Parkinsonism and Related Disorders xxx (2016) 1–5

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Highly specific radiographic marker predates clinical diagnosis in progressive supranuclear palsy

Emily Owens [a, *], Karl Krecke [b], J.E. Ahlskog [a], Robert Fealey [a], Anhar Hassan [a], Keith A. Josephs [a], Bryan Klassen [a], Joseph Matsumoto [a], James Bower [a]

[a] Mayo Clinic Department of Neurology, 200 Second St. SW, Rochester, MN 55905, USA
[b] Mayo Clinic Department of Neuroradiology, 200 Second St. SW, Rochester, MN 55905, USA

ARTICLE INFO

Article history:
Received 1 February 2016
Received in revised form
5 April 2016
Accepted 2 May 2016

Keywords:
Progressive supranuclear palsy
Imaging
MRI

ABSTRACT

Introduction: The diagnosis of progressive supranuclear palsy is often challenging early in the course of the disease, when clinical signs of the condition may be less apparent and patients do not clearly meet diagnostic criteria. In this study, we examine a potential radiographic marker in progressive supranuclear palsy, and assess the timing of its presence in relation to diagnosis.

Methods: A retrospective review of patients fulfilling clinical research criteria for multiple system atrophy, Parkinson's disease, and progressive supranuclear palsy (total n = 75) was performed. Midbrain and pontine diameters, and the midbrain to pons ratio were calculated by a neuroradiologist blinded to the clinical diagnosis. The timing of the presence of a midbrain to pons ratio of less than or equal to 0.52 was assessed in the progressive supranuclear palsy group in reference to the time of diagnosis.

Results: The midbrain to pons ratio was significantly reduced in the progressive supranuclear palsy cohort ($p < 0.0001$), and a midbrain to pons ratio of less than or equal to 0.52 was 100% specific for progressive supranuclear palsy. This radiologic sign predated the clinical diagnosis of progressive supranuclear palsy by a mean of 15 months (range 1–47 months) in 14 of 17 (82%) of patients in whom it was found.

Conclusions: The midbrain to pons ratio is an easily applied and highly specific tool in the diagnosis of progressive supranuclear palsy, and is frequently present before the diagnosis is made.

1. Introduction

The diagnosis of progressive supranuclear palsy (PSP) is often challenging, particularly early in the course of the disease, when clinical signs of the condition may be less apparent. Numerous radiographic markers of the condition have been investigated. Some of these have included various measurements related to the midbrain, pons, and/or cerebellar peduncles, such as the midsagittal midbrain area, midbrain to pons area ratio, pontine to midbrain area ratio, and various middle cerebellar and superior cerebellar measurements and ratios, including the MR parkinsonism index [1–8]. Other imaging modalities have also been investigated, such as FDG-PET, SPECT, MRS, diffusion-weighted imaging, diffusion tensor imaging, optical coherence tomography, and tau imaging [3,9,10,11]. However, many of these findings are not present until later in the course of the syndrome, when the diagnosis may already be observable clinically, or have not been investigated in relationship to the timing of diagnosis. Furthermore, many are restricted to the research setting and are difficult to practically apply in the clinical setting.

Massey and colleagues [1] investigated the midbrain to pons ratio (calculated as shown in Fig. 1) in a clinical and pathologically confirmed cohort of PSP, multiple system atrophy (MSA), and Parkinson's disease (PD). Using receiver operating characteristic curve analysis, a midbrain to pons ratio of less than 0.52 was found to be 100% specific for PSP in both groups. The potential usefulness of this tool was further suggested in an additional small pathological cohort, which also found the midbrain to pons ratio to be a specific finding in PSP [12]. Our study assessed the midbrain to pons ratio

* Corresponding author.
E-mail addresses: owens.emily@mayo.edu (E. Owens), kkrecke@mayo.edu (K. Krecke), eahlskog@mayo.edu (J.E. Ahlskog), rfealey@mayo.edu (R. Fealey), hassan.anhar@mayo.edu (A. Hassan), josephs.keith@mayo.edu (K.A. Josephs), klassen.bryan@mayo.edu (B. Klassen), jmatsumoto@mayo.edu (J. Matsumoto), bower.james@mayo.edu (J. Bower).

http://dx.doi.org/10.1016/j.parkreldis.2016.05.006
1353-8020/

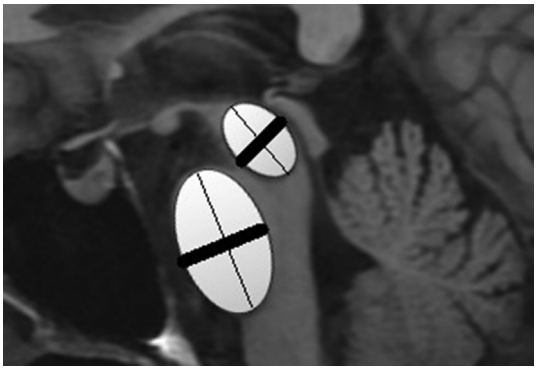

Fig. 1. Process by which the midbrain to pons ratio is calculated. An ellipse is placed over the pons and midbrain tegmentum on midsagittal imaging. A line is then drawn to define the major axes of the ellipses (thin lines). The maximal measurement perpendicular to the major axis is taken (thick lines), from which the midbrain to pons ratio is then derived.

