Published in final edited form as:

Parkinsonism Relat Disord. 2011 June ; 17(5): 365–371. doi:10.1016/j.parkreldis.2011.02.017.

Neuropathological Findings of PSP in the Elderly Without Clinical PSP: Possible Incidental PSP?

Virgilio Gerald H. Evidente, M.D.^{1,***}, Charles H. Adler, M.D., Ph.D.¹, Marwan N. Sabbagh, M.D.², Donald J. Connor, M.D., Ph.D., Ph.D.², Joseph G. Hentz, M.S.³, John N. Caviness, M.D.¹, Lucia I. Sue, B.S.⁴, and Thomas G. Beach, M.D., Ph.D.⁴

¹ Department of Neurology, Mayo Clinic, Scottsdale, Arizona

² The Cleo Roberts Center for Clinical Research, Banner Sun Health Research Institute, Sun City, Arizona

³ Section of Biostatistics, Mayo Clinic, Scottsdale, Arizona

⁴ W. H. Civin Laboratory for Neuropathology, Banner Sun Health Research Institute, Sun City, Arizona

Abstract

Aims—We aimed to describe cases with incidental neuropathological findings of progressive supranuclear palsy (PSP) from the Banner Sun Health Research Institute Brain and Body Donation Program.

Methods—We performed a retrospective review of 277 subjects with longitudinal motor and neuropsychological assessments who came to autopsy. The mean Gallyas-positive PSP features grading for subjects with possible incidental neuropathological PSP was compared to those of subjects with clinically manifest disease.

Results—There were 5 cases with histopathological findings suggestive of PSP, but no parkinsonism, dementia or movement disorder during life. Cognitive evaluation revealed 4 of the 5 cases to be cognitively normal; one case had amnesic mild cognitive impairment (MCI) in her last year of life. The mean age at death of the 5 cases was 88.9 years (range 80-94). All 5 individuals had histopathologic microscopic findings suggestive of PSP. Mean Gallyas-positive PSP features grading was significantly lower in subjects with possible incidental neuropathological PSP than subjects with clinical PSP, particularly in the subthalamic nucleus.

Conclusions—We present 5 patients with histopathological findings suggestive of PSP, without clinical PSP, dementia or parkinsonism during life. These incidental neuropathological PSP findings may represent the early or pre-symptomatic stage of PSP. The mean Gallyas-positive PSP features grading was significantly lower in possible incidental PSP than in clinical PSP, thus suggesting that a threshold of pathological burden needs to be reached within the typically affected areas in PSP before clinical signs and symptoms appear.

© 2011 Elsevier Ltd. All rights reserved.

*** Address All Correspondence to: Virgilio Gerald H. Evidente, M.D., Professor of Neurology, Dept of Neurology, Mayo Clinic, 13400 E. Shea Blvd., Scottsdale, AZ 85259, Tel (480)3018100, Fax (480)3018451, evidentevirgilio@mayo.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Keywords

progressive supranuclear palsy; PSP; incidental; autopsy; parkinsonism; neuropathology

Introduction

Progressive supranuclear palsy (PSP) is an important differential diagnosis in patients presenting with parkinsonism [1]. The key clinical signs that strengthen the clinical diagnosis of PSP in a parkinsonian patient include supranuclear downgaze palsy, early onset of falls, emotional lability, dysphagia, axial rigidity or dystonia, hyperextension of the trunk and/or neck and poor response to levodopa [2]. However, PSP patients often do not present with the typical features described, and thus are mistaken for some other clinical entity. Up to 50% of subjects lack the classic vertical gaze palsy throughout their course and these cases are usually misdiagnosed [3]. Even among specialists, PSP can be misdiagnosed as Parkinson's disease (PD), multiple system atrophy (MSA), Alzheimer's disease (AD), dementia with Lewy bodies (DLB) or corticobasal degeneration (CBD) [4,5]. Those that are clinically misdiagnosed as PSP pre-mortem are only confirmed as PSP on autopsy. The National Institute of Neurological Disorders (NINDS) along with the Society of PSP published consensus research criteria for the pathological diagnosis of PSP (NINDS-SPSP criteria) in 1994 [6]. These were mainly dependent on the presence of neuronal loss, gliosis and neurofibrillary tangles in selected subcortical and brainstem regions. Most experts now recommend the presence of Gallyas-positive or phosphorylated tau-immunoreactive tufted astrocytes when making the diagnosis, along with tau-positive intracellular lesions, including neurofibrillary tangles (NFT) and pretangles, threads, oligodendroglial coiled bodies, and tufted astrocytes [7,8,9].

