Nonmotor Symptoms in Genetic Parkinson Disease

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Objectives: To review current knowledge on nonmotor symptoms (NMS), particularly psychiatric features, in genetic Parkinson disease (PD) and to provide original data for genetic and idiopathic PD.

Data Sources: A MEDLINE search using Parkinson and known PD genes focused on the presence of depression, anxiety, hallucinations, and dementia was performed. Original data from 82 outpatients with idiopathic (n=55) and genetic (n=27) PD were obtained.

Study Selection: All studies including information on NMS and patients with genetic PD.

Data Extraction: Study methods and clinical and genetic information were summarized.

Data Synthesis: The literature search yielded 1855 citations; 305 included genetic information on PD patients, of which 119 also contained information on any type of NMS (990 cases). Availability of information varied by gene and type of NMS; studies differed by recruitment and examination method. Literature search and original data showed high frequencies of the following NMS: depression, 8% to 37% (literature) and 33% to 40% (our data); anxiety, 7% to 37% (literature) and 10% to 22% (our data); hallucinations, 3% to 23% (literature) and 23% to 29% (our data); and dementia, 5% to 26% (literature), absent in our own data.

Conclusions: Data on NMS in genetic PD are limited. Specific data needs include a systematic approach to NMS assessment reporting permitting comparability of studies. Overall, the frequency of NMS in genetic PD does not appear to be higher and may even be lower than in idiopathic PD. Nonmotor symptoms have a high impact on the patients’ quality of life and caregiver burden and should be considered important and often treatable concomitant features of genetic PD.

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Since the discovery of the first Parkinson disease (PD) genes, more than 1000 genetic cases have been published and in certain populations monogenic cases may represent 20% to 40% of PD. Genetic PD is an important and well-defined group that is etiologically more homogeneous than idiopathic PD and therefore offers unique opportunities to discover disease pathways that could then be used as a model for idiopathic PD. The clinical diagnosis of PD is based on motor signs, which have been systematically studied in both genetic and idiopathic PD. These investigations revealed group differences, but the presence of a mutation cannot usually be predicted at the individual level.

Nonmotor symptoms (NMS) are increasingly recognized as important features of idiopathic PD and genetic PD. For example, psychiatric features may be part of the phenotypic spectrum conferred by PINK1 mutations and appear to be more common in patients with LRRK2 mutations than in non–mutation carriers. However, NMS have not been studied systematically to date. It is unknown whether genetic and idiopathic cases are similar in frequency, severity, and subtypes of NMS. The natural history of most NMS remains elusive and may differ by type of NMS. For example, while impaired sense of smell is known to often precede the onset of motor signs and to persist, depression may also manifest prior to motor dysfunction but often takes an episodic course. Nonmotor symptoms may dominate the clinical picture of later stages of PD, suggesting progression of NMS. A clear association with PD has been shown for some NMS, such as decreased sense of smell. Other NMS are common in many circum-
stances, leaving the association with PD uncertain. Embracing a more comprehensive phenotypic spectrum of genetic PD may yield new insights into its pathophysiological basis, will improve diagnostic accuracy, and will inform the choice of treatments of NMS.

In this article, we pursue 2 aims: (1) to review the current knowledge on NMS, focusing on psychiatric features in genetic forms of PD, and (2) to present the NMS data of a study, trying to solve the methodological problems discovered in the literature review and present methodological considerations for future investigations.

METHODS

LITERATURE REVIEW

We searched the MEDLINE database for publications from January 1966 to January 2008, using the search terms Parkinson and the name of known PD genes (SNCA/PARK1, Parkin/PARK2, UCHL-1/PARK5, PINK1/PARK6, DJ-1/PARK7, LRRK2/PARK8, ATP13A2/PARK9 Omi/HtrA2/PARK13, and glucocerebrosidase/GBA). This resulted in 1853 citations, of which 305 studies included genetic information on PD patients. Review of the individual article references led to an additional 4 articles (309 articles total) being included. Avoiding double counts, we included a total of 119 articles containing information on any type of NMS (990 total); cTable 1, available at http://www.neuro.uni-luebeck.de/arch.neurol_kasten.et.al/. In the following, we focus on well-established forms of genetic PD with sufficient information, ie, SNCA/PARK1; LRRK2/PARK8 (dominant) and Parkin/PARK2; PINK1/PARK6; and ATP13A2/PARK9 (recessive).

