Midbrain area and the hummingbird sign from brain MRI in progressive supranuclear palsy and idiopathic normal pressure hydrocephalus

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ABSTRACT
Background and Purpose: The main radiological finding in progressive supranuclear palsy (PSP) is reduced midbrain volume. Both qualitative (e.g., hummingbird sign) and quantitative (e.g., area measurements) markers have been noted. Recent studies have shown a similar reduction also in idiopathic normal pressure hydrocephalus (iNPH). The purpose was to investigate the reliability and accuracy of these markers in discriminating PSP from iNPH and controls.

Methods: Eight neuroradiologists viewed sagittal MR images of the midbrain from 104 subjects: 26 PSP patients, 40 iNPH patients, and 38 healthy controls. They visually assessed whether the hummingbird sign was present or not, grading their confidence from 1 to 5. Assessments were translated into a score between +5 and −5: from maximum confidence of presence to maximum confidence of absence. A positive median score was considered to indicate hummingbird sign. Sagittal midbrain area was manually measured in each subject.

Results: Seventy-seven percent of PSP patients, 65% of iNPH, and 3% of controls were visually assessed as having the hummingbird sign. Manually measured midbrain area also showed overlap between PSP and iNPH. Regarding discrimination of PSP patients, midbrain area measurements, using a cutoff of 90 mm², yielded a higher area under the curve (AUC = 0.86) than visual assessment scores (AUC = 0.83), and higher reliability.

Conclusions: Measuring sagittal midbrain area is more accurate and reliable than visual assessment. Due to significant overlap in appearance, a midbrain with a hummingbird sign or reduced sagittal area should raise the suspicion of PSP only after other signs of iNPH have been considered.

KEYWORDS
area measurement, idiopathic normal pressure hydrocephalus, midbrain, neurodegeneration, progressive supranuclear palsy, visual assessment
INTRODUCTION

Progressive supranuclear palsy (PSP) is a primary tauopathy that causes an atypical parkinsonian syndrome with neurodegenerative properties. Several clinical phenotypes have been identified with typical symptoms, including ocular motor dysfunctions and postural instability. The prevalence of PSP is 5.8–6.5 per 100,000, with an average of 7 years between symptom onset and death. Midbrain degeneration is a cardinal feature of PSP and midbrain atrophy is a common and well-known finding on magnetic resonance imaging (MRI) scans. In a sagittal midline view, the thinned-out midbrain has been described as resembling a hummingbird or penguin often being referred to as the hummingbird sign (a.k.a. penguin silhouette sign). Other visual signs of midbrain atrophy have been proposed, such as the Mickey Mouse sign and the morning glory sign, but these have not been widely popularized.

Though the hummingbird sign is widely used to strengthen the suspicion of PSP, it is a subjective marker and there is no recognized consensus on cutoff values or mandatory features for the hummingbird sign. Radiological differentiation between PSP, Parkinson’s disease, and multiple-system atrophy of the Parkinson type has been shown to be possible through the use of the hummingbird sign. Successful differentiation has also been shown using area measurements of the midbrain and the more advanced (and time-consuming) Magnetic Resonance Parkinsonian Index (MRPI).

Several of the aforementioned studies have focused on midbrain morphology in PSP as compared to other parkinsonian syndromes, but comparison to non-parkinsonian diseases with motor symptoms is scarce. Idiopathic normal pressure hydrocephalus (iNPH) can be a potential differential diagnosis when considering PSP. Common symptoms in both diseases include repeated falls, cognitive decline, and gait disturbance. However, iNPH is much more common than PSP, with a reported prevalence up to 5.9% in those 80 years or older. One of many morphological features in iNPH is affected midbrain morphology, caused either by abnormal flow of cerebrospinal fluid between the third and fourth ventricles or by actual atrophy. In a midsagittal image, the appearance of the midbrain may be visually similar to that of a PSP patient, with a diminished midbrain and an unaffected pons.