Reports on incidental PSP findings in patients with no neurological signs, symptoms, or premortem diagnosis are scarce [10]. We herein report 5 elderly patients with PSP findings on histopathology, who did not present with the classical features of clinical PSP during life.

Methods

A retrospective database query was done of subjects who have had prospective longitudinal neurological examinations and postmortem neuropathological examinations as part of the Banner Sun Health Research Institute (SHRI) Brain and Body Donation Program (BBDP) [11]. All subjects enrolled in the BBDP or their legal representatives have given informed consent approved by the Banner Health Institutional Review Board for clinical assessment during life and the donation and research usage of their brain tissue after death. We specifically looked for patients with possible neuropathological "incidental PSP", which we defined as histopathological findings consistent with PSP in individuals without dementia, parkinsonism, movement disorder, or other defined neurological syndrome, and who did not fulfill the clinical criteria for possible or probable PSP [2]. Clinically-manifest PSP was defined as those with histopathology meeting diagnostic criteria of PSP as well as a syndrome of dementia, parkinsonism or other movement disorder. We retrospectively reviewed the clinical charts and histories of all patients with clinically manifest PSP, as well as those with possible incidental PSP on neuropathology. In all cases, a neuropathological diagnosis of PSP included the presence of Gallyas or tau-positive "tufted astrocytes" in the putamen and/or neocortex [6,8,12,13], along with a characteristic pattern of neurofibrillary tangle distribution in the basal ganglia, thalamus, cerebellum and brainstem [6,13,14]. The pathological diagnosis of PSP was also supported by the finding of grumose degeneration in the dentate nucleus, but this last feature was not a required element of the diagnosis. All subjects except one received a basic neuropsychological battery consisting of the Rey

Auditory Verbal Learning Test, WAIS-III digit span, Controlled Oral Word Fluency, Animal Fluency, Judgment of Line Orientation, Stroop Interference Test and Trails A/B.

The density of all Gallyas-positive features of PSP, including neurofibrillary tangles and all types of glial tau pathology, was compared in subjects with incidental PSP and clinically-manifest PSP in the following brain regions: frontal, temporal and parietal lobe neocortices, putamen, subthalamic nucleus (STN), globus pallidus (GP), thalamus, substantia nigra (SN), basal pons and dentate nucleus of the cerebellum. Scoring of the density of total Gallyas-positive features was as follows: 0-zero, 1-sparse, 2-moderate and 3-frequent density. The scoring was done by one neuropathologist who was blinded to both the clinical and neuropathological diagnoses. Nominal statistical significance was calculated by using the permutation test. We then accounted for multiple comparisons by using the Hochberg method. In addition, grades were categorized whether above the sample grand median and proportions were compared using the Fisher exact test.

Accompanying Alzheimer's disease-related histopathology (senile plaque and neurofibrillary tangle densities) was graded semi-quantitatively as follows. Standardized fixed and cryoprotected 4×5 cm tissue blocks were sectioned at 40 micrometers on a sliding freezing microtome and sections were stained using thioflavine S, Campbell-Switzer and Gallyas silver stains [11,15]. Average total (neuritic and diffuse) plaque densities as well as average neurofibrillary tangle densities were estimated using the CERAD templates [16] as zero, sparse, moderate or frequent in the following regions: frontal lobe cortex at the coronal level of the genu of the corpus callosum; temporal lobe cortex at the coronal level of the amygdala and at the level of the lateral geniculate nucleus; parietal lobe cortex at a level 1 cm caudal to the splenium of the corpus callosum. Density descriptive terms were converted to a 0-3 scale for statistical purposes. Braak neurofibrillary tangle stage was established according to the original publication [17].

