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MRI measurements predict PSP in unclassifiable parkinsonisms
A cohort study

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ABSTRACT
Objective: Magnetic resonance parkinsonism index (MRPI) has been proposed as a powerful tool to discriminate patients with progressive supranuclear palsy (PSP) from those with Parkinson disease (PD) or other parkinsonisms, on an individual basis. We investigated the usefulness of MRPI in predicting the clinical evolution in PSP of patients with clinically unclassifiable parkinsonism (CUP), i.e., parkinsonism not fulfilling the established clinical diagnostic criteria for any parkinsonian disorders, using a cohort study.

Methods: Forty-five patients with CUP underwent baseline clinical evaluation and MRI with calculation of MRPI. All patients were divided in 2 groups according to MRPI values. A group included 30 patients with CUP with normal MRPI values while the other group included 15 patients with CUP with MRPI values suggestive of PSP (higher than 13.55). A clinical follow-up was performed in all patients.

Results: Duration of clinical follow-up in these 2 groups was 28.4 ± 11.7 months (mean ± SD). None of the patients with CUP with normal MRPI values fulfilled established clinical criteria for PSP (follow-up ranging from 24 to 60 months). By contrast, 11 of 15 patients with CUP with abnormal MRPI values (higher than 13.55) developed during the follow-up (range from 6 to 48 months) additional clinical features characteristic of probable (1 patient) or possible (10 patients) PSP. MRPI showed a higher accuracy in predicting PSP (92.9%) than clinical features, such as vertical ocular slowness or first-year falls (61.9% and 73.8%, respectively).

Conclusions: Our findings suggest that MRPI is more powerful than clinical features in predicting the evolution of CUP toward PSP phenotypes.

For decades, the diagnosis of parkinsonian disorders has relied upon the presence and progression of characteristic clinical features. To improve the diagnostic accuracy, various sets of clinical criteria have been proposed for diagnostic workup of parkinsonian disorders, such as Parkinson disease (PD), progressive supranuclear palsy (PSP), multiple system atrophy (MSA), or corticobasal degeneration (CBD).

Nonetheless, some patients may have a phenotype that does not fulfill the established clinical criteria for the most common parkinsonian disorders, and therefore they can be considered as affected by clinically unclassifiable parkinsonism (CUP). To predict the prognosis and to guide management of these patients, an accurate diagnosis is crucial and additional diagnostic biomarkers are needed.

Recently, magnetic resonance parkinsonism index (MRPI) has been proved to be a highly accurate measure to discriminate patients with PSP from those with PD, those with MSA, and...
control subjects, on an individual basis.7–12 To date, no data are available concerning the usefulness of MRPI in predicting the clinical evolution of CUP to defined clinical phenotypes. We used a cohort study in which patients with CUP were followed up for a long period of time (up to 5 years). The aim of the present study was to investigate whether abnormal MRPI values in patients with CUP may predict the clinical evolution in PSP.

**METHODS Patients.** We used a cohort study, which involved 45 consecutive patients with CUP who underwent MRI and were followed over a period of time ranging from 6 to 60 months. Patients were defined as affected by CUP when they did not fulfill the standard operational clinical diagnostic criteria for PD,3 PSP,4 MSA,2 dementia with Lewy bodies,10 frontotemporal lobar degeneration,11 CBD,6 or vascular parkinsonism.15 Patients were consecutively recruited among those referred to the Movement Disorders Center of the Institute of Neurology at the University “Magna Graecia” of Catanzaro, Italy, from June 2005 to September 2010. All patients were clinically evaluated by 2 neurologists (M.M. and G.A.) with more than 10 years of experience in movement disorders. For each patient, a complete medical history, neurologic examination, and clinical assessment using Unified Parkinson’s Disease Rating Scale–Motor Examination (UPDRS-ME) and Hoehn & Yahr (H&Y) rating scale in an “off” phase (off medications overnight) were available. The Mini-Mental State Examination (MMSE) was used to assess cognitive performance. In patients treated with levodopa or dopamine agonists, dopaminergic responsiveness was assessed by presence or absence of a substantial and sustained response to an adequate trial of these drugs. Exclusion criteria for all patients were as follows: history of neuroleptic use within the past 6 months, presence of serum or urinary abnormalities (iron, ferritin, transferrin, calcium, parathormone, copper, ceruloplasmin), presence of acanthocytes in peripheral blood, evidence of Gly2019Ser and Ile2020Thr mutations in the LRRK2 gene, and presence of normal striatal uptake in dopamine transporter $^{123}$I-FP-CIT-single-photon emission CT (DAT SPECT).

**Standard protocol approvals, registrations, and patient consents.** All study procedures and ethical aspects were approved by the institutional review board. In addition, written informed consent was obtained from all subjects who were examined as part of the study.

