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Diagnostic delay in Parkinson's disease caused by *PRKN* mutations

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ABSTRACT

Objective: To confirm that there is a diagnostic delay in Parkin-related Parkinson Disease and to explore possible factors causing such a delay.
Methods: We retrospectively analyzed our patients with mutations in the parkin RBR E3 ubiquitin protein ligase gene (*PRKN*). We collected a total of 34 patients and focused on 18 cases (14 homozygous, 4 compound heterozygous). An arbitrary cut-off of 10 years from disease onset to diagnosis was considered to define patients with delayed diagnosis.
Results: Eight of 18 cases had a significant delay in their diagnosis (25.3 ± 17 years). By comparing patients with and without a delayed diagnosis and subsequently, comparing these groups to a group of young onset PD negative for mutations of *PRKN, SNCA, DJ1, PINK1, LRRK2, GBA,* and *ATP13A2*, we identified a specific phenotype associated with a diagnostic delay: young age, lack of tremor, and involvement of lower limbs (particularly dystonia affecting gait) at the time of disease onset.
Conclusions: Our findings emphasize the diverse phenotypes associated with *PRKN* mutations and the related diagnostic challenges they present.

1. Introduction

Loss of function mutations in the *PRKN* gene are the most common form of autosomal recessive juvenile parkinsonism (AR-JP) [1]. This gene encodes parkin RBR E3 ubiquitin protein ligase, loss of activity of which contributes to AR-JP by causing an impaired mitophagy, protein accumulation, and mitochondrial dysfunction [2].

Parkinson's disease (PD) due to *PRKN* mutations has been referred to as "parkin disease" due to its distinctive clinical and pathological features. Clinically, it demonstrates a wide phenotypic spectrum. A distinctive phenotype was initially proposed for patients with these mutations, characterized by prominent leg tremor [3], foot dystonia [4], normosmia [5], and marked behavioral disturbances [6]. However, it has been hypothesized that the early age at onset rather than the presence of a *PRKN* mutation is the critical determinant of the clinical picture [7].

Given the early age at onset and variability of phenotypic presentation, we hypothesize that *PRKN*-related PD is commonly associated with long diagnostic delay. To confirm this hypothesis and explore the possible factors causing such a delay, we retrospectively analyzed our patients with mutations in the *PRKN* gene.

2. Methods

Clinical data have been collected from patients, with the diagnosis of PD according to the UK PD Society Brain Bank clinical diagnostic criteria [8], seen at the movement disorder clinic of the Toronto Western Hospital between 2007 and July 2017. Some of these patients were first clinically diagnosed in other hospitals, but all of them achieved their genetic diagnosis in our center throughout a diagnostic panel for genetic parkinsonisms (DNA sequencing for *SNCA*, *PRKN*, *DJ1*, *PINK1*, *LRRK2*, *GBA*, and *ATP13A2* as well as multiplex ligation-dependent probe amplification for *SNCA*, *PRKN*, *DJ1*, *PINK1*, *ATP13A2* – Athena Diagnostics, Centogene, Rostock, Germany). PD patients with genetic

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testing showing at least one pathogenic mutation in *PRKN* were identified and their clinical records were retrospectively reviewed to collect all genetic, demographic and clinical information. Patients were classified according to their genetic diagnosis in two groups: homozygous or compound heterozygous (Ho/Co) and heterozygous (He), but only Ho/Co cases were included in the main analysis, since these mutations are known to be the cause of disease development [9].

We arbitrarily considered 10 years from symptoms onset to clinical diagnosis of PD as the cut-off to define patients with delayed diagnosis, and divided the Ho/Co group into two subgroups: delayed diagnosis (DE) and not-delayed diagnosis (nDE).

Ho/Co patients were finally compared to a group of age- and sex-matched early-onset PD (EO-PD) with a negative diagnostic genetic panel (EO-PD genes negative, EO-PDgn).

For descriptive statistics we used mean ± standard deviation for continuous normal distributed variables and median ± interquartile range for continuous non-normal distributed variables. Comparison between groups was done by means of *t*-test, Mann-Whitney *U* test or Chi-Square test depending on data type and distribution. Statistical significance was set at p-value < 0.05.

