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Short communication

The diagnostic accuracy of the hummingbird and morning glory sign in patients with neurodegenerative parkinsonism

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ABSTRACT

Introduction: The hummingbird sign and the morning glory flower sign, reflecting midbrain pathology on MRI, have previously been shown to separate patients with progressive supranuclear palsy (PSP) from those with Parkinson's disease (PD) and multiple system atrophy (MSA). The aim of the present study was to determine the diagnostic accuracy and reproducibility of visual assessment of midbrain atrophy patterns in a large cohort of patients with neurodegenerative parkinsonism.
Methods: Retrospective analysis of midbrain atrophy patterns on T1-weighted MRI in a large cohort of patients with neurodegenerative parkinsonism and healthy controls who underwent MR imaging during their diagnostic work-up.
Results: 481 patients with neurodegenerative parkinsonism and 79 healthy controls were included in the present study. The presence of the hummingbird sign had a specificity of 99.5% and a positive predictive value of 96.1% for a diagnosis of PSP while sensitivity was suboptimal with 51.6%. Similarly, the presence of the morning glory flower sign yielded a specificity of 97.7% for a diagnosis of PSP, but sensitivity was only 36.8%. Sensitivity of both signs was 35.3% in early, clinically unclassifiable parkinsonism. Visual assessment of these midbrain alterations showed excellent inter-rater agreement.
Conclusion: Midbrain atrophy patterns are useful in the differential diagnosis of neurodegenerative parkinsonism but both the hummingbird sign and more so the morning glory flower sign suffer from low sensitivity, especially in early disease stages.

1. Introduction

The early differential diagnosis of (neurodegenerative) parkinsonism is challenging at times [1] and several studies have suggested that the use of MRI can assist in the diagnostic process [2]. In particular, visual assessment of midbrain atrophy patterns including atrophy of the rostral midbrain tegmentum ("hummingbird sign") and the detection of a concavity of the lateral margin of the tegmentum ("morning glory sign") was previously reported to discriminate progressive supranuclear palsy (PSP) from patients with related parkinsonian disorders such as patients with Parkinson's (PD) or multiple system atrophy (MSA) in small-sized studies [2,9–11].

The main objective of the present study was to evaluate the diagnostic accuracy of the "hummingbird" and the "morning glory" sign in a large sample of patients with neurodegenerative parkinsonsim as well as healthy controls. Moreover, we determined inter-rater reliability of the visual assessment of these two imaging signs typical for PSP.

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2. Methods

2.1. Subjects

Patients with suspected neurodegenerative parkinsonism and healthy controls who underwent routine MRI at 1.5T were identified in the MRI database on movement disorders patients followed at our department from 2000 to 2011 (patients n = 396, healthy controls n = 58). Moreover, all patients and healthy controls recruited in a prospective, cross-sectional clinical study at the Department of Neurology, Innsbruck Medical University (Innsbruck, Austria) who received consecutively a 1.5T routine MRI between 2011 and 2013 according to the study protocol where included in this study (patients n = 85, healthy controls n = 21). All patients had at least two years of clinical follow-up and clinical diagnoses of PSP, MSA and PD were based on patients fulfilling current research diagnostic criteria at last follow-up [3–5] by movement disorder experts (K.S., G.K.W. and W.P.). Although novel diagnostic criteria for PSP were recently published [6], we decided to maintain previous criteria since (1) the study was finished before the new criteria were published and (2) the new criteria have not been validated thus far. Criteria for PSP [5] were modified in an attempt to incorporate recent criteria for PSP-P [7].

Patients who – at the time of MRI – were considered indeterminate by their treating neurologist were classified as clinically unclassifiable parkinsonism (CUP). Reasons for uncertainty were assessed by movement disorder specialists. For qualification as CUP, patients had to meet at least one of the following criteria: presence of two cardinal signs of parkinsonism if the patient presented without bradykinesia [8], parkinsonism of mild intensity, newly diagnosed untreated parkinsonian patients, or disease duration of less than 18 months. Moreover, they had to fulfil step two of the UK Parkinson's Disease Society Brain Bank Diagnostic Criteria [3].