**MRI protocol and analysis.** All patients with CUP underwent brain MRI using a 1.5-T imager (Signa NV/I; GE Medical Systems, Milwaukee, WI) after the baseline clinical evaluation. All MRI examinations included transverse intermediate-weighted and T2-weighted dual-echo fast spin-echo (repetition time msec/echo time msec, 3,500/10.2, 85; section thickness, 4 mm; frequency- and phase-encoding matrix, 288$^{192};$ flip angle, 20$^\circ$), and T1-weighted volumetric spoiled gradient-echo (15.2/6.8; section thickness, 0.6 mm; frequency- and phase-encoding matrix, 256 × 256; flip angle, 15$^\circ$) show midbrain area (1), pons area (2), middle cerebellar peduncle (MCP) width (3), and superior cerebellar peduncle (SCP) width (4) in (A) a patient with clinically unclassifiable parkinsonism (CUP) with normal magnetic resonance parkinsonism index (MRPI) and in (B) a patient with CUP with abnormal MRPI. Images show marked atrophy of both midbrain and SCP in the patient with CUP with abnormal MRPI (B) in comparison with the patient with CUP with normal MRPI (A). In the patient with CUP with normal MRPI (A), values were as follows: midbrain area, 125 mm$^2$; pons area, 475 mm$^2$; MCP width, 9.40 mm; SCP width, 3.95 mm; MRPI, 9.04. In the patient with CUP with abnormal MRPI (B), values were as follows: midbrain area, 48 mm$^2$; pons area, 392 mm$^2$; MCP width, 5.55 mm; SCP width, 1.65 mm; MRPI, 27.47.
The midbrain area and pons area were measured on midsagittal T1-weighted volumetric spoiled gradient echo MRI in all patients as previously described (figure 1). Measurement of middle cerebellar peduncle (MCP) width was performed on midsagittal T1-weighted volumetric spoiled gradient-echo MRI. Superior cerebellar peduncle (SCP) was measured on the T1-weighted volumetric spoiled gradient-echo high-spatial-resolution oblique coronal MRI (figure 1). MRPI was calculated by multiplying the pons area–midbrain area ratio (P/M) by MCP width–SCP width ratio (MCP/SCP) \[(P/M) \times (MCP/SCP)\] (7). MRPI values were considered abnormal if they exceeded the previously reported cutoff of 13.55.

The 45 patients with CUP were divided in 2 groups according to MRPI values. The first group included 30 patients with CUP with normal MRPI values (below the cutoff value of 13.55). The second group included 15 patients with CUP with abnormal MRPI values (equal or higher than 13.55). For all study subjects, we computed the follow-up time between the date of baseline evaluation (clinical examination and MRPI calculation) and the appearance of clinical features allowing the classification as probable or possible PSP. Follow-up clinical assessment was performed in all patients with CUP every 6 months by the same physicians blinded to the MRPI results.

**Statistical analysis.** The difference in categorical variables distributions between groups was evaluated with the \( \chi^2 \) test or Monte Carlo exact test when the expected frequencies were low. To compare age at examination, age at onset, and disease duration, we used the unpaired \( t \) test. To assess the difference in the UPDRS-ME score, H&Y score, MMSE, SCP width, MCP width, midbrain area, and pons area among the groups we used the Mann-Whitney \( U \) test. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were determined for differentiating patients with final diagnosis of PSP from not-PSP, using the MRPI cutoff value of 13.55 and the following clinical features: isolated postural instability with falls in the first year of disease, slowness of vertical saccades, postural instability with falls after the first year of the disease associated with slowness of vertical saccades, and freezing of gait in the first 3 years of disease. In the present study population, we also calculated the optimal cutoff value for the MRPI using the receiver operating characteristic curve analysis. To assess the intrarater and interrater reliability the intraclass correlation coefficient was calculated. Statistical analysis was performed with statistical software (SPSS for Windows, version 17.0; SPSS, Chicago, IL).

