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Tremor and Other Hyperkinetic Movements

Brief Reports

Levodopa Responsiveness in Adult-onset Lower Limb Dystonia is Associated with the Development of Parkinson's Disease

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Abstract

Background: Adult-onset primary lower limb dystonia (AOPLLD) has been reported as an early sign of Parkinson's disease (PD) or Parkinson-plus syndrome in case series. No prior systematic analysis has assessed clinical clues predicting later development of PD or Parkinson-plus syndrome.

Methods: We identified patients with AOPLLD from medical records. We excluded patients who had not been diagnosed by a neurologist, and who had a pre-existing diagnosis of PD, psychogenic, or secondary dystonia. Records were subdivided into those who later developed PD or Parkinson-plus disorders and those who did not. The following clinical characteristics were compared between the two groups: dystonia onset age, type of dystonia, levodopa response, anticholinergic response, and family history of Parkinsonism or tremor.

Results: Twenty-two AOPLLD patients were identified: 77% female; the median dystonia onset age was 53 years. Eight (37%) developed Parkinson's disease; 2 (9%) developed corticobasal syndrome. Twelve patients (54%) did not develop Parkinsonism after a median follow-up period of 1.5 years. There was a significant difference in leg dystonia levodopa response between the two groups ($p=0.02$).

Conclusion: In patients with AOPLLD, leg dystonia with levodopa response is associated with the future development of PD.

Keywords: Dystonia, Parkinson's disease, leg dystonia, levodopa

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Introduction

Childhood-onset lower limb dystonia characterizes primary dystonia such as DYT1 or DYT6, whereas adult-onset primary lower limb dystonia (AOPLLD) can be an initial presentation of Parkinson's disease (PD),[1] corticobasal syndrome, psychogenic dystonia, or stiff-limb syndrome.[2] AOPLLD that does not progress to a secondary cause is being increasingly recognized.[3,4] There has been no systematic analysis for the clinical indicators towards a later development of PD or Parkinson-plus syndrome.

Methods

We performed a retrospective medical record review of adult patients with an initial diagnosis of primary lower limb dystonia using the Medical Records Linkage System, from 1998 to 2011. Patients were excluded if not diagnosed by a neurologist or if they had a pre-existing diagnosis of PD, Parkinson-plus syndrome, or psychogenic or secondary dystonia. The diagnosis of parkinsonism was based on the presence of bradykinesia with at least two of the three following signs: rest tremor, rigidity, or impaired postural reflexes. Records were subdivided into those who later developed PD or Parkinson-plus disorders and those who did not. Clinical characteristics such as age of onset, type of dystonia, response to levodopa, anticholinergics, and family history of parkinsonism or tremor were compared between the two groups. The leg dystonia response to levodopa or anticholinergic medication was defined by serial clinical examinations by a neurologist. Group comparisons were made using the χ^2 test for binary data and the Mann–Witney U-test for continuous variables, using JMP software. Statistical significance was set at $p<0.05$.

Table 1. Comparison of the Clinical Characteristics between the Two Groups

	Developed Parkinsonism (n=10)	Did Not Develop Parkinsonism (n=12)	p Value
Leg dystonia with levodopa response	7 (70%)	2 (16%)	0.02
Family history of Parkinson's disease or tremor	5 (50%)	3 (25%)	0.22
Type of dystonia (action/rest)	7 (70%)/3 (30%)	7 (58%)/5 (42%)	0.57
Gender (F/M)	9 (90%)/1 (10%)	8 (66%)/4 (33%)	0.19
Age of onset (years; range)	49 (22–75)	53 (31–71)	0.59