3. Results

In our cohort of PD cases, 34 patients were found to have pathogenic mutations in the *PRKN* gene: 14 Ho, 4 Co and 16 He. We only consider the Ho/Co groups (18 patients) for the main analysis. Demographic, phenotypic and genetic information is presented in Supplementary Table 1 for the Ho/Co and in Supplementary Table 2 for the He patients.

In the Ho/Co group, eight patients were categorized as DE with a delay of 25.3 ± 17 years and 10 patients as nDE with a delay of 3.1 ± 2.1 years (p < 0.001). The diagnosis in the Ho/Co group was delayed longer than in the EO-PDgn group (12.9 years vs. 5.1 years), although the difference did not reach statistical significance (p = 0.056) (Table 1).

Comparisons between groups are presented in Table 1: DE patients were found to have a younger age at onset, lack of tremor or symptoms in the upper body at onset (all p < 0.05). In addition, the Ho/Co group showed more lower body involvement comparing to the EO-PDgn group (p < 0.001) and had a milder motor phenotype based on UPDRS III and H and Y scales (all p < 0.05), which probably translates into less use of advanced therapies on these patients (p < 0.05).

In the He group, only two patients were categorized as DE, with a delay of 2.8 ± 4.1; age at onset was 39.1 ± 7 years and, almost all of them (14/16) had upper limb involvement at symptoms onset.

Finally, Supplementary Table 3 shows the clinical differences between the Ho/Co and He patients: notably, diagnostic delay was significantly longer in the former group: median of 6 years (1–52) versus 1 year (1–16) (p = 0.004) as only 2 out of 16 patients (12.5%) of the latter group could be qualified as patients with delayed diagnosis (p = 0.04).

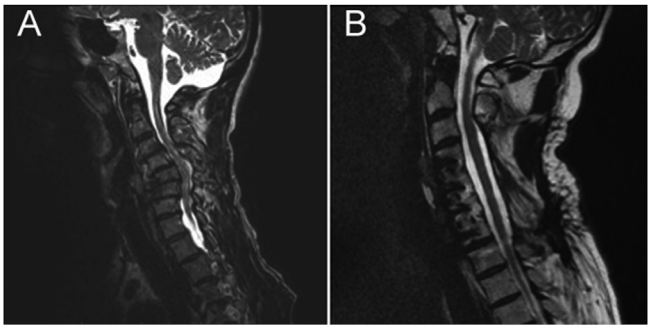

Fig. 1. A) Case 1's T2w cervical MRI shows multilevel degenerative disc disease with listhesis resulting in moderate spinal cord compression at C5-C6 associated with increased T2 signal intensity in the cord. **B)** Case 2's T2w cervical MRI shows evidence of previous laminectomy extending from C4 down to C7 level, with posterior fusion/instrumentation from C3 to C7; there are signs of a focal myelomalacia, primarily in the left hemi-cord at level C6, associated with focal volume loss.

3.1. CASE reports

3.1.1. Case 1

A 61-year-old Philippine man, born from non-consanguineous parents, was referred to our clinic with the initial diagnosis of a juvenile cerebral palsy due to a longstanding history of generalized dystonia. He developed dystonia when he was 8 years old, initially affecting his left foot and progressively involving the rest of the body. There was no family history of any relevant neurological condition. Over the last 10 years he has developed pyramidal signs with radicular pain in both arms. Cervical spine MRI showed severe abnormalities likely due to prolonged dystonic posturing of the neck (Fig. 1A). Given the symptoms at onset and the Filipino ethnicity, he was tested for the most common dystonia genes (including genes causing dopa-responsive dystonia, *TOR1A* and *TAF1*), which were negative. Further genetic testing detected a *PRKN* mutation, thus leading to a PD diagnosis.

Since he was never treated with levodopa, before considering deep brain stimulation (DBS), he was started on levodopa/carbidopa 100/25 mg three times a day. Although objectively he achieved a poor response (Video 1), he reported a remarkable subjective benefit with a reduction in the frequency of falls.

Supplementary video related to this article can be found at https://doi.org/10.1016/j.parkreldis.2019.01.010.

Table 1
Comparison in between groups: delayed vs. not delayed diagnosis and Ho/Co vs. the EO-PDgn group. Bold-typed text indicates statistically significant differences.