**RESULTS** A flow diagram of our study is shown in figure 2. Data on demographic and clinical features of patients with CUP at the baseline evaluation are listed in table 1. Data on measurements of the single brainstem structures (SCP width, MCP width, midbrain area, pons area) in patients with CUP with normal (<13.55) or abnormal (≥13.55) MRPI values are shown in table e-1 on the Neurology® Web site at www.neurology.org. Twenty-eight out of 30 patients with CUP with normal MRPI values (MRPI mean value ± SD: 9.9 ± 1.9, range values: 6.1–13.1) completed the study while 2 patients were lost during the follow-up. The duration of clinical follow-up in this group, expressed as mean ± SD, was 29.6 ± 10.1 months (range from 24 to 60 months). At the follow-up, none of these 28 patients developed additional clinical features allowing a diagnosis of possible or probable PSP. Some of them developed some additional features, such as dysarthria (14%), occasional dysphagia (7%), or pyramidal signs (11%), keeping the diagnosis of CUP. Among the 15 patients with CUP with abnormal MRPI values (MRPI mean value ± SD: 16.6 ± 2.7, range values: 13.6–21.4), 14 patients completed the study. One patient died during the follow-up. The latter patient along with the 2 patients lost to follow-up were excluded from the analyses. In this group, the mean duration of clinical follow-up was 26.1 ± 14.6 months (range from 6 to 48 months). Eleven out the 14 patients developed during the follow-up additional clinical features that fulfilled the established consensus criteria for probable (n = 1 patient) or possible (n = 10 patients) PSP. More in detail, 7 of these patients with CUP developed vertical supranuclear gaze palsy, while the remaining 4 patients, who presented with falls in the first year of disease, developed slowing of the vertical saccades during the follow-up (table e-2). The remaining 3 out of the 14 patients with CUP with abnormal MRPI values did not develop additional features after a follow-up period of 24 months. More in detail, 2 patients continued to have only freezing
of gait while the other patient showed falls that appeared 3 years after the disease onset with slowness of vertical saccades.

Box plots of MRPI in patients with CUP evolving to PSP or not evolving to PSP are shown in figure 3. Sensitivity, specificity, PPV, NPV, and accuracy for MRPI values (cutoff value 13.55) and for the clinical features in patients with CUP for differentiating PSP vs not-PSP are listed in table 2. In the present study population, the optimal cutoff value for the MRPI using the receiver operating characteristic curve analysis was 13.35. There were no differences, in terms of number of patients in the 2 CUP groups and of sensitivity, specificity, PPV, NPV, and accuracy values, both using this latter cutoff and the previously published MRPI cutoff value of 13.55. There was excellent correlation between intrarater measurements of MRPI, SCP, MCP, midbrain, and pons (intraclass correlation coefficient of 0.991, 0.992, 0.989, 0.990, and 0.992, respectively) and between interrater measurements (intraclass correlation coefficient of 0.989, 0.988, 0.990, 0.991, and 0.991, respectively).

**DISCUSSION**

Our study shows that MRPI was highly accurate in predicting the clinical evolution of patients initially affected by CUP in PSP. In particular, the majority (78.5%) of patients with CUP with abnormal MRPI values at baseline developed after a 2-year mean follow-up period additional clinical features that fulfilled established criteria for possible or probable PSP.

The clinical diagnostic criteria for PSP have been described to have high sensitivity, specificity, and PPV in patients with the classic presentation (Richardson syndrome; PSP-RS) characterized by a poorly responsive parkinsonism, postural instability with falls backwards within the first year of the disease, and supranuclear vertical gaze abnormalities. More in detail, the early falls due to postural instability and supranuclear gaze palsy or slowed vertical saccades have been described as the most helpful defining features to identify reliably patients for clinical research who had underlying PSP-tau pathology. However, these criteria are not able to detect PSP in patients who show, in the early stages of disease, atypical features such as isolated postural instability with falls, slowness of vertical saccades isolated or associated with late postural instability, and isolated freezing of gait. At the present time, to our knowledge, none has assessed the power of specific imaging markers in predicting the evolution in PSP of patients with atypical parkinsonian features. Our study demonstrates that the MRPI, an imaging measure...
Table 2: Validity of clinical features and MRPI for PSP in patients with CUP

<table>
<thead>
<tr>
<th>Baseline evaluation</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>PPV, %</th>
<th>NPV, %</th>
<th>Accuracy, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical features</td>
<td></td>
<td></td>
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<tr>
<td>Isolated postural instability with falls in the first year of disease</td>
<td>45.4</td>
<td>83.9</td>
<td>50</td>
<td>81.2</td>
<td>73.8</td>
</tr>
<tr>
<td>Slowness of vertical saccades</td>
<td>18.2</td>
<td>77.4</td>
<td>22.2</td>
<td>72.7</td>
<td>61.9</td>
</tr>
<tr>
<td>Postural instability with falls after the first year of the disease and slowness of vertical saccades</td>
<td>27.3</td>
<td>93.5</td>
<td>60</td>
<td>78.4</td>
<td>76.2</td>
</tr>
<tr>
<td>Freezing in the first 3 years of disease</td>
<td>9.1</td>
<td>58.1</td>
<td>7.1</td>
<td>64.3</td>
<td>45.2</td>
</tr>
<tr>
<td>MRI features</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRPI value ≥13.55</td>
<td>100</td>
<td>90.3</td>
<td>78.6</td>
<td>100</td>
<td>92.9</td>
</tr>
</tbody>
</table>