METHODS OF EVALUATING THE SELECTED STUDIES FROM THE LITERATURE

Whenever a symptom was reported for some of the subjects in a study, we assumed that it was assessed for all subjects in the study, unless otherwise specified by the authors. All available information on NMS was summarized, even if no details about the diagnostic procedure were available. For example, a positive Beck Depression Inventory result, a history of depression, or treatment for depression counted as depression present. Of note, depression is a multifaceted term and does not necessarily refer to a disorder defined by the Diagnostic and Statistical Manual of Mental Disorders. We adopted a broad definition to best reflect the reviewed literature. The category of anxiety included panic attacks. We chose the term psychotic symptoms to represent all types of hallucinations disregarding their frequency, type, and severity together with other forms of psychotic symptoms (paranoia and delusion). We defined dementia based on a Mini-Mental State Examination cutoff of 24 points or less; if unavailable, mention of cognitive impairment, memory loss, confusion, recall of 0 of 3 words, and lack of orientation counted as dementia present. Sleep problems included restless legs syndrome, rapid eye movement sleep behavior disorder, daytime sleepiness, or the subject stating that he or she had a sleep disturbance.

Only articles with information on at least 1 NMS of interest were selected for review. Therefore, the numbers and percentages of cases without information correspond to these articles. A complete list of the reviewed articles is available at http://www.neuro.uni-luebeck.de/arch.neurol_kasten.et.al/.

The quality of the molecular genetic analyses in the reviewed studies could not be evaluated systematically. Furthermore, mutation type and individual case report could not always be clearly assigned. For recessive genes, carriers of 1 or 2 mutations were often grouped together in the different studies and were both counted as mutation positive.

METHODS OF THE PILOT STUDY

Consecutive PD outpatients and participants in family studies of the Movement Disorders Section of the Department of Neurology, University of Lübeck, participated in a questionnaire survey and personal examination. Upon examination by a movement disorder specialist (N.B., J.H., and C.K.), the UK brain bank criteria were established for definite PD cases; probably and possibly affected cases were defined as described previously.

The study sample (n=82) was composed of 3 groups:

1. Group 1. Subjects with genetic PD (n=27) categorized as definitely (n=19), probably (n=3), or possibly (n=5) affected on clinical examination. Within our genetic patients group, some had an early age at onset, whereas others had mild motor signs or both. To account for this, we chose 2 groups for comparison: one with an early age at onset and one with mild motor signs (Hoehn and Yahr stages 1 and 2). The 8 probably and possibly affected subjects were asymptomatic, ie, unaware of their motor signs. For these, the age at onset is indicated as not available. All 8 subjects had a documented nigrostriatal deficit in dopamine transporter single-photon emission computed tomographic or fluorodopa positron emission tomographic scans.

2. Group 2. Subjects with idiopathic PD and age at onset of 50 years or younger (n=33).

3. Group 3. Subjects with idiopathic PD at Hoehn and Yahr stages 1 or 2 (n=30). Eight of the 55 idiopathic patients had mild disease and early onset, leading to an overlap between groups 2 and 3. All subjects in these 2 groups were symptomatic and definitely affected.

Motor symptoms were assessed via the Unified Parkinson’s Disease Rating, the Hoehn and Yahr, and the Schwab and England scales. To assess nonmotor function, all patients underwent the Mini-Mental State Examination, the Montreal Cognitive Assessment, the screening questions for major depressive episodes from the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition) (DSM-IV) (SCID), and the SCID Axis I screening. All participants completed a basic demographic and PD risk factor questionnaire, the Unified Parkinson’s Disease Rating Scale parts I and II, the Beck Depression Inventory, the Epworth Sleepiness Scale, the Parkinson’s Disease Sleep Scale, and the Parkinson Disease Non-Motor Symptom Scale.

