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Midbrain atrophy is not a biomarker of PSP pathology

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Abstract

Background—Midbrain atrophy is a characteristic feature of progressive supranuclear palsy (PSP), although it is unclear whether it is associated with the PSP syndrome (PSPS) or PSP pathology. We aimed to determine whether midbrain atrophy is a useful biomarker of PSP pathology, or whether it is only associated with typical PSPS.

Methods—We identified all autopsy-confirmed subjects with the PSP clinical phenotype (i.e. PSPS) or PSP pathology and a volumetric MRI. Of 24 subjects with PSP pathology, 11 had a clinical diagnosis of PSPS (PSP-PSPS), and 13 had a non-PSPS clinical diagnosis (PSP-other). Three subjects had PSPS and corticobasal degeneration pathology (CBD-PSPS). Healthy control and disease control groups (i.e. a group without PSPS or PSP pathology) and a group with CBD pathology and corticobasal syndrome (CBD-CBS) were selected. Midbrain area was measured in all subjects.

Results—Midbrain area was reduced in each group with clinical PSPS (with and without PSP pathology). The group with PSP pathology and non-PSPS clinical syndromes did not show reduced midbrain area. Midbrain area was smaller in the subjects with PSPS compared to those without PSPS ($p < 0.0001$), with an area under the receiver-operator-curve of 0.99 (0.88, 0.99). A midbrain area cut-point of 92 mm² provided optimum sensitivity (93%) and specificity (89%) for differentiation.

Conclusion—Midbrain atrophy is associated with the clinical presentation of PSPS, but not with the pathological diagnosis of PSP in the absence of the PSPS clinical syndrome. This finding has important implications for the utility of midbrain measurements as diagnostic biomarkers for PSP pathology.

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DISCLOSURES

The authors report no disclosures.

Keywords

Progressive supranuclear palsy; tau; neuropathology; MRI; midbrain

INTRODUCTION

Progressive supranuclear palsy (PSP) is a pathological disorder defined by deposition of the microtubule associated protein tau characterizing astrocytic pathology and globose neurofibrillary tangles [1, 2]. The majority of PSP cases present with typical features of vertical supranuclear palsy, postural instability with falls, and symmetric parkinsonism [3]; referred to as the progressive supranuclear palsy syndrome, or PSPS (also known as Richardson's syndrome). However, atypical clinical syndromes can also be associated with PSP pathology, such as corticobasal syndrome, frontotemporal dementia, primary progressive aphasia and primary progressive apraxia of speech, and patients with PSPS can have non-PSP pathologies [4–8]. Given this clinicopathological heterogeneity, biomarkers are needed to help predict the presence of PSP pathology. Atrophy of the midbrain is the most recognized anatomical characteristic of PSPS [9–12]. However, few studies have assessed midbrain atrophy in autopsy confirmed cases and it is therefore unknown whether midbrain atrophy is a useful biomarker of PSP pathology. We aimed to determine whether midbrain atrophy is a useful biomarker of PSP pathology, or whether it is simply associated with the PSPS clinical syndrome.

METHODS

Subject selection

We used the Mayo Clinic neuropathological database to identify autopsy-confirmed subjects with either PSPS [3] or PSP pathology [2] that had undergone a volumetric MRI at Mayo Clinic, Rochester, MN. All subjects had seen a movement disorders specialist or a behavioral neurologist from the Department of Neurology during life and undergone a standard pathological examination, as previously described [13].

Twenty-four subjects were identified with PSP pathology. Of these, 11 had been given a diagnosis of PSPS according to clinical criteria [3] at the time of scan (PSP-PSPS), and 13 had been given a non-PSPS clinical diagnosis (PSP-other). Three subjects diagnosed with PSPS [3] that had non-PSP pathology, namely corticobasal degeneration (CBD-PSPS), were identified. Three control groups were also identified. Firstly, the PSP-other group was matched by age at MRI, gender and clinical diagnosis to 13 cases that had non-PSP pathology. This group will be referred to as “disease controls” (i.e. a group with a neurodegenerative disease but without PSPS or PSP pathology) and was selected to control for any midbrain atrophy that occurred in these syndromes with disease progression, regardless of pathology. Second, in order to provide a comparison group for the CBD-PSPS cases, we identified six cases that had CBD pathology and fulfilled clinical criteria for corticobasal syndrome [14] (CBD-CBS). Lastly, we selected a group of 13 healthy control subjects that had the same age range, and gender ratio, as the disease subjects.