Results

Between 1997-2008, a total of 706 subjects in the BBDP have come to autopsy. The subjects consist of patients that were clinically categorized as parkinsonism, dementia, tremor, dystonia, restless legs syndrome or normal controls. Of these, 45 cases had clinically manifest disease and met neuropathologic diagnostic criteria for PSP, while 5 individuals met neuropathologic criteria but had no definite neurological syndrome and did not meet clinical criteria for possible or probable PSP [2]. The mean age was 84 years (SD = 8.2) for the 45 clinical PSP patients, 89.1 years (SD = 5.6) for the 5 incidental PSP patients, and 82.6 years (SD = 8.7) for the rest of the cohort without clinical or incidental PSP. Females accounted for 34% of clinical PSP, 60% of incidental PSP, and 45% of the rest of the cohort without clinical or incidental PSP. All five patients with incidental PSP were Caucasian and are described below.

Case descriptions

Case 1—This 80 year old male died from complications of metastatic gastric carcinoma. His past medical history was significant for hypertension, hypercholesterolemia, coronary artery disease, coronary bypass graft surgery, transient ischemic attack and anemia. He had a 31 pack-year smoking history and no family history of any neurological disorder. He developed dysphagia at age 78, though an esophagram done at that time was normal. He tripped and fell at age 79, but there was no history of repeated falls. His last assessments at SHRI were at age 78. At that time, his Mini-Mental Status Examination (MMSE) score was 29/30 and his neuropsychological assessment showed no cognitive impairment. He demonstrated performance in the average range on a memory task, on semantic and lexical fluency tests, on a visual perception task, on executive function tasks and on tests of

attention. Movement examination revealed normal gait, posture and extraocular eye movements, with no tremor, bradykinesia or increased tone. Neuropathological findings were significant for microscopic features suggestive of PSP (Table 1, Figure 1).

Case 2—This 87 year old female died from complications of lung cancer. Her past medical history was significant for hypercholesterolemia, diabetes mellitus type II, coronary artery disease, myocardial infarction, carotid stenosis, melanoma, peptic ulcer disease, chronic obstructive pulmonary disease, hysterectomy and bilateral salpingo-oophorectomy. She had no history of tobacco or alcohol abuse, nor any family history of any neurological disorder. Up to the time of her death, she had no complaints of cognitive impairment, gait abnormality, tremor or slowness of movements. Two years prior to death, her MMSE score was 29/30 and her neuropsychological assessment showed she was cognitively normal. She demonstrated high average to superior performance on a memory task, on semantic and lexical fluency tests and on a visual perception task. She was unimpaired on tests of executive function and attention. Her last movement examination was performed 7 months prior to death, and there was no tremor, bradykinesia or rigidity. She had some mild postural instability on backward pull test. Her extraocular eye movements were full. Neuropathological examination revealed microscopic changes suggestive of PSP (Table 1, Figure 1).

Case 3—This female died in her early 90's with a clinical diagnosis of mild cognitive impairment (MCI) the year before her death. Her past medical history was significant for coronary artery disease, myocardial infarction, carotid stenosis s/p right carotid endarterectomy, peripheral vascular disease, depression, anxiety, panic attacks, hearing loss, cataracts, osteoarthritis, spinal osteoporosis with L1 compression fracture, lumbar spinal stenosis, polymyalgia rheumatica and oral squamous cell carcinoma. She had a 25 pack-year history of smoking and was a social alcohol user. Family history was significant for her father dying of cerebral hemorrhage at age 54. At age 91, she first complained of some forgetfulness and some difficulty walking due to her osteoarthritis. Her last movement examination was two years prior to death, and she had minimal slowness of hand movements consistent with her arthritic hands, but no tremor, rigidity or gait disorder. Her neuropsychological testing at that time was normal with a MMSE score of 29/30. Ten months prior to death, her MMSE score was 26/30 (missing 2 points for delayed recall and 2 points for orientation), and her neuropsychological assessment suggested the presence of mild memory impairments with other areas of cognition being in the average range (attention, executive function, semantic and lexical fluency and visual perception). She was diagnosed as having amnesic MCI. Neuropathological findings suggestive of PSP were noted at autopsy (Table 1, Figure 1).

