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Morphometric analysis of subcortical structures in progressive supranuclear palsy: In vivo evidence of neostriatal and mesencephalic atrophy

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ABSTRACT

Progressive supranuclear palsy (PSP) is a neurodegenerative disease characterized by gait and postural disturbance, gaze palsy, apathy, decreased verbal fluency and dysexecutive symptoms, with some of these clinical features potentially having origins in degeneration of frontostriatal circuits and the mesencephalon. This hypothesis was investigated by manual segmentation of the caudate and putamen on MRI scans, using previously published protocols, in 15 subjects with PSP and 15 healthy age-matched controls. Midbrain atrophy was assessed by measurement of mid-sagittal area of the midbrain and pons. Shape analysis of the caudate and putamen was performed using spherical harmonics (SPHARM-PDM, University of North Carolina). The sagittal pons area/midbrain area ratio (P/M ratio) was significantly higher in the PSP group, consistent with previous findings. Significantly smaller striatal volumes were found in the PSP group — putamina were 10% smaller and caudate volumes were 17% smaller than in controls after controlling for age and intracranial volume. Shape analysis revealed significant shape deflation in PSP in the striatum, compared to controls; with regionally significant change relevant to frontostriatal and corticostriatal circuits in the caudate. Thus, in a clinically diagnosed and biomarker-confirmed cohort with early PSP, we demonstrate that neostriatal volume and shape are significantly reduced in vivo. The findings suggest a neostriatal and mesencephalic structural basis for the clinical features of PSP leading to frontostriatal and mesocortical-striatal circuit disruption.

1. Introduction

Progressive supranuclear palsy (PSP) is a neurodegenerative disorder characterized by postural instability and gait disturbance, bradykinesia and axial rigidity, vertical gaze palsy and bulbar palsy (Steele et al., 1964), in combination with neuropsychiatric symptoms such as apathy and utilization behavior. Cognitive and behavioral features in PSP involve functional domains ascribed neuroanatomically to the fronto-striato-pallido-thalamic-cortical (frontostriatal) reentrant circuits (Alexander et al., 1986; Cummings, 1993). PSP has a progressive and irreversible course, with disease duration usually between 6 and 12 years (Williams and Lees, 2009).

The molecular pathology of PSP is characterized by accumulation of tau protein and neuropil filaments within the pallidum, subthalamic nucleus, red nucleus, oculomotor nucleus, dentate nucleus, medulla, ventral tegmentum and neostriatum (caudate and especially putamen) (Williams and Lees, 2009). Macroscopic atrophy of the frontal cortex (Cordato et al., 2002) and subcortical structures (Schulz et al., 1999; Schrag et al., 2000) distinguishes PSP from other parkinsonian syndromes on MRI. Subcortical atrophy in PSP affects the midbrain (particularly the ventral tegmentum), neostriatum, mamillary bodies and the superior cerebellar peduncle (Schrag et al., 2000), with the neostriatum and midbrain involved in frontostriatal circuits. Hence, there is morphological evidence that frontostriatal pathways may be disrupted by PSP.

Given the strategic location of the neostriatum in frontostriatal circuits, there have been surprisingly few attempts to quantify neostriatal atrophy as a structural basis for the neuropsychiatric

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clinical features of PSP. A post-mortem study of four patients with PSP found non-significant reductions in the cross-sectional area of striatal structures (Mann et al., 1993). Another small ($n=6$) MRI study found significant reductions in striatal volume in PSP patients (Schulz et al., 1999). Cordato et al. (2002) identified 15% reduction in caudate volume (normalized for intracranial volume) in a PSP sample ($n=21$), but this was not significant once corrected for whole brain size. The Schulz et al. (1999) study is therefore the only study to our knowledge that has successfully quantified previously pathologically observed striatal atrophy in PSP in vivo.

Previous morphometric research has demonstrated that neostriatal shape and volume change in vivo, assessed via MRI, is apparent in neurodegenerative disease that involves fronto- or cortico-striatal neuronal circuits such as frontotemporal lobar degeneration and subtypes, Alzheimer's disease, and choreoacanthocytosis (Looi et al., 2010, 2011; Madsen et al., 2010; Walterfang et al., 2011). The neuroanatomical correlates of such research yield volume and shape. Form or shape is closely related to function (Thompson, 1945), and deformity to dysfunction in the neostriatum (Looi et al., 2010, 2011; Madsen et al., 2010; Walterfang et al., 2011). Medium size densely spiny projection neurons comprise 90–95% of the neostriatum and virtually all the cortical mantle projects as inputs to the neostriatum in a highly topographic pattern (Bolam et al., 2000). In turn, the output projections are directly to substantia nigra pars compacta and globus pallidus interna, and indirectly to globus pallidus externa (Bolam et al., 2000). In addition, the ventral tegmental area and substantia nigra pars compacta, both located in the midbrain, provide dopaminergic inputs to the neostriatum (Fields et al., 2007; Utter and Basso, 2008). Thus, the neostriatum serves as a topographically organized map of its cortical and subcortical connections (Haber, 2003; Draganski et al., 2008). Based upon the previous findings of neuropathologic and in vivo striatal atrophy in PSP and other neurodegenerative disease, we hypothesized that altered neostriatal morphology should be evident in PSP.

