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Pathologic correlates of supranuclear gaze palsy with parkinsonism

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ABSTRACT

Introduction: Supranuclear gaze palsy (SGP) is a classic clinical feature of progressive supranuclear palsy (PSP) but is not specific for this diagnosis and has been reported to occur in several other neurodegenerative parkinsonian conditions. Our objective was to evaluate the association between SGP and autopsy-proven diagnoses in a large population of patients with parkinsonism referred to a tertiary movement disorders clinic.

Methods: We reviewed clinical and autopsy data maintained in an electronic medical record from all patients seen in the Movement Disorders Clinic at Washington University, St. Louis between 1996 and 2015. All patients with parkinsonism from this population who had subsequent autopsy confirmation of diagnosis underwent further analysis.

Results: 221 unique parkinsonian patients had autopsy-proven diagnoses, 27 of whom had SGP documented at some point during their illness. Major diagnoses associated with SGP were: PSP (9 patients), Parkinson disease (PD) (10 patients), multiple system atrophy (2 patients), corticobasal degeneration (2 patients), Creutzfeld-Jakob disease (1 patient) and Huntington disease (1 patient). In none of the diagnostic groups was the age of onset or disease duration significantly different between cases with SGP and those without SGP. In the PD patients, the UPDRS motor score differed significantly between groups ($p = 0.01$) with the PD/SGP patients having greater motor deficit than those without SGP.

Conclusion: Although a common feature of PSP, SGP is not diagnostic for this condition and can be associated with other neurodegenerative causes of parkinsonism including PD.

1. Introduction

Supranuclear gaze palsy (SGP) refers to an impairment of horizontal gaze, vertical gaze or both secondary to dysfunction in the connections responsible for conducting voluntary gaze commands to the brainstem gaze centers. Although a classic clinical feature of progressive supranuclear palsy (PSP), it is not specific for this diagnosis and occurs in several other neurodegenerative parkinsonian conditions [1].

Our objective was to evaluate the association between SGP and autopsy-proven diagnostic entities in a large population of patients with parkinsonism referred to a tertiary movement disorders clinic over a period of 19 years. We hypothesized that, in this population of movement disorders patients, SGP would be associated with PSP in many but not all cases with a significant proportion of cases associated with other neurodegenerative disorders.

2. Methods

We reviewed clinical and autopsy data maintained in an electronic medical record from all patients seen in the Movement Disorders Clinic at Washington University, St. Louis between 1996 and 2015 ($n = 19{,}822$). All patients seen in this Clinic are routinely invited to participate in our brain donation program, regardless of clinical diagnosis. All those with parkinsonism ($n = 5818$) from this population who had subsequent autopsy confirmation of diagnosis underwent further analysis. Each patient was examined by a subspecialty-trained movement disorders neurologist who recorded the clinical exam in the medical record at each visit. A complete eye movement examination is routinely performed on all

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movement disorder patients seen in this clinic. From this record, cases who demonstrated clinical evidence of SGP at any point during their illness, were identified retrospectively and compared to those with the same pathological diagnosis who did not develop SGP. The study was approved by the Washington University Institutional Review Board. Informed consent was provided by either the patient premorbidly or a next-of-kin at the time of death.

Autopsy diagnoses were based on standard criteria [2–4]. The diagnosis of Parkinson disease (PD) was based on the loss of pigmented neurons from the substantia nigra combined with the presence of Lewy bodies. Cortical alpha-synuclein-positive inclusions consistent with Lewy bodies, although not required for the diagnosis of PD, were present in many of these patients. PSP patients had tau-positive neurofibrillary tangles in the typical distribution in cortex and subcortical nuclei [5]. Those with multiple system atrophy (MSA) had α-synuclein–positive glial cytoplasmic inclusions with neurodegenerative changes in striatonigral or olivopontocerebellar structures [6]. The diagnosis of corticobasal ganglia degeneration (CBD) was based on the presence of tau-positive neuronal inclusions, astrocytic plaques and neuronal loss in cortex and basal ganglia [7]. The diagnosis of Creutzfeld-Jakob disease (CJD) was based on the typical spongiform degeneration as well as immunoblot evidence of abnormal protease resistant prion protein (PrPSc). Huntington disease (HD) was diagnosed based on marked neuronal loss and astrocytosis in the caudate, putamen and globus pallidus in addition to the presence of the characteristic genetic trinucleotide repeat abnormality.