Case 4—This male died in his early 90's from complications of recurrent pleural effusions. His past medical history was remarkable for peripheral neuropathy with sensory ataxia, chronic ventricular arrhythmia, syncope, hypertension, mitral valve prolapse and unspecified thyroid disease. At age 86 years, he scored 27/30 in the MMSE. Formal neuropsychological testing was essentially normal for age. His last examination one year before death showed peripheral neuropathy, sensory gait ataxia, slightly stooped posture and mild postural instability on backward pull test. A brain CT scan at that time was unremarkable. Neuropathological changes suggestive of PSP were seen on autopsy (Table 1, Figure 1).

Case 5—This female died in her early 90's of presumed natural causes. Her past medical history was significant for benign positional vertigo, coronary artery disease, chronic obstructive pulmonary disease, pneumonia, osteoarthritis, diverticulosis, paroxysmal atrial tachycardia and central retinal artery occlusion. Neither she nor her immediate family had

any history of neurologic or psychiatric illness. At age 89 and 90 years old, she had a number of falls resulting from attacks of vertigo, though her balance was otherwise intact interictally. She had a brain MRI at age 90 years which showed mild to moderate cerebral atrophy, mild to moderate periventricular white matter ischemic changes and a lacunar infarct in the right basal ganglia. Formal neuropsychological testing at age 89 and 90 years showed scores within the normal range for age, except for a significant deficit in category fluency. Her last physical examination a few months prior to death did not reveal any parkinsonism, other movement disorder, square wave jerks or vertical gaze palsy. Neuropathological findings suggestive of PSP were seen on autopsy (Table 1, Figure 1).

Grading of Gallyas-positive PSP features: Mean grades of Gallyas-positive PSP features were significantly lower in subjects with neuropathological incidental PSP than subjects with clinical PSP. The STN and putamen showed the greatest difference (Table 2). The mean density grading in the STN was only 0.8 for neuropathological incidental PSP versus 2.5 for clinical PSP. Only 20% of subjects with neuropathological incidental PSP had a density grade greater than 1.5 in the STN, versus 84% of the subjects with clinical PSP (Table 3). The GP, thalamus, and pons were next most likely to differ between incidental and clinical PSP. Gallyas-positive glia were not present in any of the graded regions in our age-similar BBDP control subjects.

Distribution of neuronal loss and gliosis: We sought to compare the distribution of neuronal loss and gliosis between clinical PSP versus possible incidental PSP cases (Table 4). The most consistently involved brain areas in both groups were the substantia nigra and brainstem tegmentum. Whereas 1/3 to 1/4 of clinical PSP cases had neuronal loss and gliosis in the globus pallidus and subthalamic nucleus, none of the incidental PSP cases had those findings in the said nuclei.

Degree of pigmented neuron loss of the substantia nigra: We further compared the degree of pigmented neuron loss in the substantia nigra between clinical PSP versus possible PSP cases using the following scoring system: 0 – no pigmented neuron loss; 1 – mild loss; 2 – moderate loss; and 3 – severe loss (Table 5). The mean pigmented neuron loss score was significantly lower ($p = 0.03$) in the incidental PSP group (1.20, SD 0.84) than in the clinical PSP group (2.28, SD 0.92) ($p = 0.03$).

Accompanying Alzheimer's disease-related histopathology: Table 6 presents the comparison of possible incidental versus clinical PSP cases in terms of regional total senile plaque density, NFT density, and Braak NFT staging. There were no significant differences between possible incidental versus clinical PSP.