Abbreviations: CUP = clinically unclassifiable parkinsonism; MRPI = magnetic resonance parkinsonism index; NPV = negative predictive value; PSP = progressive supranuclear palsy; PPV = positive predictive value.

which is known to be highly specific in differentiating PSP from PD and MSA, was also accurate in predicting the clinical evolution of patients with CUP in PSP. MRPI showed a higher accuracy in predicting PSP (92.9%) than isolated vertical ocular slowness or first-year falls (61.9% and 73.8%, respectively), 2 clinical features typically occurring in patients with this parkinsonian disorder.

Among our patients with CUP evolving to PSP, 7 (1 probable and 6 possible PSP) had a phenotype compatible with its classic presentation of PSP-RS while the remaining 4 patients presented with different phenotypes. In recent years, a new nosology has emerged confirming the original observations of Richardson et al. but also separating out several other useful clinical subtypes that would otherwise not satisfy the established consensus criteria for PSP. Currently, the term PSP-tau pathology includes, in addition to the classic PSP syndrome, such as PSP-RS, other clinicopathological variants such as PSP parkinsonism (PSP-P) and pure akinesia with gait freezing (PSP-PAGF). In our study, among the 4 patients with PSP variants, 3 had a clinical phenotype suggestive of PSP-P and the other a phenotype compatible with PSP-PAGF. The 3 patients with PSP-P who had long-duration parkinsonism with late-onset falls (occurring several years after the disease onset), initially responsive to levodopa, developed a vertical supranuclear gaze palsy during the follow-up period. The other patient presented with a PSP-PAGF phenotype characterized by freezing of gait occurring within the first 2 years of disease and postural instability with falls and vertical supranuclear gaze palsy developed during the follow-up. Recent studies have demonstrated that the clinical evolution of PSP-P and PSP-PAGF in clinical phenotypes that fulfill the established diagnostic criteria for possible PSP may require up to 10 years. Although the diagnosis of PSP-P and PSP-PAGF needs neuropathologic confirmation, our findings suggest that high MRPI values could be used as an in vivo supportive biomarker for the identification of these disorders in a disease stage in which diagnosis is still uncertain.

Among our patients with CUP with abnormal MRPI values, 3 of 14 did not evolve to PSP after 2 years of follow-up; 2 of them continued to have only freezing of gait and one slowness of vertical saccades with late-onset postural instability. It could be hypothesized that these patients with CUP might require a longer follow-up period to evolve to PSP.

In our study, MRPI also showed an optimal negative predictive power since our patients with CUP with normal MRPI values did not develop in the follow-up clinical features allowing inclusion in PSP phenotypes. All these patients remained as unclassified parkinsonisms and an ongoing clinical and MRI long-term follow-up will allow to clarify the clinical diagnosis of these patients.

There were some limitations to this study. We used clinical criteria for the diagnosis of the diseases, and we did not have a pathologic confirmation. Thus, it is possible that in some patients the clinical diagnosis may be in error. However, this seems unlikely because of the sensitivity and specificity of clinical diagnostic criteria for PSP that we applied in our patients. We also considered that vertical gaze palsy may develop in other parkinsonian disorders, such as corticobasal degeneration. However, the absence of the core clinical features of this latter syndrome, as progressive asymmetric rigidity, ideomotor apraxia, alien limb phenomena, and cortical sensory loss, allowed us to make an accurate differential diagnosis. Moreover, all patients included in our study were evaluated in a standard fashion by 2 of the authors (G.A. and M.M.) who had more than 10 years of experience in movement disorders. The duration of clinical follow-up may have been too short for those patients who remained clinically unclassifiable, and a longer follow-up period could allow to ascertain further clinical evolution. Yet further studies are warranted.

Our study show that MRPI is a useful tool in predicting the clinical evolution of CUP in PSP phenotypes, even in the stages of the disease when clinical features such as isolated postural instability with falls, isolated slowing of vertical saccades, or freezing of gait do not allow to make a diagnosis of PSP using established consensus criteria.

**AUTHOR CONTRIBUTIONS**

Dr. Morelli: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data. Dr. Arabia: drafting/revising the manuscript, study concept or design, analysis or interpre-
tation of data. Dr. Novellino: analysis or interpretation of data. Dr. Salsone: analysis or interpretation of data. Dr. Giofre`: analysis or interpretation of data. Dr. Condino: analysis or interpretation of data, statistical analysis. Dr. Messina: study concept or design, analysis or interpretation of data, acquisition of data. Prof. Quattrone: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, study supervision.

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