METHODS

Subjects

The subjects for this study were gathered from three groups: patients diagnosed with PSP (n = 26, 62% male), patients diagnosed with iNPH who improved after shunt surgery (n = 40, 50% male), and controls in the form of healthy elderly (n = 38, 47% male). The median age was 74 years for the PSP group (range 62–84), 70.5 years for the iNPH group (range 56–86), and 68 years for the control group (range 56–85). The clinical diagnosis for each patient was confirmed retrospectively through medical chart review performed by two neurologists (JV and DN), in accordance with published criteria.

The iNPH patients had been included in previous studies of iNPH imaging findings, with other aims than the present study. All patients were diagnosed at Uppsala University Hospital. Response to shunt surgery in iNPH patients was defined as a >5 point improvement in a modified iNPH scale (neuropsychological tests not included) 12 months after surgery, as previously described. Controls were included via a separate project.

Clinical examination and cognitive tests (including Mini-Mental State Examination, trail making test, and 7-minute test) showed no signs of neurodegenerative disease. All patients and controls had been investigated through an MRI of the brain. Assessments were made primarily on sagittally acquired 3D T1-weighted gradient echo images with 1 × 1 × 1 mm voxel size, but in cases with motion artifacts, supportive assessments were made on sagittally acquired 3D fluid-attenuated inversion recovery images with 1 × 1 × 1 mm voxel size instead.

Regarding the PSP and iNPH patients, ethical approval was granted by the Swedish Ethical Review Authority for the purpose of retrospective analysis in differential diagnostics studies (Dnr 2015-1742-4). Regarding the healthy controls, informed consent was given at inclusion to their original project, which also allowed for differential diagnostics studies (Dnr 2010–161).

Visual assessment

Eight neuroradiologists with differing amounts of experience (2–20 years), working at different hospitals in Sweden, visually assessed MR images as described below. Sagittal images from midsagittal sections were cropped to minimize nonmesencephalic clues to diagnosis (such as elevated corpus callosum). Thus, it was not possible to detect radiological signs of iNPH on the presented images, other than an enlarged third ventricle. This was done to ensure a completely unbiased assessment of the midbrain. The readers were asked to assess only presence or absence of the hummingbird sign, and were not informed about the purpose of the study or that subjects with iNPH were included in the material. The images were shown in a random order through a web-based questionnaire that started with a short explanation of both the project and the hummingbird sign. Two brief descriptions of the hummingbird sign were shown to all readers, to ensure a similar baseline understanding of the concept.
For each image/subject, there were two questions: Can you identify the hummingbird sign (YES/NO) and How sure are you of your answer (5/VERY SURE, 4, 3, 2, 1/NOT SURE AT ALL).

There was no time restriction for the readers to fill out the form, and it could be filled out during several sessions if needed. Individual answers were converted from two numerical scales, Yes (5,4,3,2,1) and No (5,4,3,2,1), to a joint numerical scale: Yes/No (5,4,3,2,1,−1,−2,−3,−4,−5). The median visual assessment score from the eight readers was calculated for each subject and is henceforth referred to as the visual assessment score. A positive visual assessment score was considered to indicate presence of the hummingbird sign.

**Area measurements**

In all subjects, area measurements of the midbrain were carried out directly in the picture archiving and communication system. Using a straight midsagittal section, a line was defined, starting from the inferior edge of the tectum and ending on the corner of the interpeduncular cistern in the superior notch of the pons. From there, the silhouette that outlined the midbrain was drawn with a freehand tool that measured the encircled area in mm². Where the midbrain narrows off toward the mamillary body, the line crossed the “beak,” where the two sides are parallel to each other, and was drawn back along the silhouette to the first line. The procedure was performed as described in existing literature.5,8,26 All area measurements were performed twice and averaged for each image. If the results differed by more than 10%, the procedure was repeated to get a more consistent average.

