Enlarged Substantia Nigra Hyperechogenicity and Risk for Parkinson Disease

A 37-Month 3-Center Study of 1847 Older Persons

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Objective: To evaluate whether enlarged substantia nigra hyperechogenicity (SN+/H11001) is associated with an increased risk for Parkinson disease (PD) in a healthy elderly population.

Design: Longitudinal 3-center observational study with 37 months of prospective follow-up.

Setting: Individuals 50 years or older without evidence of PD or any other neurodegenerative disease.

Participants: Of 1847 participants who underwent a full medical history, neurological assessment, and transcranial sonography at baseline, 1535 could undergo reassessment.

Main Outcome Measure: Incidence of new-onset PD in relation to baseline transcranial sonography status.

Results: There were 11 cases of incident PD during the follow-up period. In participants with SN+/H11001 at baseline, the relative risk for incident PD was 17.37 (95% confidence interval, 3.71-81.34) times higher compared with normoechogenic participants.

Conclusions: In this prospective study, we demonstrate for the first time a highly increased risk for PD in elderly individuals with SN+/H11001. Transcranial sonography of the midbrain may therefore be a promising primary screening procedure to define a risk population for imminent PD.

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The primary outcome of the study was the incidence of new-onset PD in relation to SN+ in TCS, as indicated by the relative risk (RR). Analysis of different study groups was performed using commercially available software (SPSS 17 for Windows; SPSS Inc, Chicago, Illinois) applying parametric statistics for the study co-

<table>
<thead>
<tr>
<th>Table 1. Comparison of the Follow-up Cohort and the Cohort Lost to Follow-upα</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study centers</strong></td>
</tr>
<tr>
<td>All</td>
</tr>
<tr>
<td>Tübingen, Germany</td>
</tr>
<tr>
<td>Homburg/Saar, Germany</td>
</tr>
<tr>
<td>Innsbruck, Austria</td>
</tr>
<tr>
<td>Reason for loss to follow-up</td>
</tr>
<tr>
<td>Died</td>
</tr>
<tr>
<td>Declined participation</td>
</tr>
<tr>
<td>Moved or reason not specified</td>
</tr>
<tr>
<td>Demographic and ultrasonographic data at baseline</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
</tr>
<tr>
<td>Male sex</td>
</tr>
<tr>
<td>Positive family history</td>
</tr>
<tr>
<td>SN+</td>
</tr>
<tr>
<td>Echogenic status not availabled</td>
</tr>
</tbody>
</table>
| Abbreviation: SN+, enlarged hyperechogenic substantia nigra.  
α Unless otherwise indicated, data are expressed as number (percentage) of participants.  
β Unless otherwise indicated, Fisher exact test was used to calculate statistics.  
P values apply to comparisons between cohorts.  
γ By 2-tailed t test.  
δ Owing to insufficient bone window.

**METHODS**

**STUDY POPULATION**

The PRIPS Study (Prospective Validation of Risk Factors for the Development of Parkinsonian Syndromes) is a prospective cohort study designed to define the value of midbrain ultrasonography to detect preclinical PD. Individuals 50 years or older without evidence of PD or any other neurodegenerative disease were recruited at 3 centers (Tübingen and Homburg, Germany, and Innsbruck, Austria). Detailed information about baseline characteristics (including inclusion and exclusion criteria and sample size estimation) has been published recently.9 In brief, participants at the German centers were recruited using advertisements in local newspapers and from local companies. The Innsbruck center recruited the participants of the Bruneck study, providing a population-based sample from the town of Bruneck in South Tyrol (Italy) that was originally recruited for a prospective study of risk factors for carotid atherosclerosis. All participants gave written informed consent. The study was approved by all local ethical committees.

The study was performed during an 8-year period from January 1, 2001, through March 30, 2009. At baseline, 1847 participants (812 from Tübingen, 500 from Homburg/Saar, and 535 from Innsbruck) were found to be free of PD, as defined by the United Kingdom Parkinson Disease Society Brain Bank (UK-PDSBB).10 Three hundred twelve study participants were lost to the follow-up (Table 1). Thus, the study population with evaluable data consisted of 1535 participants. The total mean (SD) follow-up interval was 37.0 (15.6) months.

