Brain bank questionnaire helps in differential diagnosis of parkinsonian disorders: an autopsy study of 150 patients

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Brain bank questionnaire helps in differential diagnosis of parkinsonian disorders: an autopsy study of 150 patients

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ABSTRACT

**Background**: As part of the CurePSP brain donation program, a questionnaire was developed to capture basic information from the next-of-kin or someone familiar with the brain donor with respect to symptoms and clinical course. The usefulness of information from the questionnaire has not been assessed.

**Objective**: To assess the value of information from the brain donation questionnaire as it relates to differential diagnosis of parkinsonian disorders.

**Methods**: We reviewed 150 questionnaires, including 50 patients, each with a neuropathologic diagnosis of Lewy body disease (LBD), multiple system atrophy (MSA), or progressive supranuclear palsy (PSP). The frequency of clinical features recorded in the questionnaires was compared for the three disorders, and machine learning algorithm, XGBoost, was applied to tabulated information from the questionnaires to identify features that had predictive value with respect to neuropathologic diagnosis.

**Results**: The information from the questionnaires correlated with core clinical features for each disorder - hallucinations for LBD, autonomic dysfunction for MSA, and early falls for PSP. Age at onset and early falls were identified as the key variables that contributed most to prediction of neuropathology.

**Conclusion**: While less optimal than prospectively collected information, a questionnaire can provide useful clinical information for clinicopathological correlative studies.
**Introduction**

Clinical diagnosis of neurodegenerative diseases, such as Parkinson's disease (PD) and atypical parkinsonian disorders, poses a significant challenge for physicians.\(^1\) PD, the most common neurodegenerative movement disorder, is characterized by bradykinesia, rigidity, and resting tremor with responsiveness to levodopa.\(^2\) Dementia with Lewy bodies (DLB) is the second most common neurodegenerative dementia after Alzheimer's disease and is characterized by fluctuations in cognition, attention and alertness, as well as spontaneous parkinsonism and visual hallucinations.\(^3\) Multiple system atrophy (MSA) and progressive supranuclear palsy (PSP) are atypical parkinsonian disorders, characterized by levodopa non-responsive parkinsonism. In addition to parkinsonism, patients with MSA have variable combinations of autonomic failure and cerebellar ataxia,\(^4\) while patients with PSP have postural instability, falls and vertical supranuclear gaze palsy.\(^5\) Although biomarkers for these disorders remain under development,\(^6\)-\(^8\) postmortem neuropathologic evaluation is currently the gold standard for diagnosis. Discrepancies between clinical and postmortem pathological diagnoses for a given patient are not uncommon. For example, MSA can be clinically misdiagnosed as Lewy body disease (LBD), PSP or other disorders.\(^9,10\) Clinicopathological studies have played a pivotal role in identifying features useful in the differential diagnosis of movement disorders.\(^11\)

Nevertheless, collecting brain tissues comes with certain challenges. Clinical information gathered from medical records and ancillary documents is crucial for clinicopathological research, but the quality and quantity of medical records can vary in retrospective autopsy studies.\(^9\) To address this limitation, questionnaires have been developed by some brain banks to collect missing clinical information. These forms can be a valuable source of information that might otherwise be unavailable due to the timeliness and incompleteness of medical records available for clinicopathologic studies of brain bank patients.
In the present study, we assessed the usefulness of a brain bank questionnaire developed by CurePSP, the leading patient support group in the United States for PSP and atypical Parkinsonian disorders, in the differential diagnosis of parkinsonian disorders. We tabulated data from the questionnaires and determined which features were most associated with three atypical parkinsonian disorders – PSP, MSA, and LBD. Additionally, we used a machine learning algorithm to analyze tabulated data to determine if information from the questionnaire can predict neuropathological diagnoses and to identify which features were valuable in predicting the underlying pathology.

Methods

Subjects and Neuropathological Diagnoses

The study consisted of 150 consecutive cases of autopsy-confirmed LBD, MSA, and PSP (50 cases of each disorder) received by the Mayo Clinic brain bank between 2020 and 2022. All neuropathological diagnoses were made by a single, experienced neuropathologist (DWD) as previously described.³, ¹²-¹⁵

Data collection

The following clinical information was collected from the CurePSP questionnaire: age at onset, family history, symptoms early in the disease course, symptoms present at any time, and personality change. The symptoms present at any time were obtained from a checklist on the questionnaire that included the following: disorientation, tremors, wandering, visual problems, agitation, stiffness, violent outburst, weight loss, delusions, hallucinations, difficulty walking, eating disorder, sleeping disorder, and falls. The early symptoms and personality change
sections of the questionnaire are open-ended questions filled in by the applicant or family member in their own words.