**Statistics**

Assessment scores and area measurements are presented in median values and interquartile range (IQR). Differences between groups were tested with the Mann–Whitney U-test. Correlations were analyzed with Spearman’s correlation coefficient. Interrater reliability of the eight readers for the visual assessment score was tested with Kendall’s coefficient of concordance using data from all patients. Interrater reliability for two readers of midbrain area measurements was tested in 30 subjects (10 from each group) using intraclass correlation coefficient (ICC). Receiver operating characteristic (ROC) curves were calculated to assess area under the curve (AUC) and theoretical optimal cutoffs, to discriminate between diagnoses using Youden’s index.

**RESULTS**

**Age differences**

There was a significant age difference between the PSP group and controls (p < .01), but not between PSP and iNPH or between iNPH and controls. Midbrain area correlated with age in healthy controls (r = −0.63, p < .001), but not in patients with PSP (r = −0.18, p = .39) or iNPH (r = 0.098, p = .55).

**Presence of hummingbird sign**

Using only the dichotomous question “Hummingbird sign yes/no,” the sensitivity for identifying patients with PSP ranged from 46.2% to 92.3% among the individual readers, while specificity ranged from 43.6% to 84.6%. No correlation between a reader’s length of experience with neuroradiology and the assessment outcome was found.

Median visual assessment score of the hummingbird sign was 3.5 (IQR: 0.5–4) in the PSP group, 2.3 (IQR: −2.5 to 3) in iNPH, and −5.0 (IQR: −5 to −4.4) in healthy controls. There were significant differences between all groups, as shown in Figure 1A. The median visual assessment score was positive (i.e., > 0), indicating a hummingbird sign with any level of confidence, in 77% of the PSP subjects, 65% of the iNPH subjects, and 3% in the control subjects. Table 1 shows results for different median visual assessment scores, representing different levels of confidence in the assessment of positive hummingbird sign.

**Area measurements**

Median midbrain area was 80 mm² (IQR: 69–90) in patients with PSP, 92 mm² (IQR: 84–105) in patients with iNPH, and 129 mm² (IQR: 125–142) in controls. The area was significantly smaller in the PSP group than in both other groups, but with overlap at the individual level, as shown in Figure 1B. The sensitivity and specificity of identifying PSP using area measurements varied with different cutoff values, see Table 2. A specificity of 95% for PSP was reached at a cutoff value of ≤ 75.3 mm².

**Comparison between visual assessment and area measurement**

The median visual assessment score for each subject was compared to the respective midbrain area measurement. Spearman correlation between the two methods was r = −0.88, p < .001. The results are plotted in Figure 2.

**ROC analysis**

For visual assessment score, the AUC was 0.83, with the highest diagnostic accuracy in distinguishing PSP calculated with Youden’s index identified at a cutoff value of 3.25. This cutoff value generated sensitivity 58% and specificity 91% in distinguishing PSP.

For midbrain area measurement, the AUC was 0.86 with a theoretical optimal cutoff 89.8 mm², generating sensitivity 77% and specificity 82%. Sensitivity and specificity for different cutoffs are presented in Table 2.
**Figure 1** Results of visual assessment and area measurement for PSP and iNPH patients, and for healthy controls. (A) Median visual assessment scores. Positive values indicate the presence of hummingbird sign and the numerical shows the level of confidence. (B) Sagittal midbrain area measurements in mm\(^2\). *, **, and *** indicate p values of ≤ .05, ≤ .01, and ≤ .001, respectively. Abbreviations: iNPH, idiopathic normal pressure hydrocephalus; PSP, progressive supranuclear palsy.