Age of onset was defined as the age of the first symptom of disease. Disease duration was defined as the interval between onset and death. UPDRS motor scores at the time of the first clinic visit were recorded when available. For each diagnostic entity, quantitative measures were compared in those with SGP vs those without SGP with a Student t-test when appropriate.

3. Results

A total of 221 unique parkinsonian patients had autopsy proven diagnoses. Of these 221 patients, 27 had supranuclear gaze palsy documented in the medical record (see supplementary material). In all cases, the gaze palsy was evident at the last clinical examination before death, i.e. in no patient was it a transient phenomenon. Autopsy-proven diagnoses were the following: 9 patients with PSP, 10 with PD, 2 with MSA, 2 with CBD, and 1 with each of CJD and Huntington disease. In addition, one patient had postmortem findings of mild argyrophilic grain disease [8] and one patient had sparse beta amyloid plaques with alpha-synuclein-positive inclusions in olfactory cortex but none in neocortex and no midbrain changes. The mean interval between the last clinical evaluation and death was 16.9 months in PD, 16.1 months in PSP, 7.8 months in MSA, and 10.4 months in CBD. This interval did not differ significantly between those with SGP vs those without. Table 1 lists the causes and demographics of the major autopsy-proven disease entities associated with SGP.

In none of the diagnostic groups was the age of onset or disease duration significantly different between cases with SGP and cases without SGP. In the PD patients, the UPDRS motor score differed significantly between the two groups (32.8 vs 44.1; $p = 0.01$) with the PD/SGP patients having greater motor deficit.

4. Discussion

SGP is a neurological sign that implies dysfunction in supranuclear pathways involved in generating voluntary gaze. In our population, as expected, the majority of autopsy-proven PSP patients had clinical evidence of SGP at some point during their illness although a significant minority (5/14) did not. As shown in Table 1, in this movement disorder clinic population, there were as many patients with autopsy-proven PD and SGP as there were with PSP/SGP, largely because PD was a much more common diagnosis amongst autopsied patients than was PSP (146/261 vs 14/261). SGP was also evident in other neurodegenerative parkinsonian disorders (2/23 autopsied patients with MSA; 2/7 patients with CBD). These entities were much less common as compared to PD in our study population and therefore associated with fewer cases. In all diagnostic groups, age of onset and disease duration were essentially the same in patients with parkinsonism with SGP and those without.

PSP is classically associated with SGP that typically manifests initially with impaired convergence and conjugate eye movements in the vertical plane and later with a lateral gaze palsy that may be less severe [9,10]. Impaired downward gaze is said to be particularly significant in the diagnosis since upward gaze impairment may be present in other neurological disorders, including PD, and in some normal elderly individuals [11]. SGP is often absent early in the course of the disease with one study reporting supranuclear gaze palsy in only 11/67 patients at initial evaluation and ultimately clinically diagnosed with PSP [12]. Our findings are consistent with the clinical mantra that SGP develops by the time of death in the majority of patients with PSP although we found that a significant minority retained normal eye movements, similar to previous reports in the literature [13,14]. The retrospective nature of our data does not allow us to assess the differential involvement of horizontal vs vertical gaze or of up-vs down-gaze.

Most of the PD/SGP patients in our patient population had autopsy evidence of cortical disease with cortical synucleinopathy. One PD/SGP patient had extensive cortical Alzheimer-like changes with neuronal plaques and neurofibrillary tangles. Pathological changes were restricted to the brainstem in only 2 PD/SGP patients. This occurrence of cortical disease with SGP is consistent with reports that the loss of saccades and pursuit movements with preservation of oculocephalic responses may be a feature of hemispheric disease, upper brain stem lesions or both [10,15]. This

Table 1
Diagnoses and demographics in patients with SGP vs those without SGP.

Diagnosis	Cases without SGP			Cases with SGP		
	Number	Age at Onset	Disease Duration	Number	Age at Onset	Disease Duration
PSP	5	68.7	10.2	9	66.9	9.1
PD without cortical synucleinopathy	22	57.0	17.0	2	71.7	6.5
PD with cortical synucleinopathy	114	62.4	16.1	8	63.8	14.0
MSA	21	58.2	6.4	2	59.4	8.8
CBD	5	70.3	5.5	2	60.3	6.3
CJD	1	66.8	1.6	1	76.0	6.4

SGP supranuclear gaze palsy; PSP progressive supranuclear palsy; PD Parkinson disease; MSA multiple system atrophy; CBD cortical basal degeneration; CJD Creutzfeld-Jakob disease.

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