Eighteen or more points on the Beck Depression Inventory was used as an indicator of current depressive symptoms. The SCID questions were used as an indicator for lifetime depression, and use of antidepressants was assessed as an additional indicator of depression without distinguishing current or lifetime prevalence. Psychotic symptoms were assessed via the Unified Parkinson’s Disease Rating Scale, yielding point prevalence only. Similarly, we measured the point prevalence of nighttime sleep problems using item 1 of the Parkinson’s Disease Sleep Scale (subjective impression of sleep quality) and daytime sleepiness via Epworth Sleepiness Scale. Questions 4 through 7 of the SCID Axis I screening tool assessed symptoms of lifetime anxiety. To evaluate cognitive function, we used the Mini-Mental State Examination and the Montreal Cognitive Assessment (for both: 24-30; normal; 0-23, dementia).

All 82 cases were screened for mutations in the Parkin and PINK genes and for known mutations in the SNCA, LRRK2, and ATP13A2 genes using qualitative (sequencing) and quantitative (multiplex ligation-dependent probe amplification assay) methods. Owing to small numbers in some of the subgroups, results are presented at the descriptive level.
RESULTS

STUDIES REPORTING ANY TYPE OF NMS IN PATIENTS WITH GENETIC PD FROM THE LITERATURE

Few studies specifically addressed NMS in genetic PD (for example, cognitive function, psychiatric disorders, rapid eye movement sleep behavior disorder, and cardiac denervation). An additional 2 investigations covered NMS as one of their main aims (olfactory, neuropsychological, and neuropsychiatric function). Otherwise, only a few studies provided detailed clinical information that included NMS. A subgroup of the remaining studies described more detailed information on selected features of NMS, including psychiatric features, autonomic features, sleep, sensory disturbances, and a decreased sense of smell.

Examination methods ranged from in-person specialist examination to medical record review. Some authors screened for NMS, and others reported treatments for certain NMS, yielding highly variable symptom frequencies. Furthermore, point vs lifetime prevalence of NMS was not clearly distinguished. While this leads to highly variable and sometimes unknown data quality for most NMS, the situation is quite the opposite for sense of smell. Herein, the examination method is mostly uniform and the data quality homogenous and high. However, very little data are available.

Reported genetic cases were identified in clinical (mostly tertiary care centers) series (n=609), family studies (n=189), epidemiological studies (n=51), single case reports (n=10), or as autopsy-proven cases (n=12). Frequently, highly selected subgroups were targeted for genetic screening.

RESULTS OF THE LITERATURE REVIEW

Information on sex was given for 782 patients (373 men and 409 women). Most patients were white (n=495). Owning to a known founder effect for the G2019S mutation in the LRRK2 gene in North African Arab and Ashkenazi Jewish individuals, we combined these 2 groups. The combined group was frequently screened for mutations in the LRRK2 gene (n=127). Among the dominant forms (SNCA and LRRK2), 40 (14.3%) patients had an age at onset of 40 years or younger and 240 (85.7%) had an age at onset above 40 years. For the recessive forms (Parkin, PINK1, and ATP13A2), 100 (73.5%) patients had an age at onset of 40 years or younger and 36 (26.5%) patients had an age at onset above 40 years (Table 1).

Among the different NMS, psychotic symptoms and dementia were most frequently commented on (information given for 55% and 54%, respectively), followed by depression and anxiety (44% and 41%). The least amount of information was available on sleep (11%). Stratified by gene, NMS are almost always described for carriers of SNCA mutations and least frequently for LRRK2 mutation carriers (Figure and eTable 2). Data on olfaction were available in carriers of Parkin and LRRK2 mutations. LRRK2 carriers seem to have a decrease in sense