**BASELINE ASSESSMENTS**

**Transcranial Sonography**

Transcranial sonography was standardized for all centers according to the consensus criteria.11 In Tübingen and Homburg, a Sonoine Elegra ultrasound machine (Siemens, Erlangen, Germany) equipped with a 2.5-MHz transducer was used; in Innsbruck, a 2.5-MHz transducer was adapted to a Logic 7 ultrasound machine (General Electric, Milwaukee, Wisconsin).

The mesencephalic scanning plane was visualized parallel to the orbitomeatal line. In this plane, the butterfly-shaped mesencephalic brainstem surrounded by the echogenic basal cisterns was depicted, and echogenicity of the ipsilateral SN was planimetrically measured. Therefore, the image was frozen and zoomed 2- to 3-fold to manually surround the hyperechogetic signals in the anatomical area of the SN, thereby calculating the size of the area automatically. In this study, SN+ was defined as any value above the median of the 90th percentile of the right and/or left SN side within each center, according to the threshold for SN+ set in former studies.8 All other cases were classified as normoechogenic (SN−, Figure).

**Medical History and Clinical Assessment**

Medical history and family history of PD were recorded in a semistructured interview according to the criteria of Marder and coworkers.12 Clinical examinations were performed by neurologists with expertise in movement disorders blinded to the results of the ultrasonographic examinations to exclude individuals with clinical PD at baseline.

**FOLLOW-UP ASSESSMENTS**

At follow-up, all participants underwent reassessment for the presence of clinical PD according to the UK-PDSBB criteria10 requiring the presence of bradykinesia and at least 1 symptom of rigidity, resting tremor, or postural instability as well as asymmetric presentation. All participants diagnosed as having PD at this visit were invited for a short-term follow-up assessment by independent movement disorders specialists at the outpatient clinic of the corresponding study center to confirm or reject the diagnosis.

**STATISTICAL ANALYSES**

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horts and, owing to the small number of participants, nonparametric statistics for the group with incident PD. Differences were assumed to be significant at \( P < 0.05 \) (2 sided).

**RESULTS**

The follow-up cohort did not differ significantly from the cohort lost to follow-up with regard to age, sex, and SN echogenic status but did differ with regard to family history (more prevalent in those who underwent a follow-up visit). An insufficient bone window was present in 8.8% of the entire follow-up cohort. We found SN+ at baseline in 18.3% of the participants without PD in the follow-up examination and in 80.0% of the participants who at follow-up were diagnosed as having PD \( (P < 0.001) \). Detailed data on the follow-up cohort are given in Table 2.

**COMMENT**

In this prospective multicenter longitudinal study with 1535 participants followed up during a mean observation period of 37 months, the RR of incident PD was more than 17 times higher in elderly participants with SN+ compared with those with SN−, thus demonstrating an association between SN+ and subsequent development of PD in healthy adults.

A 17-fold increased RR for developing PD among SN+ participants while being studied during this rela-
Table 3. Characteristics of the 11 Participants With Incident PD

<table>
<thead>
<tr>
<th>Center, Participant ID No./Sex/Age, y</th>
<th>Diagnosis According to UK-PDSBB Criteria</th>
<th>Clinical Presentation at Follow-up Examination</th>
<th>Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Confirmed ≤ 1 y</td>
<td>Confirmed by DAT-SPECT</td>
<td>UPDRS-III</td>
</tr>
<tr>
<td>Tübingen, Germany</td>
<td>Yes</td>
<td>ND</td>
<td>15</td>
</tr>
<tr>
<td>1052/M/78</td>
<td>Yes</td>
<td>ND</td>
<td>33</td>
</tr>
<tr>
<td>1076/F/82</td>
<td>Yes</td>
<td>ND</td>
<td>23</td>
</tr>
<tr>
<td>1320/M/51</td>
<td>Yes</td>
<td>Yes</td>
<td>10</td>
</tr>
<tr>
<td>Homburg, Germany</td>
<td>Yes</td>
<td>Yes</td>
<td>36</td>
</tr>
<tr>
<td>70/M/62</td>
<td>Yes</td>
<td>ND</td>
<td>19</td>
</tr>
<tr>
<td>420/M/69</td>
<td>Yes</td>
<td>ND</td>
<td>24</td>
</tr>
<tr>
<td>Innsbruck, Austria</td>
<td>Yes</td>
<td>ND</td>
<td>12</td>
</tr>
<tr>
<td>2077/F/82</td>
<td>Yes</td>
<td>ND</td>
<td>7</td>
</tr>
<tr>
<td>2108/F/75</td>
<td>Yes</td>
<td>ND</td>
<td>15</td>
</tr>
<tr>
<td>2165/F/72</td>
<td>Yes</td>
<td>ND</td>
<td>13</td>
</tr>
<tr>
<td>2312/M/82</td>
<td>Yes</td>
<td>ND</td>
<td>23</td>
</tr>
<tr>
<td>2340/M/79</td>
<td>Yes</td>
<td>ND</td>
<td>30</td>
</tr>
</tbody>
</table>