(MTPR) in a clinical cohort evaluated in the Movement Disorders clinic at Mayo Clinic, Rochester. We additionally determined the timing of the presence of a MTPR of less than or equal to 0.52 in relation to the time of diagnosis of PSP, as diagnosed by the clinician, to assess whether the radiographic finding may predate the clinical diagnosis and potentially be used as an addition to the diagnostic criteria.

2. Methods

2.1. Subjects

The study was approved by the Mayo Clinic Institutional Review Board. A retrospective review of clinical records was performed for patients with a clinical diagnosis of PSP, MSA, PD, or parkinsonism, as diagnosed by a movement disorders neurologist at the Mayo Clinic, Rochester. Patients who were evaluated between June 2012 to November 2013 were reviewed for inclusion in consecutive order, to obtain a total of 75 patients who met inclusion criteria in each of the PSP (n = 25), MSA (n = 25), and PD (n = 25) groups.

For the PSP group, patients were included who met the NINDS-SPSP clinical research criteria for probable PSP, with a gradually progressive disorder beginning at age 40 or later, falls during the first year of onset, vertical supranuclear gaze palsy, prominent postural instability, and no other disease to account for the findings [13]. MSA patients included met probable criteria as described by the 2nd consensus conference, with autonomic failure with urinary incontinence and erectile dysfunction in males, or orthostatic hypotension, and parkinsonism poorly responsive to levodopa, or a cerebellar syndrome with gait ataxia and cerebellar dysarthria, limb ataxia, or oculomotor dysfunction of the cerebellar type [14]. Patients were included in the Parkinson's disease group who had parkinsonism (two of resting tremor, bradykinesia, rigidity, and impaired postural reflexes), no prominent or early evidence of more diffuse involvement of the nervous system, and no other apparent cause [15]. In addition, patients in this group were excluded from the study if they did not have Parkinson's disease for at least 5 years, as to maximize the certainty that they did not later evolve to another condition. All patients included had undergone an MRI of the brain with midsagittal images after symptom onset.

2.2. Data collection and analysis

Clinical records were reviewed by a neurologist. Gender, date of symptom onset and presenting symptoms, date at which patients were diagnosed with parkinsonism, date of final clinical diagnosis, date of MRI, and disease duration at MRI were recorded. A neuroradiologist blinded to the clinical diagnosis ascertained midbrain and pons diameters from midsagittal images as shown in Fig. 1, using the methodology previously described by Massey and colleagues [1]. All of the calculations were obtained from 1.5T or 3T T1-weighted images that were determined to be of good diagnostic quality. Measurements were obtained on an Advantage Workstation (GE Healthcare), and the MTPR was calculated. Using a MTPR cutoff of 0.52 for the PSP group, sensitivity, specificity, and negative and positive predictive values were calculated, and further analysis was performed with Wilcoxon/Kruskal-Wallis and Chi-square statistical analysis.

3. Results

3.1. Patient characteristics and findings

Presenting symptoms and group characteristics are shown in Tables 1 and 2, respectively. Boxplots summarizing results from midbrain and pons diameter, and MTPR are shown in Fig. 2.

3.1.1. Midbrain diameter

Mean midbrain diameter in mm was 9.1 (median 9.0, range 7.3–12.3), 11.4 (median 11.4, range 9.0–13.1), and 11.7 (median 11.8, range 9.9–13.5) in the PSP, MSA, and PD groups, respectively, and was significantly smaller in the PSP group ($p < 0.0001$). A midbrain diameter of less than 9 mm was 100% specific and 44% sensitive for PSP.

3.1.2. Pons diameter

Mean pons diameter was 17.3 (median 17.2, range 14.3–20.4), 16.0 (median 16.0, range 7.5–20.9), and 17.3 (median 17.1, range 15.0–19.9) in the PSP, MSA, and PD groups. It was significantly smaller in the MSA group ($p < 0.0193$). A pons diameter of 14.2 or less was 100% specific though only 8% sensitive for MSA.

3.1.3. Midbrain to pons ratio

Mean MTPR was 0.52 (median 0.51, range 0.41–0.69) in PSP, 0.73 (median 0.70, range 0.54–1.5) in MSA, and 0.67 (median 0.67, range 0.58–0.82) in PD. The MTPR was significantly reduced in the PSP group ($p < 0.0001$). There was no significant difference in ratio between the MSA and PD groups. A MTPR of less than or equal to 0.52 was 100% specific and 68% sensitive for PSP, with positive and negative predictive values of 100% and 86%, respectively. Additionally, a MTPR of less than or equal to 0.52 predated the clinical diagnosis in PSP by 1 month or more in 82% (14 of 17) of patients in whom it was found, by a mean of 15 months (range 1–47 months).

Of the 17 patients with the MTPR less than or equal to 0.52, in only 3 patients was the diagnosis of PSP the leading diagnosis at the time of MRI; in 8 patients it was not suspected or not the leading diagnosis at time of MRI; in 6 patients data regarding clinical

Table 1
Group presenting symptoms.

Presenting symptom(s)	PSP	MSA	PD
Gait, imbalance, and/or falls	19	10	8
Speech	2	0	0
Cognition	2	0	0
Coordination/dexterity, bradykinesia, and/or rigidity	3	3	5
Autonomic	0	10	0
Visual	2	0	0
Tremor	0	2	11
Antecollis	0	1	0

Please cite this article in press as: E. Owens, et al., Highly specific radiographic marker predates clinical diagnosis in progressive supranuclear palsy, Parkinsonism and Related Disorders (2016), http://dx.doi.org/10.1016/j.parkreldis.2016.05.006