Previous clinical neuroimaging studies have confirmed the diagnostic accuracy of the 'penguin' or colibri (hummingbird) MRI sign of mesencephalic atrophy (Schrag et al., 2000) which has been quantified by decreased pons area/midbrain area ratio from a midsagittal MRI image (Oba et al., 2005; Quattrone et al., 2008). Named for the silhouette appearance of the pons and atrophic midbrain as a 'standing penguin' in cases of PSP, this sign may serve as a useful in vivo biomarker (see Fig. 1). Mesencephalic atrophy may also lead to meso-cortical and meso-striatal disconnection, resulting in further frontostriatal dysfunction (Fields et al., 2007; Ikemoto, 2007; Sesack and Grace, 2010).

Given the implications of frontostriatal circuits, mesencephalic and neostriatal atrophy in the etiopathology of PSP, and, as dysfunction arises from deformation, we hypothesized that altered neostriatal morphology should be evident in PSP. Our primary aim in this study was to perform morphometric analysis on neostriatal structures in order to quantify differences between patients with PSP and healthy age-matched controls measured as volume and shape of the caudate and putamen. Secondly, we hypothesized that subcortical mesencephalic atrophy would be evident through quantitative assessment of the penguin sign, and thus would serve as a confirmatory biomarker of PSP (Oba et al., 2005; Quattrone et al., 2008).

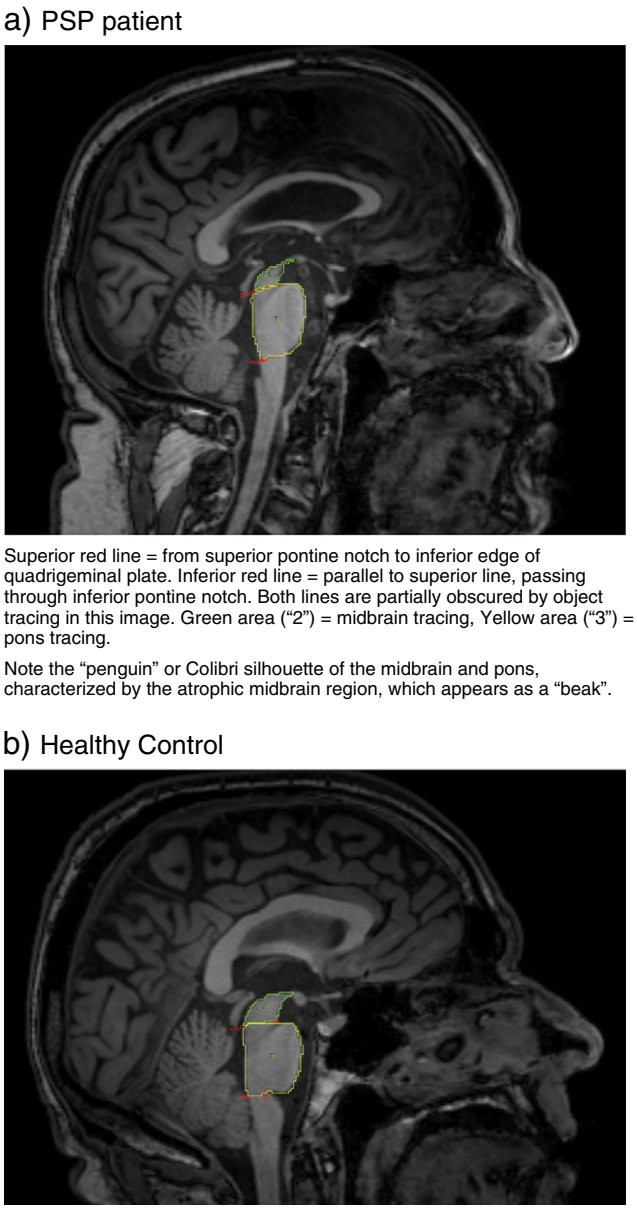

Fig. 1. Mid-sagittal view showing the penguin or Colibri silhouette of the midbrain and pons.

2. Method

2.1. Participants

Fifteen patients with progressive supranuclear palsy (PSP) were recruited for the study, representing an expanded cohort (patients and controls) of a previous study (Kvickström et al., 2011). The diagnosis of probable PSP was made using established clinical criteria (Litvan et al., 2003) in combination with clinical investigations. The presence of fronto-subcortical symptoms (grouped into three categories: dysexecutive symptoms, apathy/lack of initiative and personality change) were recorded on the basis of clinical examination, review of medical records and interview with a caregiver. Disease severity was characterized by the Schwab and England (1969) scale for Parkinson's disease. The patients were followed up for an average of 3 years (range 2–5), to improve the accuracy of the clinical diagnosis. All MRI scans were performed a maximum of 4 years after symptom onset according to patient and caregiver interview. Fifteen healthy age-matched controls, assessed via interview and clinical examination, were recruited for comparison. Patients and controls were recruited from Lund University Hospital and Landskrona Hospital, Sweden. All patients and controls