**Table 1** Results using five different visual assessment scores as cut-off levels, representing different (increasing) levels of confidence regarding the presence of the hummingbird sign on a scale from 0–5. Sensitivity and specificity refer to the discrimination of PSP patients from iNPH patients and healthy controls.

| Median visual assessment score | PSP\(^a\) | iNPH\(^a\) | Control\(^a\) | Sensitivity (PSP) | Specificity (PSP) |
|-------------------------------|----------|------------|--------------|------------------|------------------|
| >0                            | 77%      | 65%        | 3%           | 77%              | 65%              |
| >1                            | 73%      | 58%        | 3%           | 73%              | 69%              |
| >2                            | 69%      | 50%        | 3%           | 69%              | 73%              |
| >3                            | 58%      | 18%        | 0%           | 58%              | 91%              |
| >4                            | 15%      | 3%         | 0%           | 15%              | 99%              |

\(^a\)Proportion of individuals in each group with median visual assessment score above the cutoff. Abbreviations: iNPH, idiopathic normal pressure hydrocephalus; PSP, progressive supranuclear palsy.

**Reliability**

There was significant agreement between the eight readers for the visual assessment score, Kendall's W = 0.76, p < .001. The same analysis with healthy controls excluded resulted in lower reliability, Kendall's W = 0.66, p < .001. Reliability with controls excluded for readers with more than 5 years of experience was slightly higher than for less experienced readers, Kendall's W = 0.75 and Kendall's W = 0.67, respectively.

**Table 2** Results for using different midbrain area measurements as cut-off levels, regarding discrimination of PSP patients from iNPH patients and healthy controls.

| Cutoff value | PSP\(^a\) | iNPH\(^a\) | Control\(^a\) | Sensitivity (PSP) | Specificity (PSP) |
|--------------|----------|------------|--------------|------------------|------------------|
| <60 mm\(^2\) | 7.8%     | 0%         | 0%           | 7.7%             | 100%             |
| <70 mm\(^2\) | 23.1%    | 5.0%       | 0%           | 23.1%            | 97.4%            |
| <80 mm\(^2\) | 50.0%    | 20.0%      | 0%           | 50.0%            | 89.7%            |
| <90 mm\(^2\) | 76.9%    | 35.0%      | 0%           | 76.9%            | 80.8%            |
| <100 mm\(^2\) | 80.8%   | 60.0%      | 0%           | 80.8%            | 69.2%            |
| <110 mm\(^2\) | 96.2%    | 95.0%      | 7.9%         | 96.2%            | 47.4%            |

\(^a\)Proportion of individuals in each group with midbrain area below the cutoff value. Abbreviations: iNPH, idiopathic normal pressure hydrocephalus; PSP, progressive supranuclear palsy.
The median visual assessment score for each subject is = hummingbird sign) to <. Similarities between midbrain appearances and different species of hummingbird. 1: A PSP patient. (A) A hummingbird sign) in the midbrain. We found no such overlap between different midbrain appearances and iNPH patients containing iNPH patients, + hydrocephalus; PSP, progressive supranuclear palsy. The overlap between different midbrain appearances and iNPH patient. (B) An Eulampis jugularis. 3: A healthy control. (C) A Florisuga mellivora. Regarding dichotomous discrimination of PSP patients using "hummingbird sign yes/no," all eight readers were unanimously correct on 35% (n = 36) of the images and unanimously incorrect on 1% (n = 1, an iNPH patient). Interrater reliability for midbrain area measurement was significant: ICC = 0.96 and p < .001.

**DISCUSSION**

The main finding of this study was a large overlap between PSP and iNPH regarding the presence of the hummingbird sign and the sagittal midbrain area. It was possible to distinguish PSP patients from iNPH patients and controls at a group level, both visually and with area measurements, but with considerable overlap at an individual level. Area measurement was more accurate and more reliable than visual assessment of the hummingbird sign. In principle, our main findings are in line with a recent study by Constantinides et al., who also found significant differences between PSP (n = 43) and iNPH (n = 17) at a group level, but with considerable overlap regarding midbrain area measurements and presence of hummingbird sign.18

The overall agreement in visual assessment scores of the hummingbird sign was substantial, with kappa values of 0.66—0.76. However, on the individual level, there was considerable disparity between different neuroradiologists, raising further doubts about the usefulness of the sign. In several instances, the individual visual assessments ranged from +5 (maximum confidence in positive hummingbird sign) to −5 (maximum confidence in negative hummingbird sign) in the same image. This can be compared to an intraclass correlation value of 0.96 for area measurements, which indicates excellent reliability and is in line with previous publications.5,9,26