*Prediction of the pathological diagnosis using machine learning algorithm*

To examine whether the information from the questionnaire alone can predict the pathological diagnosis of parkinsonian disorders, we performed an analysis with Extreme Gradient Boosting (XGBoost). XGBoost is an open-source implementation of the gradient boosted trees algorithm, which attempts to accurately predict a target variable by combining the estimates of a set of simpler, weaker models.\textsuperscript{16} The variables used were age at onset, as well as the presence of hallucinations, delusions, disorientation, agitation, autonomic dysfunction, tremors, wandering, personality change, memory loss, and violent outbursts throughout the disease course, as well as the presence of falls and word-finding difficulty as early symptoms. The dataset was split into training and test datasets at a ratio of 4:1. The number of trees was 100, and the maximum depth of trees was 4. The code was prepared in python, and all analyses were performed on Google Colaboratory.

*Statistical Analysis*

All statistical analyses we performed used Rcmdr 2.8-0. (R. Boca Raton, FL). A $\chi^2$ test was used for group comparisons of all categorical data, and a one-way analysis of variance was used for continuous variables. $P$ values $<0.05$ were considered statistically significant.
Results

General Information

Questionnaires were most frequently completed by the spouse of the donor (42%), followed by their child (20%). LBD cases had longer average disease durations than MSA and PSP. MSA had the earliest average age at onset compared with LBD and PSP. The frequency of a positive family history of neurodegenerative disorders was not significantly different between the three disorders (Table 1).

Clinical Symptoms from the checklist

This section of the questionnaire (Supplementary Figure 1, section 6) is composed of 14 symptoms that the informant checks if they occurred at any point in the disease course. On average, LBD had the most positive responses from the checklist (LBD: 8.4 ± 3.1, MSA: 5.9 ± 2.3, PSP: 5.9 ± 2.7; p <0.001). LBD cases had more frequent responses on the following: disorientation, tremors, wandering, agitation, violent outbursts, delusions, and hallucinations. The other symptoms were similar in frequency between the three disorders (e.g., stiffness, weight loss, difficulty walking, etc.) (Table 2).

Symptoms in early stages

In this section of the questionnaire (Supplementary Figure 1, section 4), family members were asked to describe clinical features in the early stage of the disease in their own words, such as dizziness, memory problems or slurred speech. MSA had higher frequencies of autonomic dysfunction (e.g., urinary dysfunction, hypotension and erectile dysfunction) and dream enactment behavior. PSP had a higher frequency of falls. Of the PSP cases that reported falls,
29% of patients had falling backward. LBD cases had the highest frequency of memory loss as early symptoms (Table 2).

**Personality changes**

For this part of the questionnaire (Supplementary Figure 1 section 7), family members were asked to describe personality changes in their own words. Responders would state whether a change was present and describe how it was presented. MSA cases less frequently had personality changes compared to the other two disorders. (Table 2). The most common personality change was agitation/irritability, followed by social withdrawal. Agitation/irritability was the least frequent in MSA. The frequencies of social withdrawal and depression/anxiety were not different among the three diseases. Apathy was most frequent in PSP.

**Prediction of the pathological diagnosis based on the information from the questionnaire**

We examined whether the machine learning algorithm, XGBoost, could predict the pathological diagnosis based on information tabulated from the questionnaire. The resultant model demonstrated a diagnostic accuracy of 63%. Analysis of the “feature importance” revealed that the age at onset, falls as early symptoms, and hallucinations were the key variables that significantly contributed to the prediction (Supplementary Figure 2).

**Discussion**

In the present study, we found that the CurePSP questionnaire provides basic clinical information that can differentiate three parkinsonian disorders. The checklist of symptoms successfully identified key clinical features for LBD, MSA and PSP. For example, LBD cases
had the highest frequency of hallucinations, a core clinical feature, and delusions, a supportive clinical feature of DLB\(^3\). Progressive cognitive decline is the central feature of DLB, and the checklist includes disorientation and wandering as features suggestive of cognitive impairment. The checklist was supplemented by the section on symptoms in the early stages, which was formatted as an open-ended question (Section 4). A subset of LBD patients had a record of memory loss, a common feature of dementia. By combining information from both sections, we were able to gather the characteristic clinical features of each disease.

The checklist does not list any symptoms of autonomic dysfunction, a core clinical feature of both clinically established MSA and clinically probable MSA,\(^4\) but in Section 4, many patients documented symptoms consistent with autonomic dysfunction (e.g., urinary incontinence, constipation, erectile dysfunction, and orthostatic hypotension). Similarly, PSP cases had higher frequencies of early falls, a core clinical feature of PSP.\(^5\) The XGBoost analysis also identified these clinical features as having strong predictive value, further validating their diagnostic value.

