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The sooner, the later – Delayed diagnosis in Parkinson's disease due to *Parkin* mutations

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ABSTRACT

The diagnosis of Parkinson's disease (PD) in patients carrying mutations in the *Parkin* gene is frequently delayed. We confirmed this finding in a sample of nine biallelic *Parkin*-PD patients with a mean delay of nine years and found an inverse relationship between diagnostic delay and age at onset.

1. Introduction

Parkin mutations are the most common cause of recessively inherited monogenic Parkinson's disease (PD), accounting for 8.6% of PD cases with disease onset below the age of 45 years [1]. Although detailed genotypic and phenotypic information on more than 1000 *Parkin* mutation carriers is available in the literature [2], little is known about the association of disease onset and time of diagnosis in *Parkin*-PD. Factors that may contribute to a delayed diagnosis are an early disease onset, unusual clinical presentation, and slow disease progression [3]. In keeping with this concept, a remarkably delayed diagnosis was recently reported in patients with *Parkin*-PD [4]. Here, the clinical diagnosis of PD was made at least 10 years after the initial disease manifestation in 8/18 patients carrying two mutated *Parkin* alleles. Young age, lack of tremor, involvement of lower limbs, and dystonic signs were discussed to be associated with the delayed diagnosis [4].

In our study, we hypothesized that the diagnosis of PD due to *Parkin* mutations is especially delayed in patients with very young disease onset due to the overall poor awareness of neurologists that PD may occur much earlier than at the average age of idiopathic PD (IPD) onset.

We analyzed data from 9 biallelic *Parkin*-PD patients (age at examination 50.0 ± 13.8 years), and 21 early-onset PD patients (age at onset < 40 years) in whom mutations in known PD-associated genes were excluded (age at examination 48.2 ± 7.6 years, non-genetic EO-PD). All patients were examined by movement disorder specialists (MB, AB, MK, and NB) at the Institute of Neurogenetics, University of Lübeck, Germany. Written informed consent was obtained from all participants. The study was approved by the local ethics committee. T-tests, Chi-square tests, Fischer's exact tests or Mann-Whitney U tests were used for group comparisons dependent on data type, data distribution, and the number of cases. Spearman's coefficient was used in case of correlations.

We found evidence for a later diagnosis in biallelic *Parkin*-PD patients (n = 9; 9.2 ± 9.0 years) compared to the EO-PD group (n = 21; 2.1 ± 2.3 years, p = 0.003, Supplementary Table 1).

Moreover, we found that in biallelic *Parkin* mutation carriers, the diagnostic delay was dependent on the age at disease onset: patients with an earlier onset had a longer diagnostic delay (n = 9; r = −0.711, p = 0.032), which was not the case in the non-genetic EO-PD group (n = 21; r = −0.042, p = 0.855, Fig. 1).

No differences were observed regarding the presence of resting tremor as initial symptom or the subjective response to dopaminergic treatment (Supplementary Table 1).

Finally, dystonia was present in 5 of 9 (55.6%) biallelic mutation carriers at the time of disease onset, while only 1 of 21 (4.8%) non-genetic EO-PD patients exhibited dystonia as an initial symptom (p = 0.001, Supplementary Table 1).

In summary, our findings are consistent with a current report confirming a remarkably delayed diagnosis in *Parkin*-PD. Of note, the earlier the age of onset, the later the diagnosis of PD was established.

Furthermore, our data highlight dystonia as an important clinical sign in the early phase of *Parkin*-PD, especially if associated with biallelic mutations, which may be useful to differentiate *Parkin*-PD from non-genetic PD [5,6]. Indeed, in the absence of genetic testing results, it is difficult, if not impossible, to distinguish *Parkin*-PD patients from EO-PD patients without monogenic cause solely on clinical grounds.

We conclude that the time of diagnosis is particularly delayed in very young-onset *Parkin*-PD-patients with two mutated alleles. Potential contributors to a delay in the diagnosis may be an unusual clinical presentation, such as predominant dystonia and a slower disease progression in patients manifesting the disease early in life, as typically found in patients with PD due to biallelic mutations in *Parkin*.

Author disclosures

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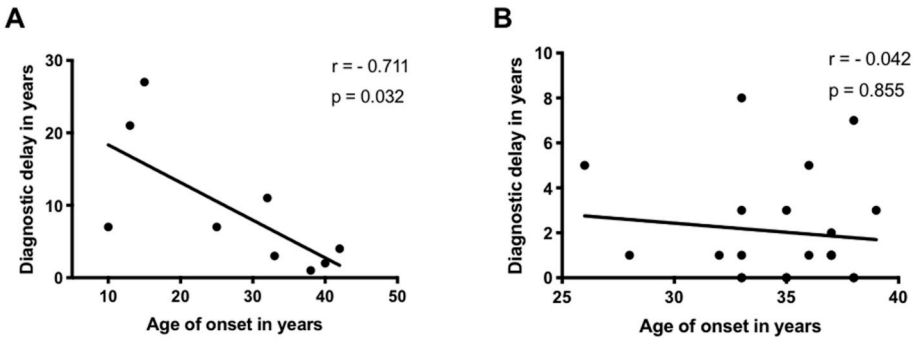

Fig. 1. Correlation between age of onset and diagnostic delay in PD with biallelic *Parkin* mutations and in non-genetic EO-PD patients. Correlation between age of onset and diagnostic delay in PD patients with two mutations in *Parkin* (n = 9, **(A)**) and in non-genetic EO-PD patients (n = 21, **(B)**). Spearman's coefficient was used. p-values < 0.05 were considered significant. Lines represent linear regression.

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Author contributions

Max Borsche participated in acquisition, analysis, and interpretation of data, and drafting the manuscript.

Alexander Balck participated in acquisition, analysis, and interpretation of data, and drafting the manuscript.

Meike Kasten participated in acquisition, analysis, and interpretation of data, drafting the manuscript, and obtaining funding.

Katja Lohmann participated in analysis, and interpretation of data, drafting the manuscript, and obtaining funding.

Christine Klein participated in study supervision, critical revision of the manuscript for important intellectual content, and obtaining funding.

Norbert Brüggemann participated in acquisition of data, contributed to the study concept and design, study supervision, critical revision of the manuscript for important intellectual content, and obtaining funding.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2019.06.020.

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