In the existing literature, cutoff values for differentiating PSP from healthy controls, without taking iNPH into consideration, vary from 70 to 98.1 mm.2,5,8 In the current study containing iNPH patients, the optimal cutoff value for area measurement was 90 mm², yielding sensitivity and specificity values that were higher compared with the averaged visual assessment of eight neuroradiologists (sensitivity 76.9% vs. 69.2%; specificity 80.8% vs. 66.7%). Using only the dichotomous question "Hummingbird sign yes/no," the specificity for identifying patients with PSP had a discouraging range from 43.6% to 84.6% among the individual readers. This can be compared to the 95% specificity of a midbrain area ≤75.3 mm². Due to the higher prevalence of iNPH, and that the clinical presentation can be similar, a high specificity is important. Any improvement in radiological distinction can enhance the diagnostic ability, and unnecessary delay to shunt treatment for iNPH patients can be avoided.

Like in the article from Mangesius et al., a negative correlation between age and midbrain area in healthy controls was found in the current study, reflecting age-related atrophy.9 We found no such correlation in the patient groups, likely reflecting that the diseases have greater impact than age-related atrophy. In the present study, the PSP patients were older than the controls, which could theoretically increase the difference in midbrain area. Due to the larger impact of disease, this was considered to have a negligible effect on the results. There was a higher proportion of males in the PSP group, but Mangesius et al. showed no gender difference in midbrain area.9

From an ornithological point of view, the concept of a hummingbird sign is in itself problematic. There are more than 330 different species of hummingbirds, all with distinct features—including the appearance of the beak (which has been described as the most valuable marker by Kim et al.).7 The overlap between different midbrain appearances and some of the different species of hummingbirds is shown in Figure 3. We consider this to illustrate an obstacle for a reliable and intuitive use of the hummingbird sign in its popularized form and suggest well-defined and quantitative methods, such as area measurements, instead.

The study has several weaknesses. First, the sample size was limited to 26 PSP patients due to the rarity of the disease. Also, we did not take into account the disease duration among the PSP patients; some subjects with less atrophy might have been newly diagnosed. A material that also included patients with widespread small vessel

**FIGURE 2** The median visual assessment score for each subject is plotted against the midbrain area measurement. The subjects are color-coded by diagnosis. Abbreviations: iNPH, idiopathic normal pressure hydrocephalus; PSP, progressive supranuclear palsy

**FIGURE 3** Similarities between midbrain appearances and different species of hummingbird. 1: A PSP patient. (A) A Glaucis hirsutus. 2: An iNPH patient. (B) An Eulampis jugularis. 3: A healthy control. (C) A Florisuga mellivora. Abbreviations: iNPH, idiopathic normal pressure hydrocephalus; PSP, progressive supranuclear palsy
disease would have higher clinical validity, but such studies are difficult to perform due to overlap of symptoms and low diagnostic certainty. Nevertheless, this ought to be further explored in future studies. The assessment system using Yes/No followed by scoring has both strengths and weaknesses compared with the nominal “definite/possible/absent” used in other publications and is easier to apply to multiple readers. Without scoring, nuances in the Yes/No would be lost; in clinical practice, the answer is seldom definitive, but somewhere on a scale from likely to unlikely. The investigators only viewed images of the brainstem. This is not a realistic scenario in clinical routine, but the purpose was rather to blind the assessors from other morphological signs of iNPH, in order to achieve a nonbiased assessment of the hummingbird sign.

Due to a significant overlap in appearance, a midbrain with a hummingbird sign or reduced sagittal area should raise suspicion of PSP only after other signs of iNPH have been considered. Measuring the sagittal midbrain area is more accurate and reliable than visual assessment alone.

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