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/H+) 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+ 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+. Transcranial sonography of the midbrain may therefore be a promising primary screening procedure to define a risk population for imminent PD.

Arch Neurol. 2011;68(7):932-937

The neuropathologic features of Parkinson disease (PD) include cell loss and α-synuclein aggregation (Lewy bodies and Lewy neurites) in multiple brain areas, including the substantia nigra (SN) of the midbrain. In addition, microglial activation and iron accumulation are found. A large body of evidence suggests that PD-specific pathologic features antedate the onset of diagnostic clinical features, and the preclinical period of nigral cell loss has been estimated to last several years. Therefore, asymptomatic individuals harboring subclinical PD pathologic features are at imminent risk for developing the clinical illness, and their identification would open a window for neuroprotective intervention.

Transcranial sonography (TCS) shows that 90% of patients with PD but only about 10% of elderly individuals without PD have enlarged midbrain hyperechogenicity in the area of the SN (SN+). The morphologic basis for this ultrasonographic signal abnormality is not entirely clear, but an association of this echogenic feature with increased tissue iron content has been demonstrated. An increased prevalence of SN+ has been observed in conditions known to be associated with an increased risk for developing PD, including a family history of PD, depression, idiopathic olfactory loss, and rapid eye movement sleep behavior disorder. In addition, SN+ was more prevalent in individuals with subtle signs of motor slowing and asymmetric arm swing, and asymptomatic SN+ individuals were found to have decreased fluorodopa F 18 uptake in the striatum.

However, a relationship between SN+ in still-healthy persons and subsequent development of PD has not yet been established. Therefore, we studied the association between SN echogenic status at baseline and the 3-year incidence of PD in a prospective study of 1847 healthy individuals 50 years or older.

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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. 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 using advertisements in local newspapers and from local companies.

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). 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. In Tübingen and Homburg, a Sonoline 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 hyperechogenic 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. All other cases were classified as normoechogenic (SN–).

### 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. 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 using advertisements in local newspapers and from local companies.

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#### STATISTICAL ANALYSES

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-

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**Table 1. Comparison of the Follow-up Cohort and the Cohort Lost to Follow-up**

<table>
<thead>
<tr>
<th>Study centers</th>
<th>Baseline Cohort</th>
<th>Follow-up Cohort</th>
<th>Lost to Follow-up Cohort</th>
<th>P Value&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>1847 (100.0)</td>
<td>1535 (83.1)</td>
<td>312 (16.9)</td>
<td></td>
</tr>
<tr>
<td>Tübingen, Germany</td>
<td>812 (100.0)</td>
<td>715 (88.1)</td>
<td>97 (11.9)</td>
<td></td>
</tr>
<tr>
<td>Homburg/Saar, Germany</td>
<td>500 (100.0)</td>
<td>376 (75.2)</td>
<td>124 (24.8)</td>
<td></td>
</tr>
<tr>
<td>Innsbruck, Austria</td>
<td>535 (100.0)</td>
<td>444 (83.0)</td>
<td>91 (17.0)</td>
<td></td>
</tr>
<tr>
<td>Reason for loss to follow-up</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Died</td>
<td>34 (1.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Declined participation</td>
<td>204 (11.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moved or reason not specified</td>
<td>74 (4.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Demographic and ultrasonographic data at baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>61.0 (8.8)</td>
<td>60.8 (8.4)</td>
<td>62.0 (10.7)</td>
<td>.08&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Male sex</td>
<td>974 (52.7)</td>
<td>824 (53.7)</td>
<td>150 (48.1)</td>
<td>.07</td>
</tr>
<tr>
<td>Positive family history</td>
<td>169 (9.1)</td>
<td>158 (10.3)</td>
<td>11 (3.5)</td>
<td>.02</td>
</tr>
<tr>
<td>SN+</td>
<td>308 (16.7)</td>
<td>262 (17.1)</td>
<td>46 (14.7)</td>
<td>.67</td>
</tr>
<tr>
<td>Echogenic status not available&lt;sup&gt;d&lt;/sup&gt;</td>
<td>181 (9.8)</td>
<td>135 (8.8)</td>
<td>46 (14.7)</td>
<td>.002</td>
</tr>
</tbody>
</table>

Abbreviation: SN+, enlarged hyperechogenic substantia nigra.

<sup>a</sup> Unless otherwise indicated, data are expressed as number (percentage) of participants.

<sup>b</sup> Unless otherwise indicated, Fisher exact test was used to calculate statistics. P values apply to comparisons between cohorts.

<sup>c</sup> By 2-tailed t test.

<sup>d</sup> Owing to insufficient bone window.

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Medical history and family history of PD were recorded in a semistructured interview according to the criteria of Marder and coworkers. 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 criteria 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.
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 < .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-
tively 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. 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 par-

cipants with a median 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. 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) and the proportion of people who will develop PD during their lifetime (1%-2%), as well as the occurrence of SN+ in putatively presymptomatic stages of other disorders, such as dementia with Lewy bodies and corticobasal degeneration.

Comparison with the literature, 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. 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,
25% to 40% of persons older than 60 years show at least mance is a common symptom in elderly individuals; about included because we argued that impaired motor perfor-

Participants with subtle motor signs were not ex-

In conclusion, the PRIPS Study demonstrates a clear association between SN+ in healthy people and subse-

Accepted for Publication: November 19, 2010. Author Affiliations: Department of Neurodegenera-

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Author Contributions: Drs Seppi and Behnke equally contributed to this study. Dr Berg had full access to all the data in the study and takes responsibility for the integ-


Funding/Support: This study was supported by the Michael J. Fox Foundation.

Disclaimer: The supporting institution had no influence on the design, conduct, or analysis of the study.

Additional Contributions: The Bosch GmbH and the Walter AG helped in recruitment and retention of particip-

Arch Neurol/Vol 68 (No. 7), July 2011 www.archneurol.com
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**Announcement**

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