The medical interview for collecting information about symptoms and family history plays an important role in the diagnosis of neurological diseases. The results of this study show that a questionnaire written in lay language can be useful for collecting clinical information from family members or someone with close contact with the patient. Although this version of the questionnaire provides standardized clinical information of the patients, there is room for improvement. For example, LBD cases had the highest frequency of symptoms in the checklist, reflecting the fact that the checklist was derived for collecting information on LBD rather than MSA or PSP; therefore, features of MSA and PSP are needed in a revised checklist. Another weakness of the checklist is that some features are not clearly defined. For example, “eating disorders” may include difficulty swallowing, but also anorexia or other conditions. Similarly,
“sleeping disorders” can include various disorders, such as insomnia, obstructive sleep apnea, and dream enactment behavior disorder.

To address some of these issues, CurePSP recently revised the questionnaire in 2022. The new version of questionnaire has a checklist with more than 40 different symptoms. For example, the checklist in the new questionnaire includes seven symptoms of autonomic dysfunction: dizziness, difficulty with blood pressure regulation/fainting, excessive sweating, changes to breathing, changes to bladder or bowel function, sexual dysfunction, and changes to circulation. Sleep changes has five separate symptoms: development of sleep apnea, acting out dreams, restless leg syndrome, difficulty falling or staying asleep, and daytime fatigue/sleepiness. This modification of the questionnaire might improve the low reporting of dream enactment behavior ascertained from the old questionnaire. It will be necessary to evaluate the usefulness of the new questionnaire as more cases come to autopsy.

In conclusion, we showed that the CurePSP questionnaire provides a baseline of clinical information for retrospective clinicopathological studies and that questionnaires filled in by the next-of-kin are a valuable source of clinical information. The quality of clinicopathological research benefits from information provided by the next-of-kin or someone with close personal contact with the patient. A questionnaire is a means for family members to actively contribute to brain banking research.
Acknowledgement
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Ethical Compliance
Neuropathologic evaluations were performed at the Mayo Clinic brain bank for neurodegenerative disorders. The brain bank operates under procedures approved by the Mayo Clinic Institutional Review Board. Brain autopsies were performed after consent of the legal next-of-kin or individuals with legal authority to grant permission for autopsy. De-identified studies of autopsy samples are considered exempt from human subject research by the Mayo Clinic Institutional Review Board.

Funding sources and conflict of interests
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Author roles
1) Research project: A. Conception, B. Organization, C. Execution;


3) Manuscript: A. Writing of the first draft, B. Review and Critique.
Nicholas Martin: 1A, 1C, 2B, 3A

Hiroaki Sekiya: 1A, 1C, 2C, 3B

Dennis Dickson: 1B, 1C, 3B

Shunsuke Koga: 1A, 1B, 1C, 2A, 2B, 2C, 3B

References

Table 1: Demographic information on all three groups.

<table>
<thead>
<tr>
<th></th>
<th>LBD (N = 50)</th>
<th>MSA (N = 50)</th>
<th>PSP (N = 50)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (men:women)</td>
<td>35:15</td>
<td>27:23</td>
<td>30:20</td>
<td>0.25</td>
</tr>
<tr>
<td>Age at onset, years</td>
<td>65 ± 7.6</td>
<td>61 ± 8.8</td>
<td>70 ± 7.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Disease duration, years</td>
<td>9.1 ± 4.6</td>
<td>6.3 ± 2.1</td>
<td>6.3 ± 2.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Family history of neurodegenerative disorders</td>
<td>17 (34%)</td>
<td>13 (26%)</td>
<td>18 (36%)</td>
<td>0.52</td>
</tr>
</tbody>
</table>
Table 2: Frequencies of symptoms present at any time.