	Ho/Co Delayed (n = 8)	Ho/Co Not delayed (n = 10)	P value	Ho/Co (n = 18)	EO-PDgn (n = 18)	P value
Current age (years)	51.8 ± 13.7	52.8 ± 13.7	0.892	52.38 ± 13.76	58.38 ± 7.49	0.113
Age at onset (years)	**19.2 ± 8.6**	**33.2 ± 8.8**	**0.004**	27 ± 11.12	31.38 ± 8.12	0.185
Delay in diagnosis (years)	**25.3 ± 17**	**3.1 ± 2.1**	**< 0.001**	12.88 ± 15.90	5.08 ± 5.33	0.056
Disease duration	32.6 ± 15.2	19.2 ± 13.8	0.068	25.38 ± 15.39	27 ± 8.54	0.700
H&Y	2.5 ± 0.6	1.5 ± 1.05	0.244	**2 ± 1.06**	**2.5 ± 0.92**	**0.038**
UPDRS-III ON	17 ± 11.2	22.1 ± 12.5	0.405	**19.56 ± 11.83**	**28.5 ± 11.90**	**0.035**
Tremor	**0/8**	**7/9**	**0.007**	7/18	11/18	0.182
Upper limb involvement	**0/8**	**6/9**	**0.009**	**6/18**	**15/18**	**0.000796**
LEDD	734 ± 711.8	967 ± 581.6	0.469	857.35 ± 636.58	1020.77 ± 666.33	0.463
Advanced therapies	1/8	5/10	0.093	**6/18**	**14/18**	**0.007**
Family history	4/8	6/10	0.301	10/18	7/18	0.316

Abbreviations: Ho/Co: Homozygous/compound heterozygous; H and Y: Hoehn and Yahr; ICD: impulse control disorder; LEDD: levodopa equivalent daily dose; n: number of patients; UPDRS III: Unified Parkinson Disease Rating Scale Motor part.

3.1.2. Case 2

A 63-year-old man has been followed in our clinic since 2002 with the initial diagnosis of spastic paraparesis. He had a history of walking on his tiptoes since he was a child. His gait difficulty progressively deteriorated over time and he started to have frequent falls. A genetic panel for the most common hereditary spastic paraplegias was performed and did not detect any mutation. Over the years he had also developed severe neck pain that finally required a laminectomy C4-C7 (Fig. 1B) and severe lumbar pain due to a spinal stenosis. He developed rest tremor in his left hand at the age of 37. Levodopa was then started with good response, particularly in terms of balance and ability to stand up and walk longer distances unaided (Video 2). In 2010, he started to experience troublesome motor fluctuations and underwent GPi DBS in 2016 with gait improvement that has been sustained for the past year.

Supplementary video related to this article can be found at https://doi.org/10.1016/j.parkreldis.2019.01.010.

3.1.3. Case 4

A 53-year-old woman had a longstanding history of anxiety and depression and developed gait difficulties at the age of 28, after giving birth to her son. The initial diagnosis of a functional gait disorder was made but years later she was referred to a neurologist who started her on levodopa with some benefit. When she was first referred to our clinic she had been well controlled on levodopa-carbidopa 100/25 mg three times a day for more than 10 years with only mild motor fluctuations (mild peak-dose choreic dyskinesia of her left hand) (Video 3).

Supplementary video related to this article can be found at https://doi.org/10.1016/j.parkreldis.2019.01.010.

3.1.4. Case 8

A 52-year-old man was referred to our clinic at the age of 38 years with a longstanding history of a bizarre gait, at the time considered as ataxic. He was born in Sri Lanka from consanguineous parents and had an older brother with a severe gait disorder. Symptoms started gradually at age 31, when he noticed difficulties with walking. He slowly started to suffer from intermittent foot dystonia and to have occasional freezing of gait (Video 4). He also described a variety of other complaints, headache when talking for a long time, anxiety and dizziness. Due to the occurrence of troublesome levodopa-induced dyskinesias, for the last 11 years he has been managed with a combination of ropirinole 13 mg/day (he had gambling and binge eating with higher doses), profenamine 50 mg and levodopa/carbidopa 50/12.5 mg twice a day. Rigidity, gait and postural instability markedly improved when dopaminergic therapy was started. Globus pallidus internus deep brain stimulation (GPI DBS) has been offered on several occasions but was refused by the patient.

