be another clue to the diagnosis, and a small proportion will exhibit features of axonal peripheral neuropathy or autonomic involvement [3]. A dramatic response to levodopa may be observed, though this is often complicated by the early development of levodopa-induced dyskinesia [3]. Response to anticholinergic medication may be equally impressive [3]. Cognition tends to remain unaffected for the majority of the illness, though behavioural and/or psychiatric symptoms are common [2,3]. What in our opinion has not been sufficiently emphasized however, is how dominant tremor can be within the presentation of Parkin disease.

'Pure' juvenile Parkinsonism (onset < 20 years) carries a limited differential diagnosis. Genetically determined parkinsonism e.g. secondary to Parkin, PINK1 and DJ-1 mutations should be high on the list [4]. Dopa-responsive dystonia is readily treatable, and should always be considered [4]. Wilson's disease must not be missed, but neurological Wilson's very rarely presents before puberty [4]. Juvenile Huntington's disease (HD) can present at a very young age, but to our knowledge a pure tremulous syndrome has not been reported (parkinsonism in juvenile HD generally takes an akinetic-rigid phenotype and is frequently accompanied by dystonia and oropharyngeal dysfunction) [5]. Drug-induced and post-infectious parkinsonism also warrant consideration, as do inborn errors of the dopamine synthesis pathways and dopamine transporter (DaT) mutations [4]. Of all the aforementioned conditions however, tremor-dominant presentations are likely, in our experience, to be the sole remit of genetic parkinsonian syndromes and Wilson's disease. Essential tremor, which has a bimodal age distribution with a first peak in late teens/early adulthood, dystonic tremor and functional movement disorders are other non-parkinsonian conditions which should be considered in young tremulous individuals [6]. Presentations in early childhood with predominant rest tremor however (e.g. case 3, onset age 5 years) are difficult to attribute to conditions other than genetic PD.

Delayed or mis-diagnosis is frequent in patients carrying Parkin mutations [7]. In our cohort, all patients were initially mis-labeled as having essential tremor or functional illnesses, with decades often elapsing prior to accurate diagnosis. The striking discordance between tremor and other PD motor features, often for decades, may have dissuaded clinicians from considering young-onset Parkinsonian syndromes. Equally, in some, tremor worsening on action or posture may have added further diagnostic confusion.

We feel it is imperative to raise awareness of the *Benign Tremulous Parkinsonism of the Young* phenotype of Parkin disease. This important nuance of clinical phenomenology, which to our knowledge has not previously been explicitly described, can prove greatly important to patients and physicians alike, facilitating early genetic testing, diagnosis and treatment.

This observation also raises many interesting questions. All of our patients had disease onset before the age of 20 years. It would be interesting to see, in a larger series, if young age at onset predisposes to a tremor-dominant phenotype in Parkin (or indeed other recessively inherited parkinsonian conditions). Equally, whether a tremor-dominant phenotype in Parkin predicts clinical progression, as with classic late-onset disease, is unknown. Certainly in this small series, many patients were managed with anticholinergic medications alone, without needing levodopa, for many years (a truly 'benign' course). The identification of

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Table 1
Demographic, clinical, imaging and genetic features of three patients with benign tremulous parkinsonism of the young secondary to Parkin mutations.

	Patient 1	Patient 2	Patient 3
Age at onset (years)	14	13	5
Sex	F	M	M
Presenting symptom	Rest tremor left leg	Rest tremor of legs > arms worsened by action and posture	Bilateral 'pill-rolling' hand rest tremor exacerbated upon posture
Initial diagnosis	Functional tremor	Essential tremor	Essential tremor
Initial treatment	benzhexol 6mg daily	benzhexol 18mg daily	Benzhexol 6mg daily
Age at appearance of other clinical manifestations (years)	- left hand and right foot tremor (15) - Anxiety(17) - Foot dystonia(19) - Right arm bradykinesia (30)	- Impotence, postural hypotension, bladder voiding difficulty (16) - Bilateral bradykinesia(20) - Foot Dystonia (21)	- Bilateral leg tremor (17) - Depression + anxiety(28) - Bilateral bradykinesia (30)
Age at PD diagnosis	25	21	30
DaT scan	Bilateral asymmetric reduction in tracer uptake, more marked in the putamen than caudate.	Markedly bilateral reduction in tracer uptake in both caudate and putamen	Bilaterally abnormal striatal uptake. Relative caudate preservation and almost complete absence of tracer uptake in the posterior putamen bilaterally.
Age at last clinical review (years)	47	47	46
Age at levodopa introduction	37	40	n/a
Current treatment	Levodopa/carbidopa 100/25mg TDS Amantadine 100mg BD Rotigotine 6mg daily Propranolol 40mg BD (Bilateral STN DBS aged 40 years)	Levodopa/carbidopa 100/25mg 1.5 tabs QDS Amantadine 400mg daily Fluoxetine 20mg daily Botulinum toxin (foot dystonia)	Trihexyphenidyl 10mg daily Selegiline 1.25mg daily Amitryptiline 25mg daily
Parkin Mutation	c. 823C > T exon 3 deletion	c. 337-376del c. 1289G > A	c. 337-376del c. 823C > T

(M = Male; F = Female; DaT = dopamine transporter; PD = Parkinson's disease; TDS = three times daily; QDS = four times daily; BD = twice daily; n/a = not applicable).

distinct clinical sub-groups within a monogenically inherited condition also affords a great opportunity to examine other determinants of disease expression.

Contributorship statement

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1A conception and design of the study; 1B acquisition of data; 1C analysis and interpretation of data; 2A drafting the article; 2B revising the article critically for important intellectual content; 3 final approval of the version to be submitted.

Ethics statement

All procedures followed were in line with the journal's ethics policy and written consent was obtained from all patients.

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Declarations of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2019.05.027.

References

[1] M. Selikhova, P.A. Kempster, T. Revesz, J.L. Holton, A.J. Lees, Neuropathological findings in benign tremulous parkinsonism, Mov. Disord. 28 (2) (2013 Feb) 145–152, https://doi.org/10.1002/mds.25220.
[2] K.M. Doherty, L. Silveira-Moriyama, L. Parkkinen, et al., Parkin disease: a clinicopathologic entity? JAMA Neurol 70 (5) (2013) 571–579.
[3] N.L. Khan, E. Graham, P. Critchley, A.E. Schrag, N.W. Wood, A.J. Lees, K.P. Bhatia, N. Quinn, Parkin disease: a phenotypic study of a large case series, Brain 126 (Pt 6) (2003 Jun) 1279–1292.
[4] D.C. Paviour, R.A. Surtees, A.J. Lees, Diagnostic considerations in juvenile parkinsonism, Mov. Disord. 19 (2) (2004 Feb) 123–135.
[5] P. Gonzalez-Alegre, A.K. Afifi, Clinical characteristics of childhood-onset (juvenile) Huntington disease: report of 12 patients and review of the literature, J. Child Neurol. 21 (3) (2006 Mar) 223–229.
[6] E.D. Louis, O. Dogu, Does age of onset in essential tremor have a bimodal distribution? Data from a tertiary referral setting and a population-based study, Neuroepidemiology 29 (3–4) (2007) 208–212.
[7] M. Ruiz-Lopez, M.E. Freitas, L.M. Oliveira, et al., Diagnostic delay in Parkinson's disease caused by PRKN mutations, Park. Relat. Disord. (2019 Jan 10), https://doi.org/10.1016/j.parkreldis.2019.01.010 pii: S1353-8020(19)30010-0.

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