Table 1. Summary of Case Characteristics in Published Studies

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>SNCA</th>
<th>LRRK2</th>
<th>Parkin</th>
<th>PINK1</th>
<th>ATP13A2</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Cases</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>34</td>
<td>255</td>
<td>165</td>
<td>20</td>
<td>1</td>
</tr>
<tr>
<td>Asian</td>
<td>4</td>
<td>44</td>
<td>28</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Hispanic</td>
<td>0</td>
<td>10</td>
<td>11</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>North African/Jewish</td>
<td>0</td>
<td>127</td>
<td>2</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Age at onset, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>0</td>
<td>0</td>
<td>16</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>20-40</td>
<td>10</td>
<td>30</td>
<td>62</td>
<td>27</td>
<td>2</td>
</tr>
<tr>
<td>&gt;40-60</td>
<td>14</td>
<td>143</td>
<td>11</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td>&gt;60</td>
<td>12</td>
<td>86</td>
<td>0</td>
<td>6</td>
<td>0</td>
</tr>
</tbody>
</table>

*One large study with 146 subjects reported age at onset as a mean of 31.4 years (SD, 11.9 years; range, 7-70 years). Similarly, several other studies provided the age at onset in a format that could not be converted to fit the style of the table presented.*
of smell comparable with that of patients with idiopathic PD, while Parkin carriers may show an average sense of smell.\textsuperscript{13-18}

Evaluating the overall frequency of individual NMS across genes revealed depression to be the most common NMS (128 of 554 [23%]). Anxiety (62 of 401 [16%]), psychotic symptoms (70 of 545 [13%]), and dementia (74 of 532 [14%]) showed similar frequencies (Figure).

**RESULTS OF THE PILOT STUDY**

Among the 27 genetic PD cases (group 1), 2 had SNCA, 2 had LRRK2, 5 had Parkin, 12 had PINK1, and 6 had ATP13A2 mutations (for details, see eTable 3). With the exception of the ATP13A2 group (5 Hispanic and 1 Persian individual), all genetic cases were of German origin. One of 4 of the patients with dominant PD and 5 of 23 of those with recessive PD had an age at onset of 40 years or younger (for asymptomatic patients, age at onset is assumed to be higher than the current age, which is above 40 years for all participants). The average Hoehn and Yahr stage of all of the genetic cases was 1.9 (SD, 0.9; range, 1-4). The mean age at onset of group 2 (idiopathic early-onset PD) was 39 years with a mean Hoehn and Yahr stage of 2.6. Group 3 (idiopathic PD with Hoehn and Yahr stages 1 and 2) had a mean age at onset of 56 years; the average Hoehn and Yahr stage was 1.7 (Table 2). Individual results for NMS by gene (group 1) are shown in Table 3.

**LITERATURE REVIEW**

Comprehension of information on NMS differed by type of NMS and gene. Of note, the frequency of mutations across genes varied under study varies, and some of the genes have been discovered only recently. Different (types of) mutations in the various genes may have differential effects on the phenotype. For example, SNCA duplications tend to result in a phenotype more reminiscent of idiopathic PD, whereas triplications are associated with comparatively rapid progression and prominent cognitive features.\textsuperscript{10} Different mutation types could not be accounted for when compiling information for the literature review. The cases varied by age at onset, sex distribution, disease duration, ethnicity, treatment, and comorbidity. While it is currently unknown whether these parameters influence frequency and type of NMS, it is conceivable that point and lifetime prevalences differ for all episodic NMS. Furthermore, dopaminergic medication may induce certain NMS such as psychosis or daytime sleepiness, but due to limited information, this could not be accounted for.

As a general observation, 48% of the genetic cases from the literature were men compared with an about 1.5 times higher incidence of idiopathic PD in men vs women.\textsuperscript{21} This suggests an even distribution of genetic PD among men and women. Given the mode of inheritance (autosomal) and lack of known sex-specific reduction of penetrance, this seems biologically plausible. As a caveat, it needs to be considered that our literature review focused on cases with reported information on NMS.

