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Magnetic Resonance Parkinsonism Index and midbrain to pons ratio: Which index better distinguishes Progressive Supranuclear Palsy patients with a low degree of diagnostic certainty from patients with Parkinson Disease?

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ABSTRACT

Introduction: Several studies have compared the performances of midbrain to pons area ratio (M/P) and the Magnetic Resonance Parkinsonism Index (MRPI) in distinguishing patients with Progressive Supranuclear Palsy (PSP) from those with Parkinson's disease (PD) with conflicting results. The current study aimed to compare the performance of these indexes in a well-characterized sample of PSP patients using either a manual or a fully automated approach to measure the brainstem structures involved in M/P and MRPI calculation.

Methods: This study involved 179 patients affected by idiopathic PD, 35 patients affected by PSP (15 probable and 20 possible) and 87 healthy controls. Sensitivity, specificity, positive predictive value (PPV) and area under the curve (AUC) of MRPI and M/P in distinguishing possible and probable PSP from PD and controls were calculated.

Results: No significant difference was found between manual and automated values for both MRPI and M/P. MRPI and M/P differentiated probable PSP from PD with similar performance. By contrast, MRPI showed higher sensitivity and specificity than M/P when patients with possible PSP were compared with PD (MRPI, sensitivity 100%, specificity 98.88%; M/P, sensitivity 85%, specificity 93.85%). A significant difference was also observed in AUC between MRPI and M/P in distinguishing possible PSP from PD.

Conclusion: Our study demonstrates that MRPI was more accurate than M/P, in differentiating patients with possible PSP from those with PD. In patients suspected of having PSP with a low level of clinic diagnostic accuracy, MRPI should be preferred to M/P for distinguishing these patients from PD.

1. Introduction

Progressive Supranuclear Palsy (PSP) is an adult-onset progressive neurodegenerative disorder leading to supranuclear vertical gaze palsy, postural instability with falls, bradykinesia, and axial rigidity [1–3]. Pathologically, PSP is a tauopathy characterized by the accumulation of neurofibrillary tangles in several brain regions. The most commonly clinical presentation is PSP-Richardson's syndrome (PSP-RS) [3], classified as possible or probable according to National Institute for Neurological Diseases and Stroke-Society for PSP criteria (NINDS-SPSP) [4], but a number of other phenotypes such as PSP-parkinsonism (PSP-P), pure akinesia with gait failure (PAGF), PSP with predominant corticobasal syndrome (PSP-CBS), PSP with behavioral variant frontotemporal dementia (PSP-F), and PSP with progressive non-fluent aphasia (PSP-PNFA) have been recognized [5].

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Among the various forms of parkinsonisms, possible PSP and PSP-P are difficult to distinguish from idiopathic Parkinson's disease (PD), especially in the early stages of disease, when the clinical signs are often subtle [6–8]. Hence, in the past years, several studies using magnetic resonance imaging (MRI) have been aimed to identify new biomarkers that could be used for enhancing the confidence of clinical diagnosis of PSP [9–12].

Quantitative MRI measurements of brainstem structures have been suggested as potentially useful markers to distinguish patients with PSP from those with PD and controls [13–17]. In particular, imaging measurements, such as the ratio of the midsagittal areas of the midbrain and pons (M/P) and the Magnetic Resonance Parkinsonism Index (pons/midbrain (P/M) multiplied by middle cerebellar peduncles (MCP)/superior cerebellar peduncles (SCP) widths ratio, MRPI), have been proven to be two accurate measures in discriminating patients affected by PSP from patients with PD and controls on an individual basis [16,18–24].

In the last few years, several studies have compared the performances of M/P and MRPI in distinguishing patients with PSP from those with PD with conflicting results mainly due to the different expertise of raters manually measuring the brainstem structures, and to phenotypic variability of PSP [16,19–21,23,24].

Differently from M/P, MRPI includes in the calculation the measurement of the SCP, a small brainstem structure that markedly atrophies in patients with PSP [13,17]. The manual measurement of SCP needs specific reconstructions on MRI, and may be influenced by the expertise of the operator more than the M/P which does not take into consideration the measurement of this small brain structure. Thus, M/P ratio is easier to be determined but the lack of SCP measurement may account for its smaller accuracy, in comparison with MRPI, for distinguishing patients with PSP from those with PD, especially in the early phases of the disease.