3. Procedures

3.1. Magnetic resonance imaging protocol and image analysis

All subjects received high-resolution MRI on three different 1.5T Siemens (Erlangen, Germany) MR Scanner (Magnetom Vision until September 2003, n = 57; Magnetom Symphony from October 2003 until December 2005; n = 53; Magnetom Avanto, all other subjects from June 2004). All patients received either a sagittal T1-weighted 3D-MPRAGE sequence with a repetition time (TR) of 9.7 ms, an echo time (TE) of 4 ms, a slice thickness of 1.5 mm, a matrix of 256 × 256, and a field of view of 230 mm (until September 2003) or a coronal T1-weighted 3D-MPRAGE sequence with a TR of 1600 ms, a TE of 3.44 ms, a slice thickness of 1.2 mm, a matrix of 256 × 224 pixels, and a field of view of 220 × 192 mm (from October 2003). Moreover, all patients received a routine MRI protocol, which besides the T1-weighted MPRAGE 3D sequence comprised a transversal double-echo fast spin echo sequence with T2 and proton density contrast. These sequences were visually assessed by experienced neuroradiologists (MS, RE) to exclude symptomatic parkinsonism. At least two independent experienced raters (KS and either AH or MS) then visually assessed the “hummingbird” and the “morning glory” signs in all patients in a blinded fashion. Discordant ratings were discussed to resolve them and the consensus rating was used for determining the diagnostic utility of the imaging sign. In addition, two junior raters (CM and BH) were trained for the visual assessment of the “hummingbird” and the “morning glory” signs and were asked to provide a consensus rating for each patient blinded to the clinical diagnosis.

Visual assessment criteria of the hummingbird sign and the morning glory sign were applied as described previously [9,10]. Midbrain tegmental atrophy without pontine atrophy associated with widening of interpeduncular cistern (findings reminiscent of the head and the body of a hummingbird) on midsagittal T1-weighted MRI of the brain were required to be present to qualify for a hummingbird shape MRI abnormality the MRI as hummingbird sign positive abnormality [9]. The morning glory flower sing was assessed on axial T1-weighted MRI parallel to both the nasion-pontomedullary line and the anterior commissure - posterior commissure (AC-PC) line [11] and an increased lateral concavity of the midbrain tegmentum was required [10].

3.2. Statistical analysis

Parametric, non-parametric tests or the chi-square test were used for group comparisons depending on the scale type of the variables. Multiple comparisons were corrected using post-hoc Bonferroni correction, where applicable. Interrater reliabilities were assessed between the experienced raters, between the junior raters and between the consensus of the experienced raters and the junior raters. Interrater agreement was determined by Cohen's kappa statistics. Kappa values were interpreted as follows according to recommendations published previously: 0 to 0.20 = slight or no agreement; 0.21 to 0.40 = fair agreement; 0.41 to 0.60 = moderate agreement; 0.61 to 0.80 = substantial agreement; and 0.81 to 1.00 = excellent agreement [12]. Statistical analysis was performed with SPSS 22.0 for Windows (SPSS, Chicago, IL).

4. Results

4.1. Patient characteristics

In total 550 participants were included in this study (289 patients with PD, 85 patients with progressive supranuclear palsy, 97 patients with MSA as well as 79 healthy controls, Fig. 1A). All patients presented with parkinsonsism. MSA patients were significantly younger than PSP patients, PD patients and HC (MSA vs. PSP p = <0.001, MSA vs. PD p = 0.019, MSA vs. HC p = 0.011). Unsurprisingly, disease duration was significantly longer in PD patients than in patients with PSP and MSA (PD vs. PSP p < 0.001, PD vs. MSA p < 0.001). There was no difference in disease duration between atypical parkinsonian disorders (p = 1.000). Despite the longer disease duration, PD patients were less severely affected (p < 0.001, Table 1). In the CUP cohort, there was no difference in disease duration, gender distribution and age (Table 1).

4.2. Diagnostic yield of visual assessment of the midbrain

47 out of 85 PSP patients (55.3%) had a hummingbird sign, whereas only 2 out of 289 PD patients (i.e. 0.7%) featured this particular atrophy pattern and it was not seen in any MSA or HC subject. These numbers yield a high specificity, but suboptimal sensitivity (Fig. 1b). In PSP patients, the presence of the hummingbird sign was directly correlated with disease severity as measured by Hoehn & Yahr staging (Pearson's correlation coefficient = 0.32, p = 0.006).

The morning glory sign was detected in 32 out of 85 patients with PSP (i.e. 37.7%) but was also seen in 9 patients with non-PSP-parkinsonism (PD n = 5, MSA n = 4) while none of the healthy controls showed this abnormality. The specificity of this concavity of the lateral margin of the tegmentum was similar to the hummingbird sign, but sensitivity for PSP was low (Fig. 1b).

Both, the hummingbird (PSP-RS n = 38, 63%; PSP-P n = 9, 36%; p = 0.021) and the morning glory (PSP-RS n = 25, 42%; PSP-P n = 7, 28%; p = 0.236) signs were more common in PSP-RS compared to PSP-P, although the difference was significant only for the

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