Dementia is suspected as a distinguishing feature of SNCA-associated PD, but dementia as well as psychotic symptoms were described in only about a quarter of the mutation carriers, despite a documented disease duration of up to 17 years.\textsuperscript{22} This may reflect the fact that several more benign SNCA duplications have recently been reported and are included in our review. Also, it needs to be taken into account that the disease duration of most reported literature cases is not reported in the short case descriptions, but may influence the likelihood of NMS as well as the NMS subtype. Specifically, disease duration is known to influence the likelihood of dementia in idiopathic PD\textsuperscript{23} and this probably also applies to genetic PD.

For LRRK2-associated PD, relatively large case numbers are available, but information on NMS is still limited. Dementia was most commonly assessed (in about 65% of the mutation carriers) and was present in about 11%. Sleep problems were least commonly assessed (16%), but present in 60% of those patients. Prevalence of depression was almost 30% in LRRK2-associated PD, similar to that in idiopathic PD.\textsuperscript{24} In contrast, the occurrence of dementia in 11% of the LRRK2 mutation carriers is lower than that reported in a systematic review of idiopathic PD (25%-30%).\textsuperscript{23,25} After completion of our literature review, 2 articles were published specifically addressing LRRK2-linked PD.\textsuperscript{17,26}

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**Table 2. Clinical and Demographic Characteristics of the Pilot Samples**

<table>
<thead>
<tr>
<th>Group</th>
<th>SNCA</th>
<th>LRRK2</th>
<th>Parkin</th>
<th>PINK1</th>
<th>ATP13A2</th>
<th>Idiopathic PD With Onset at ≤50 y</th>
<th>Idiopathic PD, Hoehn and Yahr Stages 1 and 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, M/F, No.</td>
<td>0/2</td>
<td>1/1</td>
<td>3/2</td>
<td>7/5</td>
<td>4/2</td>
<td>15/18</td>
<td>20/10</td>
</tr>
<tr>
<td>Age, range, y</td>
<td>40-47</td>
<td>56, 58</td>
<td>50-58</td>
<td>42-70</td>
<td>45-80</td>
<td>Mean (SD), 52.6 (8.9); range, 21-73</td>
<td>Mean (SD), 61.7 (13.1)</td>
</tr>
<tr>
<td>Age at onset, y</td>
<td>34, 44</td>
<td>53, 57</td>
<td>15, 36, 36, 38, 42</td>
<td>47, 53, 61, NA</td>
<td>10, NA</td>
<td>Mean (SD), 39.1 (7.2); range, 11-48</td>
<td>Mean (SD), 56.1 (13.1)</td>
</tr>
<tr>
<td>Hoehn and Yahr stage</td>
<td>3, NA</td>
<td>1, 3</td>
<td>2, 2, 2.5, 3, 3</td>
<td>5 at 1, 1.5, 1.5, 2, 2.5, 3, 2 NA</td>
<td>4, NA</td>
<td>Mean (SD), 2.6 (0.7); range, 1-4</td>
<td>Mean (SD), 1.7 (0.4); range, 1-2</td>
</tr>
<tr>
<td>Symptomatic cases, No.</td>
<td>2</td>
<td>2</td>
<td>5</td>
<td>7</td>
<td>2</td>
<td>33</td>
<td>30</td>
</tr>
<tr>
<td>No. of patients medicated</td>
<td>2</td>
<td>1</td>
<td>5</td>
<td>3, 3 NA</td>
<td>1</td>
<td>29, 3 NA</td>
<td>23, 4 NA</td>
</tr>
</tbody>
</table>

Abbreviations: NA, data not available; PD, Parkinson disease.
More than half of the patients with Parkin mutations and information on NMS are reported in 1 article that did not provide information on dementia and sleep. All cases combined, psychotic symptoms and dementia appeared to be rare in Parkin-linked PD (about 3%). These data collectively support the notion that Parkin-associated PD is less frequently complicated by NMS than idiopathic PD and probably also compared with other genetic forms of PD. While the motor phenotype is virtually indistinguishable between Parkin- and PINK1-associated PD, psychiatric and cognitive symptoms appear to be more common in PINK1-linked disease.