Results

Out of 174 patients, 152 were excluded: 37 patients with pre-existing PD, 13 patients with lower extremity trauma preceding dystonia, five patients with psychogenic dystonia, 30 patients with secondary dystonia, 10 patients with childhood-onset lower limb dystonia, 49 patients did not have a final diagnosis of dystonia (for example, spasticity, radiculopathy, complex regional pain syndrome, or stiff-man syndrome) when they saw a neurologist; six patients did not follow-up and two patients were excluded because the follow-up period was less than 0.5 years. Twenty-two patients were identified with AOPLLD with a median follow-up of 1.5 years (range 0.5–22 years) (Tables 1 and 2); 21 out of 22 patients tried levodopa whereas 17 out of 22 patients did not try anticholinergic medication. Only three patients tried a dopamine agonist and all had improvement in dystonia. Baclofen, botulinum toxin injection and clonazepam were trialed, with various successes, in a small number of subjects (Table 3). There were no statistically significant differences in the other clinical characteristics between the two groups. These characteristics were positive family history for parkinsonism or tremor, age of dystonia onset, sex, or type of dystonia.

Group 1: later developed PD or Parkinson-plus syndrome (Cases 13–22).

Ten patients developed PD or corticobasal syndrome after a median period of 1 year (0.5–3 years) after onset of lower limb dystonia. Eight patients had PD and two patients developed corticobasal syndrome. Group 1 had significantly greater leg dystonia levodopa response than group 2 (p=0.02). Only eight out of nine patients who developed PD tried levodopa as one patient had declined a levodopa trial. Seven of these eight patients had levodopa-responsive leg dystonia, and the non-responder was unable to tolerate more than 600 mg daily because of nausea. The two patients who later developed corticobasal syndrome had lower limb dystonia that did not respond to levodopa. Table 2 has a summary of the clinical characteristics.

Group 2: adult-onset primary lower limb dystonia that did not develop parkinsonism after follow-up (Cases 1–12).

Twelve patients did not develop parkinsonism or other diagnosis after a median follow-up of 1.5 years (0.5–3 years). Ten had leg dystonia not responsive to levodopa at the mean dose of 600 mg daily. Two out of four patients who tried anticholinergic medication had a beneficial response.

Discussion

The genetic forms of PD, for example, parkin, DJ-1,[5] PINK1[6] gene mutation have been associated with an initial presentation of leg dystonia. Patients with parkin mutation can present with foot dystonia with response to levodopa.[7] Foot dystonia more commonly occurs at rest, but exercise-induced foot dystonia has been reported. In the genetic causes of PD, the age of onset is 32–43 years, earlier than the age of onset of our subjects.

Glut-1 gene mutation presents mainly in childhood with paroxysmal exercise-induced dystonia. The oldest reported age of onset for Glut-1 gene mutation is 30 years. In our study, three subjects were long-distance runners who had leg dystonia during running. They did not develop PD after 2 years of follow-up. Although idiopathic PD cannot

Table 2. Summary of the Clinical Characteristics between the Two Groups

	Developed Parkinsonism (n=10)	Did Not Develop Parkinsonism (n=12)
Median follow-up period (years; range)	2 (0.5–22)	1 (0.5–9)
Median time from leg dystonia onset to Parkinsonism (years; range)	1 (0.5–3)	NA
Median effective levodopa dose (mg; range)	600 (350–800)	NA
Developed corticobasal syndrome	2	0

Table 3. Data Collected From All Subjects

Case	Develop PD (Time to Diagnosis)	Develop Corticobasal Syndrome (Time to Diagnosis)	Age Onset	Type	Sex	Levodopa Response (Dose per Day)	Anticholinergic Response?	Family History of PD or Tremor?	Years of Follow-up	Response to Other Medications/Other
1	No	No	59	Action	F	No (75 mg)	Not tried	No	9	
2	No	No	55	Rest	M	No	Not tried	No	3	
3	No	No	64	Action	F	No	No	No	5	Responded to baclofen but not to clonazepam
4	No	No	71	Rest	F	No (1500 mg)	No	No	1	Responded to botulinum toxin A injection
5	No	No	31	Action	F	No (750 mg)	Yes (12 mg)	No	0.5	
6	No	No	57	Rest	F	No (300 mg)	Not tried	No	8	Responded to pramipexole 1 mg/day, baclofen and botulinum toxin A injection
7	No	No	63	Rest	M	No	Not tried	Yes	1	
8	No	No	43	Action	M	No (300 mg)	Not tried	No	0.5	Long distance runner
9	No	No	40	Action	F	Yes (300 mg)	Not tried	No	2	Long distance runner
10	No	No	36	Action	F	No (600 mg)	Not tried	No	2	Long distance runner
11	No	No	61	Action	M	No (900 mg)	Not tried	Yes	1	
12	No	No	55	Rest	F	Yes (750 mg)	Not tried	No	1	Responded to ropinirole
13	No	Yes (8 years)	37	Action	F	No (750 mg)	Yes	No	8	
14	No	Yes (2 years)	60	Rest	F	No	Not tried	No	2	Did not respond botulinum toxin A injection
15	Yes (0.5 years later)	No	22	Rest	F	Yes (800 mg)	Not tried	Yes	0.5	