<table>
<thead>
<tr>
<th>Symptoms at any time</th>
<th>LBD (N = 50)</th>
<th>MSA (N = 50)</th>
<th>PSP (N = 50)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disorientation</td>
<td>35 (70%)</td>
<td>8 (16%)</td>
<td>16 (32%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tremors</td>
<td>35 (70%)</td>
<td>33 (66%)</td>
<td>11 (22%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Wandering</td>
<td>11 (22%)</td>
<td>0 (0%)</td>
<td>3 (6%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Visual problems</td>
<td>30 (60%)</td>
<td>28 (56%)</td>
<td>36 (72%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Agitation</td>
<td>35 (70%)</td>
<td>9 (18%)</td>
<td>25 (50%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stiffness</td>
<td>37 (74%)</td>
<td>35 (70%)</td>
<td>37 (74%)</td>
<td>0.87</td>
</tr>
<tr>
<td>Violent outburst</td>
<td>17 (34%)</td>
<td>3 (6%)</td>
<td>7 (14%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weight loss</td>
<td>29 (58%)</td>
<td>26 (52%)</td>
<td>17 (34%)</td>
<td>0.04</td>
</tr>
<tr>
<td>Delusions</td>
<td>28 (56%)</td>
<td>8 (16%)</td>
<td>8 (16%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>37 (74%)</td>
<td>11 (22%)</td>
<td>7 (14%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Difficulty walking</td>
<td>46 (92%)</td>
<td>49 (98%)</td>
<td>48 (96%)</td>
<td>0.35</td>
</tr>
<tr>
<td>Eating disorder</td>
<td>6 (12%)</td>
<td>7 (14%)</td>
<td>8 (16%)</td>
<td>0.84</td>
</tr>
<tr>
<td>Sleeping disorder</td>
<td>33 (66%)</td>
<td>33 (66%)</td>
<td>24 (48%)</td>
<td>0.10</td>
</tr>
<tr>
<td>Falls</td>
<td>42 (84%)</td>
<td>46 (92%)</td>
<td>48 (96%)</td>
<td>0.11</td>
</tr>
<tr>
<td>Symptoms in the early stages</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fall</td>
<td>0 (0%)</td>
<td>9 (18%)</td>
<td>29 (58%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Autonomic dysfunction</td>
<td>5 (10%)</td>
<td>16 (32%)</td>
<td>0 (0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dream enactment behavior</td>
<td>6 (12%)</td>
<td>14 (28%)</td>
<td>0 (0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Memory loss</td>
<td>18 (36%)</td>
<td>2 (4%)</td>
<td>10 (20%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Personality changes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any symptoms</td>
<td>38 (76%)</td>
<td>26 (52%)</td>
<td>37 (74%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Agitation/irritability</td>
<td>13 (26%)</td>
<td>2 (4%)</td>
<td>13 (26%)</td>
<td>0.005</td>
</tr>
<tr>
<td>Social withdrawal</td>
<td>10 (20%)</td>
<td>5 (10%)</td>
<td>9 (18%)</td>
<td>0.35</td>
</tr>
<tr>
<td>Depression/anxiety</td>
<td>9 (18%)</td>
<td>7 (14%)</td>
<td>6 (12%)</td>
<td>0.69</td>
</tr>
<tr>
<td>Apathy</td>
<td>3 (6%)</td>
<td>2 (4%)</td>
<td>10 (20%)</td>
<td>0.01</td>
</tr>
</tbody>
</table>
Brain Bank Questionnaire

This form must be completed by the family and sent to the Brain Bank ahead of time.

Please mail, e-mail, or fax this form to: __________________________

Name of patient: __________________________ Date of birth: __________________________

Name of next-of-kin: __________________________

Relationship to patient: __________________________

Address (of next-of-kin): __________________________

City: __________________________ State/Province: __________________________ ZIP/postal code: __________________________ Country: __________________________

Phone: __________________________ Email address: __________________________

It is necessary to have certain information to advance our research. We need to know in detail the following, as best as you can provide it. It may be helpful for the entire family to participate in piecing together this important summary. The information should be as complete as possible. Use extra pages if necessary.

1. Current diagnosis: __________________________

2. Age at onset of symptoms: __________________________

3. Is there a family history of PSP, CBD, MSA, FTD, ALS, CTE, Parkinson’s or Alzheimer’s disease, or any other form of movement disorder or dementia? __________________________

4. What were the symptoms in the early stages? __________________________

5. Was the progression of the illness rapid? __________________________

6. Check any of the following that were present. For how many years? __________________________

___ Disorientation ___ Weight loss
___ Tremors ___ Delusions
___ Wandering ___ Hallucinations
___ Visual problems ___ Difficulty walking
___ Agitation ___ Eating disorder
___ Stiffness ___ Sleep disorder
___ Violent outbursts ___ Falls

7. Personality changes (describe): __________________________

8. Other noteworthy symptoms (please list): __________________________

9. Was the patient right or left handed? _____ Right _____ Left


11. Was a CT scan or MRI performed? If yes, when, how often and where was it performed? What did the report show? __________________________

12. What kind of work did the patient do? __________________________

13. Did the patient have any other medical issues? __________________________

14. What medications did the patient take? __________________________

Supplementary Figure 1: Main page of the CurePSP brain bank questionnaire.
Supplementary Figure 2: Feature importance for predicting the pathological diagnosis.