To address this issue, in the current study we investigated the accuracy of the M/P and MRPI for differentiating patients with possible or probable PSP from patients with PD. Moreover, we compared the performance of the two indexes in a large sample using either a manual or a fully automated approach to measure the brainstem structures involved in PSP [25]. The use of an automated approach overcame the bias of the operator in the manual measurement of the brain structures considered in the calculation of M/P and MRPI.

2. Materials and methods

2.1. Study population

This study involved 179 patients affected by idiopathic PD, 35 patients affected by PSP (15 probable and 20 possible) and 87 healthy controls at the time of MRI. Patients and control subjects were consecutively enrolled from January 2010 to June 2016, and were examined by neurologists with more than 10 years of experience in movement disorders.

The patients were included in the study if they fulfilled the diagnostic criteria for PD [26] or for possible or probable PSP according to NINDS-SPSP [4]. For each patient, a complete medical history was available; neurological examination and clinical assessment using Unified Parkinson Disease Rating Scale part III (UPDRS-III) [27] and Hoehn and Yahr (H-Y) rating scale [28] were performed in all patients.

All participants gave written informed consent according to the Declaration of Helsinki for the use of their medical records for research purposes. The study was approved by the local institutional review board and ethics committee.

2.2. MRI imaging protocol

All patients and control subjects performed brain MRI using 3 T Unit and using an 8-channel head coil (Discovery MR-750, General Electric, Milwaukee, WI). Head movements were minimized using foam pads around participants' heads. The MRI protocol included a whole-brain T1-weighted scan [SPGR; Echo Time (ET) 3.7 ms, Repetition Time (TR) 9.2 ms, flip angle 12°, voxel size $1.0 \times 1.0 \times 1.0$ mm^3].

Image analysis was performed by two independent rater (M.M. and A.Q.), with more than 10 years of experience in neuroradiology and blinded to the diagnoses of the patients. To assess the intrarater reliability, a second evaluation was made 1 week after the first evaluation by one of the two raters (M.M.), who assigned scores to all images and who was blinded as before.

The midbrain area and pons area were measured on midsagittal T1-weighted volumetric spoiled gradient-echo MRI in all patients and healthy controls as previously described [16,18]. Measurement of middle cerebellar peduncles (MCP) width was performed on sagittal T1-weighted volumetric spoiled gradient-echo MRI [16]. Superior cerebellar peduncles (SCP) width was measured on the T1-weighted volumetric spoiled gradient-echo high-spatial resolution oblique coronal MRI [16].

The M/P was calculated as the ratio of midbrain area to pons area according to Oba et al. [18]. MRPI was calculated by multiplying the pons area/midbrain area ratio (P/M) by the MCP/SCP widths ratio according to Quattrone et al. [16] (see Fig. 1).

Automated measurement of MRPI and M/P ratio was performed using the method described in Nigro et al. [25] (http://mrpi.unicz.it). This fully automated approach is able to automatically measure both the pons and midbrain areas and the width of middle and superior cerebellar peduncles and then to calculate the M/P ratio and MRPI values.

2.3. Statistical analysis

The difference in sex distribution among groups was evaluated with the $\chi 2$ test. To compare age at examination, age at onset and disease duration one-way analysis of variance was used, followed by a two-sample *t*-test for pairwise comparisons. The differences in H-Y score and UPDRS-III score among PD and PSP groups were evaluated using the Kruskal-Wallis test followed by Mann-Whitney *U* test.

The difference between automated and manual measurements of SCP width, MCP width, midbrain area, pons area, MRPI and M/P in each group of subjects was evaluated using Mann-Whitney *U* test. To assess the differences in SCP width, MCP width, midbrain area, pons area, MRPI and M/P among groups the Kruskal-Wallis test was used, followed by an evaluation with the Mann-Whitney *U* test for pairwise comparisons. Resulting p values were corrected according to the Bonferroni method.

Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (L+) and negative likelihood ratio (LR-) respectively of manual and automated MRPI and M/P values were determined for differentiating probable and possible PSP patients from PD patients and healthy controls by using the optimal cut-off values determined with receiver operating characteristic (ROC) curve analysis. The optimal cut-off level was considered the value maximize the Younden index. Moreover, the classification performance and equivalency of automated and manual MRPI and M/P values were compared using the non-parametric methods developed by DeLong et al. [29].

Finally, to verify the agreement between the two raters and the intrarater reliability, the intraclass correlation coefficient was calculated.

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