Medical records of all cases without a clinical diagnosis of PSPS were re-reviewed by an expert in both Behavioral Neurology and Movement Disorders (KAJ) to assess for the presence of clinical features of PSPS at the time of MRI, including vertical supranuclear palsy, postural instability and falls within the first year of disease onset. This study was approved by the Mayo IRB. All subjects provided written informed consent.

Imaging analysis

All subjects in the study had a T1-weighted spoiled gradient echo volumetric MRI performed at 1.5T (22×16.5cm or 24×18.5cm FOV, 25° flip angle, 124 contiguous 1.6mm thick coronal slices). All scans were pre-processed to correct for intensity inhomogeneity [15] and gradient warping [16], were registered to a customized template using SPM5 to spatially align anatomy and were resampled to 1×1×1mm. The customized template was created using 400 independent subjects (200 cognitively normal and 200 with dementia). Each of the 400 scans was normalized to the Montreal Neurological Institute (MNI) template using SPM5, and all 400 were averaged to create the template. Area of the midbrain was measured manually by one rater (JLW) using Analyze software (Biomedical Imaging Resource, Mayo Clinic, Rochester, MN), based on previously published criteria [9]. Measurements were performed on the mid-sagittal image with the inferior boundary defined by a line parallel to the conjunction between the genu and splenium of the corpus callosum. All measurements were performed blinded to clinical information. Excellent intra-rater reproducibility has previously been demonstrated [17].

Statistical analysis

Group comparisons were performed using Kruskal-Wallis and Mann-Whitney U tests for continuous data and chi-squared tests with p-values based on Monte Carlo simulation for categorical data, using R statistical software environment version 2.14.2 (R Foundation for Statistical Computing, Vienna, Austria). Because of the clear correlation between midbrain area and age in healthy controls ($r=-0.75$), we calculated age-adjusted midbrain areas using residuals from a linear regression model (i.e. $y = a + b(\text{age})$) based on the data for 13 healthy controls ($\text{Area} = 377.0 - 3.468(\text{Age})$). Age-adjusted midbrain area was calculated by subtracting predicted area from observed area. Group differentiation was assessed using area under the receiver operator characteristic curve analysis. Two-factor ANOVA was performed across all subjects to simultaneously examine the relationship between adjusted midbrain area versus PSPS (factor 1; 0 = No, 1 = Yes) and PSP pathology (factor 2; 0 = No, 1 = Yes).

RESULTS

Clinical features of PSPS were identified in four PSP-other subjects. These four subjects met clinical criteria for both corticobasal syndrome [14] and PSPS [3]; hence, they will be referred to as “PSP-Hybrid” [18] and were analyzed separately from the PSP-other subjects. None of the other PSP-other, CBD-CBS or disease control subjects displayed specific clinical features of PSPS. Subject demographics are shown in Table 1.

Adjusted and unadjusted area of the midbrain differed significantly across groups (Table 1 and Figure 1). The PSP-PSPS, CBD-PSPS and PSP-Hybrid groups showed smaller midbrain areas than the healthy control, disease control, CBD-CBS and PSP-other groups. Midbrain area in the PSP-other group did not differ from healthy controls, disease controls or CBD-CBS. A representative midbrain from each group is shown in Figure 2.

Midbrain area was significantly different between all subjects with PSPS (including PSP-Hybrid) versus all those without PSPS (excluding healthy controls) ($p<0.001$ with and without age adjustment). The area under the receiver operator curve for differentiating these groups was 0.99 (0.88, 0.99), with an optimum midbrain area cut-point of 92 mm² (sensitivity=93%, specificity=89%). The presence/absence of PSPS accounted for a large proportion of the variability in midbrain area ($R^2=0.647$), with the presence/absence of PSP pathology not improving the model ($R^2=0.648$ when pathology included). A model with PSP pathology only provided an R^2 of 0.183 and adding PSPS increased this to 0.648.

