BRIEF COMMUNICATION

Discordance in monozygotic Parkinson’s disease twins – continuum or dichotomy?

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Abstract

Differences in concordance rates between monozygotic and dizygotic twin pairs with Parkinson’s disease (PD) have been used to estimate genetic influences in PD pathogenesis. We hypothesized that “discordance” may not in all cases adequately reflect the multifaceted disease manifestation of PD that involves a continuum from prodromal to definite PD. Deep clinical phenotyping, combining motor, nonmotor, and imaging modalities in five monozygotic, seemingly discordant twin pairs revealed motor and/or nonmotor features and/or nigral hyperechogenicity in all of the five putatively unaffected twins. In conclusion, our data suggest that concordance rates in monozygotic twins may be higher than previously appreciated.

Introduction

Previous epidemiological twin studies using the US National Research Council World War II Veteran Twins Registry have indicated higher concordance rates for Parkinson’s disease (PD) in monozygotic (MZ) versus dizygotic (DZ) twins with an age at onset of 50 years or younger.1,2 As concordance rates are, however, overall low and almost identical in MZ and DZ twins with an AAO above 50 years (MZ: 0.108; DZ: 0.105), factors other than a sole genetic predisposition are considered to likely be involved in the development of PD, especially when the disease has a late onset. Current consensus suggests complex genetic factors, epigenetic influences, and gene–environment interactions to be involved in the development of PD.3 In keeping with an influence of non-monoergic factors on PD pathophysiology, mutations in four PD-causing genes were excluded in the abovementioned twin pairs.4 Interestingly, a follow-up study 5–7 years after the initial examination revealed that 2 of 18 previously putatively unaffected twins had developed PD. Furthermore, the other 16 putatively unaffected twins showed a significant decline in UPSIT-scores indicating the development of at least mild hyposmia.5 Intriguingly, the authors also reported that 13 putatively unaffected twins had even displayed cardinal PD signs at baseline that did, however, not yet meet PD diagnostic criteria.

Nevertheless, it is tempting to speculate that these individuals may have had signs of prodromal PD already at the time of the first examination. Of further note, the age at PD onset differed widely both in concordant MZ and DZ twin pairs (MZ: mean 8.6 years and range 2–28 years; DZ: mean, 9.7 years and range 2–31 years).1,5

Concordance rates hinge on the accurate establishment of a diagnosis of PD. However, clinical motor features of prodromal PD (e.g., a UPDRS-III score of >3; 1987 version, excluding resting tremor) or even nonmotor signs (e.g., sleep behavior disorder or olfactory dysfunction) typically precede the onset of motor impairment and the development of full-blown PD.5 Possible early motor or nonmotor signs have thus far not been considered when determining concordance rates in twins although it has...
been suspected as early as 1990 that a subset of the putatively unaffected co-twins may have subclinical disease.7

Here, we report the results of comprehensive clinical phenotyping in five monozygotic twin pairs seemingly discordant for PD. We combined motor, nonmotor, and imaging modalities to explore whether the unaffected twin may exhibit characteristic features of prodromal PD and to test the hypothesis that ‘discordance in MZ twins’ may reflect an oversimplification. The development of PD is a long and multifaceted process that rather than a sudden conversion involves a likely continuum from a genuinely asymptomatic phase to prodromal and eventually definite PD. Finally, we compared the number of individuals with PD cardinal signs in the twin pairs with those in seemingly unaffected individuals from the previously recruited, population-based EPIPARK cohort to explore whether PD cardinal signs are more frequent than in the general population.8

Methods

Five monozygotic twin pairs, with one twin each meeting the Movement Disorder Society (MDS) clinical diagnostic criteria for PD,9 replied to a newspaper advertisement that had been placed for recruitment. They were clinically assessed for motor and nonmotor symptoms using the MDS-UPDRS I-IV, Montreal Cognitive Assessment (MoCA), Hospital Anxiety and Depression Scale (HADS), Parkinson’s Disease Sleep Scale 2 (PDSS-2), and the Brief Smell Identification Test (BSIT). Cognitive impairment was defined as a MOCA score of ≤25 and hyposmia as an age-corrected BSIT score ≤15% quartile. Videos of the neurological examination were evaluated according to the MDS-UPDRS-III protocol by three blinded movement disorder specialists (AB, MB, and NB) and focused on clinical motor signs of (prodromal) PD (e.g., an MDS-UPDRS-III score of >6, excluding resting tremor). Rigidity scores were only considered from personal examination. Additionally, transcranial sonography (TCS) using an Esaote MyLab Alpha ultrasound device equipped with a 1–4 MHz ultrasound probe was performed. Area of the substantia nigra hyperechogenicity for one individual. The probands had a lower extremity bradykinesia was present in 13.4% (n = 77/620; CI: 10.0–15.3%) of the individuals. TCS data were available for 93 individuals, showing unilateral SN hyperechogenicity for eight individuals and bilateral hyperechogenicity for one individual. The probands had an average age of 65 years (SD 7.31) and 51.1% of the individuals showed either bradykinesia or rest tremor.