Discussion

We present a series of 5 patients who had histopathological microscopic findings suggestive of PSP and yet did not manifest with dementia, parkinsonism or clinical PSP. As there were 76 autopsies of clinically normal subjects during this time, this represents a prevalence of 6.9% in the volunteer normal elderly population of the BBDP. This is much higher than the observed prevalence of clinical PSP of 1 - 5 cases per 100,000 based upon community epidemiologic studies [18]. This could be due to the fact that the BBDP is not a random sample of the surrounding community and is subject to both volunteer and autopsy biases [11]. Furthermore, the BBDP has an inherent bias of recruiting patients with movement disorders, particularly those with Parkinson's disease and other parkinsonian syndromes, and may not be representative of the actual community prevalence.

Nath et al had studied the natural history and clinical features of 187 cases who fulfilled the NINDS criteria for PSP [21]. They observed that in early PSP, 69% of patients present with mobility problems (slowness, weakness of legs, or unsteadiness); 15% with cognitive problems (memory impairment, personality change, depression, anxiety, apathy or word finding difficulties); 14% with bulbar/language problems (speech/swallowing impairment, reduced speech output, palilalia/echolalia or dysphonia); 12% with visual problems (blurred vision, diplopia, etc); and 25% with miscellaneous neurological symptoms like tremor, dizziness or localized pain. The 5 cases we present were all examined by a movement disorder specialist and 3 of them had some subtle motor sign(s) which were not deemed to represent a neurodegenerative or progressive movement disorder per se, but were thought to be due to other conditions like arthritis, advanced age, osteoporosis or peripheral neuropathy/sensory ataxia. None of them fulfilled the clinical criteria for possible or probable PSP.

Reports on pathologically diagnosed PSP without neurologic signs are scarce. Oshima et al described an 84 year old Japanese man who died of heart failure, but had no neurological or psychiatric signs or symptoms throughout his clinical course [10]. Neuropathological examination revealed neuronal loss of the substantia nigra and pallidum, and NFTs in the caudate nucleus, subthalamic nucleus, pallidum, putamen, substantia nigra, locus ceruleus, pontine nucleus, inferior olivary nucleus and dentate nucleus. Gallyas staining revealed tuft-shaped astrocytes in the caudate nucleus, putamen and thalamus.

One of the largest pathological series of PSP by Williams et al at Queen Square described 103 pathologically confirmed PSP cases which were donated from all over the United Kingdom from 1988 to 2002 [22]. The diagnosis was made retrospectively according to the NINDS-SPSP criteria [15]. These cases could be divided into two general clinical phenotypes. One phenotype (54%), named Richardson's syndrome, was characterized by the early onset of postural instability, falls, supranuclear gaze palsy and cognitive deficits. The other phenotype (32%), named PSP-parkinsonism, had features similar to PD including asymmetric onset, tremor and initial moderate responsiveness to levodopa. Fourteen cases (14%) could not be classified into those 2 phenotypes. The classic clinical description of PSP, which includes supranuclear gaze palsy, early falls and dementia, could not adequately describe one-third of cases, though those patients were not neurologically normal.

The other large brain bank series of PSP patients is from the Society of PSP at Mayo Clinic Jacksonville. Josephs and Dickson reviewed the medical records of 180 clinically diagnosed PSP patients whose brains were sent to the SPSP Brain Bank [5]. Of the 180 cases, only 137 had PSP on neuropathology. The 43 other cases had other pathologic diagnoses, most notably CBD, MSA and DLB. As the cases referred to this brain bank all had clinically diagnosed PSP, it is not surprising that no cases of incidental neuropathological PSP were seen in that series.

Neither of these large and authoritative studies reported subjects having pathological PSP in the absence of clinical expression. This is likely because these studies involved subjects that had been diagnosed with PSP or another neurological syndrome during life whereas the BBDP does autopsies of large numbers of normal elderly individuals directly recruited from the surrounding communities.

We sought to determine if there were neuropathological features that could differentiate clinical PSP from incidental PSP. The tau density grading (Table 2) was significantly higher for clinical PSP than incidental PSP for the putamen and STN. Similarly, on looking at the proportion presenting with tau density grading greater than the median (Table 3), clinical PSP cases had significantly higher scores than incidental PSP cases for the GP and STN. We

also examined if there were differences between clinical PSP versus incidental PSP in terms of distribution of neuronal loss and gliosis (Table 4). In both groups the most commonly affected areas were the substantia nigra and brainstem tegmentum. On examining the degree of neuronal loss in the most commonly affected nucleus in PSP - the substantia nigra - the clinical PSP cases had significantly greater pigmented neuron loss than the incidental PSP cases (Table 5).