DISCUSSION

This study demonstrates that midbrain atrophy is associated with the clinical presentation of PSPS, but not with a pathological diagnosis of PSP in the absence of PSPS. This finding has important implications for the utility of midbrain measurements as a biomarker for PSP pathology.

Midbrain areas were reduced in all 18 subjects that had PSPS, including the PSP-PSPS, PSP-Hybrid, and even the PSPS subjects with CBD pathology. Hence, midbrain atrophy is strongly associated with PSPS regardless of underlying pathology and whether the syndrome co-exists with corticobasal syndrome. Conversely, midbrain area was not reduced in the PSP subjects that presented with atypical clinical syndromes. The implication of these findings is that midbrain atrophy is a useful biomarker of the presence of PSPS, but not necessarily the presence of PSP pathology. It also implies that a lack of midbrain atrophy in a patient with a non-PSPS clinical syndrome does not rule out a pathological diagnosis of PSP.

There is a large degree of clinical and pathological overlap between CBD and PSP, whereby both diseases can present with corticobasal syndrome or PSPS [5, 19]. Although our study is limited by small patient numbers, we included patients representing all aspects of this spectrum, including PSP-PSPS, CBD-PSPS, CBD-CBS, and patients with PSP-CBS that were included in the PSP-other group. We also included a group of patients with PSP pathology that presented with clinical features of both corticobasal syndrome and PSPS (i.e. PSP-Hybrid). Within this spectrum, midbrain atrophy was only observed in the patients with a PSPS clinical syndrome, and not in those with only corticobasal syndrome, regardless of the presence of PSP pathology. This data suggests that midbrain atrophy may not be a useful biomarker of PSP pathology in patients with pure corticobasal syndrome, i.e. patients with corticobasal syndrome without clinical features of the PSPS.

The majority of previous studies have utilized clinical cohorts and similarly found that a high proportion, often 100%, of PSPS patients have midbrain atrophy [12]. Midbrain atrophy was also observed in 100% of patients with PSP-PSPS, and was absent in the one case with PSP without PSPS, in one autopsy study [20]. Another study assessed 22 patients with autopsy confirmed PSP and found that 86% showed evidence of midbrain atrophy on visual assessment, and only 73% of cases would have been diagnosed as PSP by a radiologist, supporting our findings that midbrain atrophy is not associated with all pathological cases of PSP [21]. Few studies have reported imaging findings in PSPS cases with non-PSP pathology, or in PSP-other cases. One autopsy study found that brainstem tau burden was higher in CBD-PSPS cases than corticobasal syndrome cases with CBD; concurring with our findings that brainstem involvement is associated with PSPS [22]. Another study did report midbrain atrophy on MRI in five PSP-other cases; however, these cases had some clinical features of PSPS and may therefore have been Hybrid cases at the time of MRI [23].

These findings are important for patient diagnosis. Midbrain atrophy is useful to support a clinical diagnosis of PSPS, but does not provide any predictive information concerning the presence of PSP pathology in patients that present with atypical syndromes. A midbrain area of less than 92mm² is particularly useful to predict PSPS. Time from onset to scan was three years or greater in all of our patients, and so the predictive ability of midbrain atrophy early in the disease course will need to be the focus of future study. Nevertheless, midbrain atrophy in patients with non-PSPS clinical diagnoses could hint towards the presence of, or perhaps future development of, PSPS symptoms. We have, for example, observed subtle midbrain atrophy in patients with primary progressive apraxia of speech [24] who later develop features of PSPS. The lack of value in predicting PSP pathology in these atypical

syndromes means that further work is needed to identify potential biomarkers of PSP pathology.

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A. **B.** **Figure 1.**

Box-plots showing age-adjusted midbrain area data as described in the methods. Data are shown for all six subject groups (Panel A) and for those subjects with the PSP syndrome only (CBD-PSPS), PSP pathology only (PSP-other), both the syndrome and pathology (PSP-Hybrid + PSP-PSPS) or neither the syndrome or pathology (healthy controls, disease controls, CBD-CBS) (Panel B). A value of zero corresponds to the subject having a midbrain area equal to what would be predicted given their age. Values below zero indicate midbrain areas smaller than what would be predicted given their age. Boxes represent 25%, median and 75 percentile, dashes represent mean, and individual subject points are shown.