Abbreviations: DAT-SPECT, dopamine transporter single-photon emission computed tomography; ND, not determined; PD, Parkinson disease; SN, substantia nigra; SN+, enlarged hyperechogenic SN; SN–, normoechogenic SN; UK-PDSBB, United Kingdom Parkinson Disease Society Brain Bank; UPDRS-III, Unified Parkinson’s Disease Rating Scale Motor Score, Part III.

a Defined as having at least 1 affected first-degree relative.
b Indicates insufficient temporal bone window.

In a prospective study on patients with mild parkinsonism,19 Other reasons for the relatively low positive predictive value are certainly the mismatch between occurrence of SN+ in the population (about 10% of individuals to the age of 79 years)21,22 and the proportion of people who will develop PD during their lifetime (1%-2%).23 as well as the occurrence of SN+ in putatively presymptomatic stages of other disorders, such as dementia with Lewy bodies24 and corticobasal degeneration.25

Compared with the literature,23 the number of incident PD cases in this study was high. This could in part be owing to a high percentage of first-degree relatives of PD patients volunteering to participate in this study (10.3% of the follow-up cohort). In addition, in the past decade it has been increasingly accepted that nonmotor manifestations of PD, such as autonomic, sensory, sleep, and neuropsychiatric disturbances, precede the motor phase.26,27 We hypothesize that some individuals at risk for PD may sense some deterioration of their general health status years before clinicians are able to diagnose the disease and may therefore have a particular motivation to participate in studies such as this one.

As a limitation, we are not able to completely exclude differing recruitment strategies between centers and different ultrasonographic equipment as having an influence on the results. In addition, we cannot entirely verify that the cohort lost to follow-up was similar to the follow-up cohort because not all preclinical PD markers considered relevant to date (eg, hyposmia, relatively short observation period makes this ultrasonographic marker a strong candidate for screening to narrow a target risk population. To our knowledge, this RR is higher than any RR of PD risk markers reported so far. In the 26-year follow-up study of approximately 8000 men enrolled in the Honolulu Heart Program, never-smoking participants had a 4-fold increased RR compared with current smokers.13 In a population-based cohort study with approximately 3800 elderly participants with a median follow-up of 3.3 years, the RR for developing PD was 4.3-fold higher than in participants with essential tremor.17

male sex, (lack of) physical activities, and head trauma.17

One of the main goals of identifying PD risk markers is the detection of individuals who may benefit from neuroprotective interventions. Because TCS is noninvasive, cheap, and quick and easy to perform by properly trained examiners, it has the potential for use as a secondary screening instrument in population-based screening batteries. Its specific role within a multistep screening battery that includes assessments of several risk markers will have to be determined in further studies.

Although SN+ occurred in 18.7% of our total follow-up cohort with sufficient temporal bone window (17.1% of non-PD and 80.0% of PD participants; Table 2), only 3.1% of them developed PD. This low conversion rate is most likely owing to the short follow-up period, which also limits further determination of diagnostic variables, such as specificity and positive and negative predictive values. Especially, the specificity of SN+ for PD is discussed controversially in the literature. It is important to realize that SN+ can also be found in a certain percentage of patients with rare neurodegenerative diseases, such as atypical parkinsonian syndromes or spinocerebellar ataxia.18,19 This finding, however, does not seem to limit its specificity for the application in cohort studies, as indicated by a prospective study on patients with mild parkinsonism.20

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REFERENCES


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