In summary, clinical motor and/or nonmotor features were present in all of the five putatively unaffected twins. Detailed results of the clinical features and ancillary investigations are presented in Table 1. In the EPIPARK cohort, rest tremor was only observed in 0.8% (n = 5/617; CI: 0.3–1.9%) of individuals without a neurological diagnosis, upper extremity bradykinesia was found in 17.6% (n = 103/620; CI: 13.9–19.8%), and lower extremity bradykinesia was present in 13.4% (n = 77/620; CI: 10.0–15.3%) of the individuals. TCS data were available for 93 individuals, showing unilateral SN hyperechogenicity for eight individuals and bilateral hyperechogenicity for one individual. The probands had an average age of 65 years (SD 7.31) and 51.1% of the individuals were male (n = 318/622; CI: 47.2–55.0%). In summary, only 25.2% (n = 155/616; CI: 71.3–78.1%; chi-square: P = 0.019) of the individuals showed either bradykinesia or rest tremor.

Discussion

Our results revealed all putatively unaffected twins to unequivocally display PD-related motor and/or nonmotor
abnormalities when phenotyped in detail, thereby challenging the dichotomous view of “affected” versus “unaffected” when aiming to determine concordance rates of PD in twins. While we undoubtedly identified major clinical differences in the severity of signs and symptoms between the twin prediagnosed with PD and the twin with mild motor and nonmotor features, we would argue that the concept of “discordance” in PD twin pairs needs to be revisited and refined. The identified abnormalities in our putatively unaffected twins may be indicative of prodromal PD. However, only one putatively unaffected twin could be classified as “probable prodromal PD” according to the MDS research criteria for prodromal PD. It should be noted, however, that these criteria have a high specificity but also a low sensitivity when applied to larger patient cohorts, likely resulting in patients being classified as non-prodromal PD incorrectly. Only a quarter of population-based elderly subjects showed either bradykinesia or rest tremor, indicating that cardinal signs of PD are much more common in putatively unaffected twins than in the general population.

At the histological level, there is good evidence that patients with minimal motor abnormalities already show intermediate degeneration of the nigrostriatal system, reduction of dopaminergic innervation of the putamen, and α-synuclein aggregation that is indistinguishable from that found in PD patients. Regarding neuroimaging, minimal motor abnormalities, as well as other prodromal features of PD (e.g., REM sleep disorder or olfactory dysfunction), correlate with abnormal dopamine reuptake transporter – single-photon emission computed tomography (SPECT) and TCS and therefore may be used as a marker of prodromal PD. While SPECT data are unavailable for published twin studies, there is an earlier [18F] Dopa Positron emission tomography (PET) study, reporting that all of 10 putatively asymptomatic monozygotic co-twins showed progressive loss of dopaminergic function over seven years. These data suggest that TCS and PET may serve as a valuable ancillary tool to assess prodromal PD in seemingly unaffected twins. To a limited extent, however, it must be noted that non-affected family members may also have increased hyperechogenicity. We conclude that – despite apparent ‘discordance’ at first sight – a susceptibility for nigral pathology may be present in both MZ twins suggesting a shared genetic influence beyond that of mutations in known PD-causing genes. Somatic mosaicism including both the nuclear and mitochondrial genome, de novo variants, or epigenetic changes may collectively contribute to the phenotypic variability seen between MZ twins even in our small sample but do not preclude the concept of a possible shared genetic basis for the underlying nigrostriatal impairment that we hypothesize may be present in all 10 of our twins. Future large twin studies with deep phenotyping and long-term follow-up of the putatively unaffected twins, stratification by the age of onset, along with comprehensive genetic studies, are warranted to establish concordance rates correctly and to identify possible genetic (and nongenetic) causes of phenotypic differences across MZ and DZ twins.

| Table 1. Clinical motor and nonmotor features of the five twin pairs. |
|--------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| PD Diagnosis       | Pair 1          | Pair 2          | Pair 3          | Pair 4          | Pair 5          |
| Subject ID         | L-10887         | L-10886         | L-11147         | L-11148         | L-11155         |
| Sex                | F               | F               | M               | M               | M               |
| AAO/AAE            | 74/76           | –/76            | 71/74           | –/74            | 57/59           |
| MDS-UPDRS III score| 61 9            | 36 22           | 36 5            | 65 9            | 65 9            |
| L-Dopa dose (mg/d) | 650 n.a.        | 400 n.a.        | 175 n.a.        | 600 n.a.        | 400 n.a.        |
| SN hyperintensity  | 0.22/0.29       | 0.16/0.35       | n.a.            | n.a.            | n.a.            |
| right/left (cm²)   | + (2)           | – (9)           | – (8)           | – (6)           | – (0)           |
| Hyposmia (Total BSIT score) | + (25) | – (23) | – (25) | – (25) | – (26) |
| Cognitive impairment (MoCA) | + (25) | – (23) | + (25) | + (25) | – (26) |
| Depression         | +/-             | +/-             | +/–             | +/–             | +/–             |
| Obstructed         | –               | –               | +/–             | +/–             | +/–             |

Hyposmia was defined as BSIT score below 15% quartile. Sleep problems were assessed with the PDSS-2. SN hyperintensity was defined as >0.24 cm². 17 Cognitive impairment was defined as a MOCA score of ≥25. L-Dopa dose reflects the daily cumulative dose of Levodopa in mg. Depression was assessed with a structured clinical interview for DSM IV. (F, female; M, male; PD, Parkinson’s disease; AAO, age at onset; AAE, age at examination; SN, substantia nigra; +/-, past episode of depression; n.a., not available).
Author Contributions

AB, NB, and CK involved in the concept and design of the study. AB, MB, MK, KL, PS, NB, and CK involved in the acquisition and analysis of data. AB, NB, and CK drafted a significant portion of the manuscript or figures.

Conflict of Interest

There is no financial conflict of interest.

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