Figure 2.

Representative midbrains from each subject group. Age at MRI and gender for each subject is shown.

M = male; F = female

TABLE 1

Subject demographics, clinical, pathological and imaging features

	Healthy controls (n=13)	Disease controls (n=13)	CBD-CBS (n=6)	PSP-other (n=9)	PSP-Hybrid (n=4)	PSP-PSPS (n=11)	CBD-PSPS (n=3)	P
Female gender, %	6 (46%)	6 (46%)	6 (100%)	5 (56%)	1 (25%)	5 (45%)	2 (67%)	0.29
Education	16 (12–18)	16 (8–18)	12 (8–14)	12 (10–18)	14 (10–18)	14 (12–18)	16 (12–20)	0.33
Age at onset, yrs	NA	62 (53–74)	66 (61–72)	69 (53–79)	61 (52–67)	59 (48–67)	53 (40–63)	0.11
Age at MRI, yrs	68 (55–82)	64 (57–81)	70 (66–75)	71 (55–81)	64 (59–70)	63 (54–71)	56 (46–67)	0.15
Age at death, yrs	NA	71 (61–83)	72 (67–80)	78 (61–83)	68 (59–73)	64 (55–72) [‡]	57 (47–67) [‡]	0.04
Onset-MRI, yrs	NA	4.0 (0–7)	3.5 (3–6)	3.0 (2–6)	3.5 (1–7)	4.0 (2–8)	4.0 (3–6)	0.89
Disease duration, yrs	NA	7 (3–13)	6 (5–8)	7 (4–10)	7 (5–8)	6 (3–8)	4.0 (4–7)	0.18
MMSE (/30)	29 (25–30)	23 (9–29) [‡]	16 (14–23) [‡]	28 (21–30) [‡]	28 (25–28) [‡]	25 (20–30) [‡]	24 (21–27)	0.007
Midbrain area, mm ²	142 (90–212)	120 (89–193)	115 (87–166)	114 (92–158)	81 (75–83) [‡]	75 (44–102) [‡]	70 (69–73) [‡]	<0.001
Age-adjusted midbrain area, mm ²	–3 (–29, 60)	–15 (–67, 22)	–22 (–37, 25)	–4 (–61, 23)	–74 (–97, –54) [‡]	–84 (–141, –46) [‡]	–113 (–148, –72) [‡]	<0.001
Clinical diagnoses, number (%)								
PSPS	NA	0	0	0	4 (100%) [‡]	11 (100%)	3 (100%)	<0.001
CBS	NA	6 (46%)	6 (100%)	2 (22%)	4 (100%) [‡]	0	0	
agPPA	NA	4 (31%)	0	4 (44%)	0	0	0	
bvFTD	NA	3 (23%)	0	3 (33%)	0	0	0	
Pathological diagnoses, number (%)								
PSP	NA	0	0	9 (100%)	4 (100%)	11 (100%)	0	<0.001
CBD	NA	3 (23%)	6 (100%)	0	0	0	3 (100%)	
FTLD-TDP type A	NA	4 (31%)	0	0	0	0	0	
PiD	NA	3 (23%)	0	0	0	0	0	
AD	NA	3 (23%)	0	0	0	0	0	

Data shown as median (range) unless stated.

[‡]Significantly different from disease controls at p<0.05

[‡]Significantly different from healthy controls at p<0.05

[§]Significantly different from CBD-CBS at $p < 0.05$

^{*}Significantly different from PSP-other at $p < 0.05$

[¶]These four subjects are shown in both rows because they displayed clinical features of both CBS and PSPS

Pair-wise group differences are not indicated due to limited power and implicit systematic differences

MMSE = Mini-Mental State Examination; PSPS = Progressive supranuclear palsy syndrome; CBS = corticobasal syndrome; agPPA = agrammatic variant of primary progressive aphasia; bvFTD = behavioral variant of frontotemporal dementia; CBD = corticobasal degeneration; FTLD-TDP = frontotemporal lobar degeneration with TDP-43 immunoreactive inclusions; PID = Pick's disease