Table 3. Continued

Case	Develop PD (Time to Diagnosis)	Develop Corticobasal Syndrome (Time to Diagnosis)	Age Onset	Type	Sex	Levodopa Response (Dose per Day)	Anticholinergic Response?	Family History of PD or Tremor?	Years of Follow-up	Response to Other Medications/Other
16	Yes (0.5 years later)	No	51	Action	M	Yes (750 mg)	Not tried	No	11	Responded to botulinum toxin A injection
17	Yes (1 year later)	No	73	Rest	F	Yes (600 mg)	Not tried	Yes	2	Responded to clonazepam, no benefit baclofen 30 mg
18	Yes (1 year later)	No	41	Action	F	Not tried	Not tried	No	1	
19	Yes (2 years later)	No	75	Action	F	Yes (300 mg)	Not tried	No	8	
20	Yes (2 years)	No	43	Action	F	Yes (600 mg)	Not tried	Yes	1	
21	Yes (2 years)	No	45	Action	F	Yes (500 mg)	Yes (4 mg)	Yes	2	Did not respond baclofen 60 mg
22	Yes (3 years later)	No	43	Action	F	Yes (750 mg)	Not tried	Yes	22	Responded to pramipexole 3 mg

Abbreviations: PD, Parkinson's Disease.

be excluded, our three patients probably had adult-onset primary lower limb dystonia or runner's dystonia[8] rather than Glut-1 gene mutation or genetic forms of PD, given the older age at onset and the lack of signs to suggest secondary dystonia.

We did not screen the patients with levodopa-responsive lower limb dystonia for dopa-responsive dystonia (DRD), which presents with dystonia in childhood. In DRD, leg dystonia presenting in adulthood has not been reported and should not be considered as a differential diagnosis of adult-onset leg dystonia.

We found approximately half the patients with an initial diagnosis of primary lower limb dystonia later developed parkinsonism. Most of these patients developed parkinsonism 2 years after the onset of leg dystonia. In our study, we found leg dystonia responsive to levodopa is associated with the later development of PD. However, an absence of levodopa response does not exclude the future possibility of developing PD.

Alternatively, the ^{123}I-ioflupane SPECT (single-photon emission computed tomography) scan can be useful to differentiate between primary lower limb dystonia and secondary dystonia from parkinsonism. A case report found the ^{123}I-ioflupane SPECT scan made an early diagnosis of PD in a patient with exercise-induced dystonia.[9] We argue that the ^{123}I-ioflupane SPECT scan is not as affordable or accessible as levodopa; in addition it does not differentiate between idiopathic PD and atypical parkinsonian syndromes,[10] which do not respond to levodopa.

Our study has two limitations: it is retrospective in nature and has a short median follow-up period of 1.5 years. The development of PD has been reported 14 years after an initial presentation with leg dystonia. Therefore, we may have missed patients who developed PD after 1.5 years. A prospective study with long-term follow-up would be useful although difficult to conduct in this rare patient population.

In summary, for patients with adult-onset primary lower limb dystonia, a response to levodopa is associated with the future development of PD. In contrast, an absence of levodopa response does not exclude the development of PD, corticobasal syndrome, or primary lower limb dystonia.

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