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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), Creutzfeldt-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.

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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.

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=5,818) 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 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 pre-mortally 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 Creutzfeldt-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.

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 disease⁸ 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.

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 is also consistent with a previous report of levodopa-responsive parkinsonism followed by dementia and supranuclear ophthalmoplegia caused by Alzheimer-type pathology without Lewy bodies,¹⁶ as well as a report of levodopa-responsive convergence insufficiency in a patient with autopsy proven PD,¹⁷ suggesting supranuclear control for convergence. PD/SGP patients had more severe motor symptomatology as indicated by a higher average UPDRS motor score than those without SGP.

Dementia with Lewy bodies (DLB) has been reported as being associated with SGP.¹⁸ This entity is underrepresented in our patient population in large part because our brain bank reflects the bias of those patients referred to a movement disorder center. By definition, patients with DLB have cognitive changes that precede or occur within one year of the onset of the movement disorder and are more likely to seek evaluation at a dementia center. Secondly, substantial pathological overlap exists between DLB and PD with dementia; DLB does not have a specific pathological marker. The majority of our PD patients had a cortical synucleinopathy, mimicking the characteristic pathology of DLB. Pathologically these two conditions are not distinguishable. In fact, both conditions represent the same synucleinopathy with predilection for neuronal pathology that are arbitrarily differentiated by the timing of onset of the dementia with respect to onset of motor parkinsonism.

In a study of oculomotor function in MSA, Anderson and colleagues suggest that the presence of clinically slow saccades, or moderate-to-severe gaze restriction, implies a diagnosis other than MSA.¹⁹ In contrast, our data indicate that SGP can be seen in patients who have subsequent autopsy-confirmation of MSA at a frequency similar to that seen in PD. Cognitive impairment is an exclusion criterion for the diagnosis of multiple system atrophy (MSA), according to the second consensus statement.⁶ However, some patients with pathologically confirmed MSA have been reported to have dementia. Cykowski and colleagues have reported that the presence of Lewy body-like inclusions in neocortex in MSA, but not hippocampal alpha-synuclein pathology, was associated with cognitive impairment.²⁰ We suggest that the association of SGP with MSA in some individuals provides further evidence for cortical pathology.

In CBD, eye movement abnormalities have not been reported to be a common feature of early disease. However, they develop rapidly with disease progression and by an average of 5.2 years after the onset of clinical symptoms, 90% have developed supranuclear eye movement defects.²¹ In our patients, SGP had developed in 2/7 patients by the time of death.

Clinically, CJD has substantial differences from the neurodegenerative forms of parkinsonism, and these patients are infrequently referred to movement disorders clinics. SGP has been reported previously in this disorder, however, one rare patient was clinically diagnosed with PSP but ultimately had CJD and not PSP at autopsy.²² This disorder was diagnosed in only 2 of our autopsied cases, 1 of whom had SGP. This patient also had alpha-synuclein-positive inclusions in the form of Lewy bodies and Lewy neurites confined largely to the brainstem and limbic areas, raising the possibility of a coincident synucleinopathy.

A single patient with HD in our population, not included in Table 1, presented with levodopa-responsive parkinsonism starting at age 34 that progressed over 8 years. He had a family history suggestive of autosomal dominant inheritance. Neurological symptoms in affected family members (on the basis of history) were limited to akinesia and rigidity. He was parkinsonian on presentation with HD diagnosed only after DNA testing showed a normal allele of 17 trinucleotide repeats and an abnormal allele with 49 repeats. Given the atypical presentation with parkinsonism rather than a hyperkinetic movement disorder and the well-established presence of oculomotor abnormalities in early HD,²³ it is perhaps not surprising that such individuals may be clinically diagnosed with possible PSP before the results of DNA analysis are available.

Other neurodegenerative causes of SGP have been reported in the literature that are not represented in our patient population, likely because of referral patterns, low prevalence or both. These include spinocerebellar degeneration, Niemann-Pick disease type C, and Whipple disease.^{24–28} Supranuclear gaze palsies have also been reported to occur in amyotrophic lateral sclerosis.²⁹

The mechanism of SGP likely differs across individuals or disease processes. While the commonality is a disconnect between the desire to generate a saccade and the gaze centers in the brainstem, this disconnect may occur either at the level of the cortical centers involved in the voluntary generation of saccades or in the white matter interconnections between cortex and brainstem. Based on diffusion tensor imaging, Whitwell and collaborators have described changes primarily in the superior longitudinal fasciculus that correlated with severity of saccadic impairments in PSP.³⁰ These authors suggest a cortical element to saccadic abnormalities in PSP, perhaps involving the frontal eye fields and premotor cortices, mediated by the superior longitudinal fasciculus. The suggestion of a cortical component may be in conflict with the apparent absence of SGP in a cortical neurodegenerative disease such as Alzheimer disease (AD). We are unaware of literature reports evaluating SGP in AD and cannot address the issue directly from our patient population which is drawn from a referral movement disorders center. We have few patients with autopsy-proven AD in our population.

Our study does have some limitations. As a retrospective chart review, it is dependent on the degree of clinical detail recorded in the medical record. While subspecialty trained movement disorders neurologists were responsible for all assessments, a neuro-ophthalmologist was not involved. The clinical diagnosis of SGP requires a detailed assessment of ocular motility including selective slowing of vertical saccades, hypometric saccades, “round the house” vertical saccades, impaired vergence, and increased square wave jerks. It is possible that a more detailed neuro-ophthalmological assessment would identify additional cases of SGP. Clinical evaluation of ocular motility requires a cooperative patient who understands the examiner’s instructions. Since cognitive impairment is a common feature of parkinsonian neurodegenerative disorders, it is possible that impaired patient cooperation impacted the detection of SGP. An additional issue is the interval between the final clinical assessment and death. While the average interval varied from 7.8 months in MSA to 16.9 months in PD, it is possible that some patients may have developed clinically evident SGP during the interval.

Conclusion

The association of SGP with PSP is a well established tenet of the clinical phenomenology of neurological disorders. Our evaluation of SGP and its relationship to specific autopsy-proven diagnostic entities confirms that it is a common, but not universal, feature of PSP with a sizeable minority of affected patients having no clinical evidence of SGP. In addition to having a low sensitivity for this diagnosis, the presence of SGP according to our criteria has a low specificity and can be seen in association with parkinsonism in several other neurodegenerative disorders.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Highlights

- Supranuclear gaze palsy (SGP) was studied in patients with autopsy-proven diagnoses
- Most (9/14) but not all progressive supranuclear palsy (PSP) patients developed SGP
- The clinical finding of SGP was not specific for a pathological diagnosis of PSP

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, Creutzfeldt-Jakob disease