Incidental neuropathological findings suggestive of PSP in otherwise neurologically intact individuals may represent the early or pre-symptomatic stage of PSP. Our cases of possible incidental PSP presumably have very early disease, and although they may not all fully meet the traditional PSP criteria by defined only by NFT density and distribution [6,15], their glial pathology (particularly the presence of frequent tufted astrocytes in the characteristic brain regions) would seem to place them firmly in the PSP category.

It should not be surprising that there are cases of possible incidental PSP in the normal elderly population, as incidental disease is well known for AD as well as Lewy body disorders. About two-thirds of all people over age 65 have the microscopic lesions of AD [28], and 25% have Lewy bodies [29]. In our Brain Donation Program, the prevalence of incidental Lewy body disease was 19.7% [30]. Notably, for both AD and Lewy body disorders, the prevalence of incidental cases is much greater than the prevalence of symptomatic cases. Thus, for neurodegenerative diseases, it is possible that the pre-symptomatic cases may only represent the “tip of the iceberg” as many elderly people may have subclinical disease but die from other causes before developing symptomatic disease, or they may have mild disease that never becomes symptomatic. It may be that if the 5 patients we present had lived long enough, each of them would have developed the typical clinical signs of PSP, or dementia or parkinsonism.

Most of our possible incidental PSP (and clinical PSP) cases had some degree of Alzheimer type histopathology. None of them, however, had dementia or AD clinically. Furthermore, there were no differences in cortical plaque density, NFT density, and Braak staging between our possible incidental and clinical PSP cases (Table 6). One study found Alzheimer-type pathology (ATP) in 69% of 32 PSP cases reviewed over a 17 year period, with only 18.75% fulfilling the CERAD criteria for definite or probable Alzheimer's disease [31]. Josephs et al attempted to determine if disease duration had any relationship to the histopathological features of PSP [33]. From the SPSP Brain Bank, they observed that tufted astrocytes were more dense in the motor cortex and striatum as the disease duration increases. They also noted that the cases with the most severe neuronal tau pathology had the longest disease duration. From our current study, we also determined that PSP features grading was significantly greater in clinical PSP patients than in possible incidental PSP cases. Thus, it is likely that a threshold of pathological burden needs to be reached within the typically affected areas of the brain in PSP before clinical signs and symptoms appear.

In summary, we present 5 elderly cases that had possible incidental PSP on neuropathology without parkinsonism, other movement disorders, or dementia during life, and who did not fulfill the NINDS-SPSP clinical criteria for possible or probable PSP. Further work comparing neurological findings between possible incidental PSP cases, controls, and clinical PSP cases will be needed to determine if there is an antecedent test battery that might be useful in predicting the development of clinical PSP. By studying cases of incidental neuropathological PSP, it may be possible to identify biomarkers that would predict this pathological state and thus lead to earlier disease modifying treatments.

Acknowledgments

The Sun Health Research Institute Brain Donation Program is supported by the National Institute of Aging (P30 AG19610 Arizona Alzheimer's Disease Core Center), the Arizona Department of Health Services (contract 211002, Arizona Alzheimer's Research Center), the Arizona Biomedical Research Commission (contracts 4001, 0011, and 05-901 to the Arizona Parkinson's Disease Consortium), and the Prescott Family Initiative of the Michael J. Fox Foundation for Parkinson's Research.