Information on NMS associated with ATP13A2 mutations is based on case reports only. Some of the reviewed articles provided more detailed data than those listed in the tables. Additional psychiatric features included, for example, an SNCA mutation carrier from a French family who committed suicide in the context of depression. LRRK2 mutations were associated with claustrophobia and alcohol and levodopa addiction, in 1 case each. Selected Parkin mutation carriers were reported to have obsessive-compulsive disorder (n=2), verbal aggression (n=1), hypersexuality (n=2), and hysterical episodes and conversional symptoms (n=1). One study specifically addressed the association of mutations in the PINK1 gene with psychiatric disorders in a large family. To our knowledge, this represents the first attempt at a systematic literature review on NMS in genetic PD. The main conclusion is that data are currently limited and extremely diverse. A frequent lack of a definition of symptoms and signs, a broad spectrum of study designs, predominance of convenience samples, and overall absence of systematic evaluations render comparisons difficult and prone to bias. Overall, the frequency of NMS in patients with genetic PD does not appear to be higher and may even be lower than that in patients with idiopathic PD. Possible exceptions include the occurrence of dementia in ATP13A2-associated disease and specific psychiatric disorders in PINK1-linked PD.

### EVALUATION OF THE PILOT DATA AND STUDY DESIGN

Whenever possible, we tailored the choice of questionnaires to cover point and lifetime prevalence of the different NMS and preferentially included instruments that allowed self-administration. We focused on psychiatric NMS, including sleep problems. Stratified or adjusted analyses to account for medication-related differences were impossible owing to small case numbers. Most patients received dopaminergic medication, some received sele-giline or amantadine, and none received anticholinergic drugs. We specifically aimed at assessing psychiatric syndromes rather than psychiatric disorders according to...
DSM-IV diagnoses, assuming that psychiatric syndromes may be part of the phenotypic spectrum of PD and may differ from psychiatric disorders as defined by DSM-IV.

Demographic and clinical characteristics of the genetic patients in our sample were similar to those in the literature and the idiopathic patients in our sample. We observed the same age at onset distribution according to the gene involved and mode of inheritance in our case series and the literature. Autonomic symptom frequency as assessed by the PD NMS seemed to be higher in our sample than in the literature description with the caveat that it was impossible to differentiate the type of autonomic symptom in most literature reports. In our sample, the frequency differed widely across symptoms.

Strikingly, we found an even distribution of men and women in the genetic cases and in the early-onset PD group. All known genetic forms were excluded from the early-onset PD group (group 2), whereas the described\(^1\) predominance of male cases can be seen in the idiopathic PD, Hoehn and Yahr stage 1/2 group (group 3). Sleep problems and daytime sleepiness were frequent in all 3 subgroups, suggesting that both are as relevant in genetic PD as in idiopathic PD.

LESSONS FROM LITERATURE AND PILOT DATA

Although genetic PD only represents a relatively small fraction of all PD, the past 12 years have seen an exponential growth of publications on genetic forms of PD with hundreds of described cases. Therefore, it seemed timely and worthwhile to review the literature for information on NMS, which are an important and often treatable concomitant feature of PD. A better understanding of the role of NMS in the individual genetic forms will lead to a more comprehensive view of the clinical expression of PD gene mutations, potential pathophysiological insights into individual genetic forms of PD, and the use of specific therapies for NMS.

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REFERENCES


**Announcement**

**Trial Registration Required.** As a member of the International Committee of Medical Journal Editors (ICMJE), *Archives of Neurology* will require, as a condition of consideration for publication, registration of all trials in a public trials registry (such as http://ClinicalTrials.gov). Trials must be registered at or before the onset of patient enrollment. The trial registration number should be supplied at the time of submission.

For details about this new policy, and for information on how the ICMJE defines a clinical trial, see the editorials by DeAngelis et al in the September 8, 2004 (2004; 292:1363-1364) and June 15, 2005 (2005;293:2927-2929) issues of *JAMA.* Also see the Instructions to Authors on our Web site: www.archneurol.com.