Supplementary video related to this article can be found at https://doi.org/10.1016/j.parkreldis.2019.01.010.

4. Discussion

Early diagnosis of PD with little diagnostic delay is ideal in order to inform patients about prognosis and – more importantly – to adopt the right treatment strategy. Breen et al. [10] determined a median time of 11 months from motor symptom onset to primary care physician visit, and a median time of 1 month from primary care physician visit to PD diagnosis. Not surprisingly, these timeframes are remarkably shorter than the ones observed in our group of *PRKN* patients. In our cohort, by comparing two groups of patients with a definitive diagnosis of *PRKN*-related PD, we have been able to identify a specific phenotype associated with a diagnostic delay: young age, lack of tremor, gait disorder and the involvement of lower limbs at the time of disease onset. In contrast, patients initially presenting with tremor and upper limb involvement had a much earlier clinical diagnosis, in keeping with data previously reported in the literature [10]. Indeed, by comparing our *PRKN* patients to a group of gene-mutation negative patients with the same age at onset (EO-PDgn), we confirmed that this particular phenotype involving lower limbs is linked to *PRKN*-related PD and not only related to the younger age at onset [7].

In addition, a delayed diagnosis was more frequently found in Ho/Co when compared to the He group and to the EO-PDgn group, leads us to conclude that a definitive diagnosis of PD due to *PRKN* mutations is a factor in diagnostic delay.

These patients are often symptomatic for a long time until the clinical diagnosis and the appropriate treatment is established. Such delay leads to preventable complications that contribute to the manifestation of other signs, thus challenging the diagnostic process even further. This is illustrated by cases 1 and 2, who developed severe cervical and lumbar spine complications due to their untreated dystonia (Fig. 1). We wonder whether these complications might have been avoided and, whether levodopa response might have been greater if treatment was started 52 and 27 years earlier, respectively. Despite the advances in the classification and assessment of dystonia [11,12], the etiology of dystonia remains unclear in a significant proportion of cases and *PRKN* mutation screening (or simply trialing patients on levodopa) should always be considered in appropriate situations.

Cases 4 and 8 were wrongly labeled as having functional movement disorders for 24 and 8 years respectively, further highlighting the diagnostic challenge of patients with ‘bizarre’ or unusual presentations.

We acknowledge the many limitations of this study, namely its retrospective nature, the limited number of subjects, and the lack of comparisons with other genetic forms of early-onset PD, thus meaning that our findings are not necessarily specific to *PRKN* mutations. We also acknowledge the fact that there other factors might have contributed to a diagnostic delay, such as the limited access to neurologists expert in movement disorders, the challenge of differential diagnosis with other types of dystonia (such as dopa responsive dystonia) or availability of diagnostic tests such as dopamine imaging. Finally, we recognize that due to the lack of agreement in the literature on what is formally considered a delay in PD diagnosis, the chosen cut-off of 10 years is arbitrary and certainly represents another limitation of the analysis. Nevertheless, our study contributes to the understanding of the diverse phenotypes associated with *PRKN* mutations and more generally to patients labeled as PD despite its very heterogeneous pathological and pathophysiological underpinnings.

Authors roles

Dr. Marta Ruiz-Lopez: Writing of the first draft, Conception and Execution of Research Project.

Dr. Maria Eliza Freitas: Conception and Execution of Research Project.

Dr. Lais M Oliveira: Conception and Execution of Research Project.

Dr. Mohammad Rohani: Review and Critique of Manuscript.

Dr. Renato P Munhoz: Review and Critique of Manuscript.

Prof. Susan H. Fox: Review and Critique of Manuscript.

Prof.Ekaterina Rogaeva: genetic analysis and Review and Critique of Manuscript.

Prof. Anthony E. Lang: Review and Critique of Manuscript.

Dr. Alfonso Fasano: Conception, Organization, and Execution of research project, Review and Critique of Manuscript.

Conflicts of interest

Authors have nothing to disclosure.

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Appendix A. Supplementary data

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