References

Note: Additional references were added to the revised manuscript in order to answer the reviewers' suggestions and comments

1. Steele JC, Richardson JC, Olszewski J. Progressive supranuclear palsy. *Arch Neurol.* 1964; 10:333–5. [PubMed: 14107684]
2. Litvan I, Agid Y, Calne D, Campbell G, Dubois B, Duvoisin RC, et al. Clinical research criteria for the diagnosis of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome): report of the NINDS-SPSP international workshop. *Neurology.* 1996; 47:1–9. [PubMed: 8710059]
3. Birdi S, Rajput AH, Fenton M, Donat JR, Rozdilsky B, Robinson, et al. Progressive supranuclear palsy diagnosis and confounding features: report on 16 autopsied cases. *Mov Disord.* 2002; 17:1255–64. [PubMed: 12465065]
4. Evidente VGH, Caviness JN, Sabbagh M, Connor DJ, Driver-Dunckley E, Adler CH, et al. Atypical progressive supranuclear palsy: clinicopathological correlation in a brain bank program [abstract]. *Neurology.* 2007; 68(Suppl 1):A48.
5. Josephs KA, Dickson DW. Diagnostic accuracy of progressive supranuclear palsy in the society for progressive supranuclear palsy brain bank. *Mov Disord.* 2003; 18:1018–26. [PubMed: 14502669]
6. Hauw JJ, Daniel SE, Dickson D, Horoupian DS, Jellinger K, Lantos PL, et al. Preliminary NINDS neuropathologic criteria for Steele-Richardson-Olszewski syndrome (progressive supranuclear palsy). *Neurology.* 1994; 44:2015–19. [PubMed: 7969952]
7. Braak H, Braak E. Neuropathological staging of Alzheimer-related changes. *Acta neuropathol (Berl).* 1991; 82:239–59. [PubMed: 1759558]
8. Dickson DW. Required techniques and useful molecular markers in the neuropathologic diagnosis of neurodegenerative diseases. *Acta Neuropathol.* 2005; 109:14–24. [PubMed: 15645265]
9. Dickson DW, Rademakers R, Hutton ML. Progressive supranuclear palsy: pathology and genetics. *Brain Pathol.* 2007; 17:74–82. [PubMed: 17493041]
10. Oshima K, Tsuchiya K, Iritani S, Nilzato K, Akiyama H, Arai H, et al. An autopsy case of “progressive supranuclear palsy” without psychiatric or neurologic signs. *No to Shinkei – Brain & Nerve.* 2004; 56:157–61. [PubMed: 15098361]
11. Beach TG, Sue LI, Walder DG, Roher AE, Lue L, Vedders L, et al. The Sun Health Research Institute Brain Donation Program: description and experience, 1987-2007. *Cell Tissue Bank.* 2008; 9:229–45. [PubMed: 18347928]
12. Chin SS, Goldman JE. Glial inclusions in CNS degenerative diseases. *J Neuropathol Exp Neurol.* 1996; 55:499–508. [PubMed: 8627339]
13. Dickson DW. Neuropathologic differentiation of progressive supranuclear palsy and corticobasal degeneration. *J Neurol.* 1999; 246(Suppl 2):II6–15. [PubMed: 10525997]
14. Jackson M, Lowe J. The new neuropathology of degenerative frontotemporal dementias. *Acta Neuropathol.* 1996; 91:127–34. [PubMed: 8787144]
15. Litvan I, Hauw JJ, Bartko JJ, Lantos PL, Daniel SE, Horoupian DS, et al. Validity and reliability of the preliminary NINDS neuropathologic criteria for progressive supranuclear palsy and related disorders. *J Neuropathol Exp Neurol.* 1996; 55:97–105. [PubMed: 8558176]
16. Mirra SS, Heyman A, McKeel D, Sumi SM, Crain BJ, Brownlee LM, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Part II. Standardization of the neuropathologic assessment of Alzheimer's disease. *Neurology.* 1991; 41:479–86. [PubMed: 2011243]

