

Isolated limb dystonia as presenting feature of Parkin disease

Parkin related disease (OMIM 602544) is a common cause of autosomal recessive young-onset Parkinson's disease (PD). The motor phenotype encompasses parkinsonian features, dystonia, sustained response to levodopa and slow progression. It has been occasionally reported that patients may present with dystonia at onset.¹ Isolated lower limb dystonia is a typical presentation of early-onset generalised dystonia, often indicating a DYT1 carrier status. DYT1 and non-DYT1 cases have also been described with onset in adulthood. It is presently unknown in how many such cases dystonia may be the presenting feature of Parkin disease.

We observed a series of Parkin gene mutation carriers who had isolated limb dystonia as the presenting feature of their disorder that lasted for several years before parkinsonian features developed. We report the clinical description of eight such cases; four patients are illustrated in the online supplementary video. Parkin

gene mutations were detected according to standard procedures.² Eight had isolated dystonia at onset. These subjects had full neurological evaluation and videotape documentation. These patients had regular follow-up twice a year, including a complete neurological and motor examination. The levodopa equivalent dose (LED, measured in milligrams)³ was calculated at each visit. Non-motor features were assessed using the Non-Motor Symptom Assessment Scale for PD.

Out of a total of 44 Parkin mutation carriers, 36 (81.8%) had parkinsonian features at onset, either with or without dystonia. Eight patients (18.2%) had isolated dystonia for an average of 5.0 ± 6.4 years (range 1–16) before parkinsonian features became apparent (table 1). In all these cases, lower limb task-specific dystonia activated by walking was the presenting feature. Three patients had also lower limb pain unrelated to dystonic spasms. Their mean age at onset was 28.9 ± 14.2 years. Onset was unilateral in six patients, bilateral in the remaining two. In all patients, ¹²³I-FP-CIT SPECT imaging showed a bilateral reduction of striatal tracer uptake.

The mean follow-up was 11.5 ± 5.9 years. In two patients, dystonia progressed and lost task specificity to occur also at rest. No patient developed cranial or cervical dystonia; the upper limbs became involved by dystonia later in the disease in three patients (patients 5, 6 and 8), on average 3.3 ± 2.1 years after onset, and distal tremor developed in two of them (patients 5 and 6).

We observed improvement of lower limbs dystonia after dopaminergic treatment in six patients (patients 3, 4, 5, 6, 7 and 8) and mild effect in two (patients 1 and 2). The mean LED was 157.5 ± 67.8 . In patient 8, complete benefit was observed in legs but no improvement was observed in writer's cramp.

Onset of dystonia in these patients resembled the presentation of DYT1 phenomenology, with limb onset and activation by walking. Three of these patients were initially thought to have DYT1 dystonia and one was misdiagnosed as having dopa-responsive dystonia (DRD). Progression was not typical for DYT1 because generalisation, which is a common feature of DYT1 dystonia, did not occur. Normal genetic testing allowed ruling out mutations in the DYT1, DYT6 and DRD genes and ¹²³I-FP-CIT SPECT imaging allowed identifying dopaminergic denervation in the striatum.

Dystonia at disease onset has been estimated to affect 14%–57% of young-onset

Table 1 Demographic and clinical features of Parkin disease patients

Patient	Patients							
	1	2	3	4	5	6	7	8
Age at onset	44	11	34	44	41	17	29	11
Duration (years)	14	19	16	4	3	17	9	10
Duration of isolated dystonia before onset of parkinsonian signs (years)	14	2	5	1	1	16	9	10
Family history of MD	No	No	Yes	Yes	No	No	No	No
Mutations	p.R275W and deletion exons 3, 4	p.C212Y homozygous	p.L211N and p.P437L	p.L211N and p.P437L	p.R275W and deletion of exon 3	Deletion of exons 2, 3, 4 and duplication of exon 3	p.R275W and deletion of exon 1	p.R275W and deletion of exons 6, 7
Dystonia onset	Right leg	Right leg	Left leg	Right leg	Left leg	Left leg	Left leg	Left leg
Dystonia at rest	No	No	No	No	No	Yes	No	Yes
Task-specific dystonia	When walking	When walking	When walking	When walking	When walking	When walking	During fast walking	When walking
Associated motor feature at onset	None	None	None	None	Action tremor in both hands	Tremor in the left leg	None	None
Non-motor features	None	Pain, anxiety	None	None	None	None	Pain, anxiety	Painful cramps, anxiety
Response to dopaminergic treatment	+	+	++	++	++	++	++	Writer's cramp: –Lower limbs dystonia: +++
LED	160 (ropinirole)	150 (levodopa)	100 (ropinirole)	200 (levodopa)	100 (pramipexole)	150 (levodopa)	100 (ropinirole)	300 (levodopa)
Misdiagnosis	Focal isolated dystonia	Dopa-responsive dystonia	Focal isolated dystonia	Focal isolated dystonia	Dystonic tremor	Dystonic tremor	Isolated dystonia	Isolated dystonia

–, no effect; +, mild effect; ++, moderate effect; +++, complete improvement; LED, levodopa equivalent dose; MD, movement disorders.

PD patients with dystonic onset being particularly common in patients under age 48.⁴ Genetic forms with dystonia at onset include many possible alternatives, such as DRD, Wilson's disease, X-linked dystonia–parkinsonism/Lubag, rapid-onset dystonia–parkinsonism and syndromes of neurodegeneration with brain iron accumulation. Recently, a patient carrying a THAP1 gene mutation was also reported to be affected by lower limb dystonia.⁵

In Parkin disease, particularly, dystonia at onset may occur in >40% of cases.⁶ We observe here that isolated dystonia can last up to 16 years before parkinsonian symptoms develop in Parkin gene mutation carriers and that dystonic onset can also occur in patients aged >40. In these patients, dystonia at onset and the associated pain responded well to dopaminergic treatment, similar to what is observed in DRD. A positive DAT SPECT scan can lead the differential diagnosis in the right direction. Remarkably, in previous studies of patients with adult-onset lower limb dystonia, no patient was investigated for Parkin gene mutations.^{7,8} We suggest that Parkin related disease be considered in patients with lower limb dystonia, regardless of age at onset.

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