17. Braak H, Braak E. Demonstration of amyloid deposits and neurofibrillary changes in whole brain sections. *Brain Pathol.* 1991; 1:213–6. [PubMed: 1669710]
18. Nath U, Ben-Shlomo Y, Thomson RG, Morris HR, Wood NW, Lees AJ, et al. The prevalence of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome) in the UK. *Brain.* 2001; 124:1438–49. [PubMed: 11408338]
19. Troncoso JC, Martin LJ, Dal Forno G, Kawas CH. Neuropathology in controls and demented subjects from the Baltimore Longitudinal Study of Aging. *Neurobiol Aging.* 1996; 17:365–71. [PubMed: 8725897]
20. White L, Small BJ, Petrovitch H, Ross GW, Masaki K, Abbott RD, et al. Recent clinical-pathological research on the causes of dementia in late life: update from the Honolulu-Asia Aging Study. *J Geriatr Psychiatry Neurol.* 2005; 18:224–7. [PubMed: 16306244]
21. Nath U, Ben-Shlomo Y, Thomson RG, Lees AJ, Burn DJ. Clinical features and natural history of progressive supranuclear palsy: A clinical cohort study. *Neurology.* 2003; 60:910–6. [PubMed: 12654952]
22. Williams DR, de Silva R, Paviour DC, Pittman A, Watt HC, Kilford L, et al. Characteristics of two distinct clinical phenotypes in pathologically proven progressive supranuclear palsy: Richardson's syndrome and PSP-parkinsonism. *Brain.* 2005; 128:1247–58. [PubMed: 15788542]
23. Sabbagh MN, Sandhu SS, Farlow MR, Vedders L, Shill HA, Caviness JN, et al. Correlation of clinical features with argyrophilic grains at autopsy. *Alzheimer Dis Assoc Disord.* 2009; 229–33. [PubMed: 19812464]
24. Togo T, Cookson N, Dickson DW. Argyrophilic grain disease: neuropathology, frequency in a dementia brain bank and lack of relationship with apolipoprotein E. *Brain Pathol.* 2002; 12:45–52. [PubMed: 11770901]
25. Bigio EH, Lipton AM, Yen SH, Hutton ML, Baker M, Nacharaju P, et al. Frontal lobe dementia with novel tauopathy: sporadic multiple system tauopathy with dementia. *J Neuropathol Exp Neurol.* 2001; 60:328–41. [PubMed: 11305868]
26. Santpere G, Ferrer I. Delineation of early changes in cases with progressive supranuclear palsy-like pathology. Astrocytes in striatum are primary targets of tau phosphorylation and GFAP oxidation. *Brain Pathology.* 2009; 19:177–87. [PubMed: 18462470]
27. Schultz C, Ghebremedhin E, Del Tredici K, Rüb U, Braak H. High prevalence of thorn-shaped astrocytes in the aged human medial temporal lobe. *Neurobiol Aging.* 2004; 25:397–405. [PubMed: 15123344]
28. Bouras C, Hof PR, Giannakopoulos P, Michel JP, Morrison JH. Regional distribution of neurofibrillary tangles and senile plaques in the cerebral cortex of elderly patients: a quantitative evaluation of a one-year autopsy population from a geriatric hospital. *Cereb Cortex.* 1994; 4:138–50. [PubMed: 8038565]
29. Beach TG, Adler CH, Lue LI, Sue LI, Bachalakuri J, Henry-Watson J, et al. Unified staging system for Lewy body disorders: correlation with nigrostriatal degeneration, cognitive impairment and motor dysfunction. *Acta Neuropathol.* 2009; 117:613–34. [PubMed: 19399512]
30. Adler CH, Connor DJ, Hentz JG, Sabbagh MN, Caviness JN, Shill HA, et al. Incidental Lewy body disease: clinical comparison to a control cohort. *Mov Disord.* 2010; 25:642–6. [PubMed: 20175211]
31. Keith-Rokosh J, Ang LC. Progressive supranuclear palsy: a review of co-existing neurodegeneration. *Can J Neurol Sci.* 2008; 5:602–8. [PubMed: 19235444]
32. Oshima K, Dickson DW. Cortical Alzheimer type pathology does not influence tau pathology in progressive supranuclear palsy. *Int J Clin Exp Pathol.* 2009; 2:399–406. [PubMed: 19158937]
33. Josephs KA, Mandrekar JN, Dickson DW. The relationship between histopathological features of progressive supranuclear palsy and disease duration. *Parkinsonism Relat Disord.* 2006; 12:109–12. [PubMed: 16337422]

FIGURE 1.

Photomicrographs a-g show neurons and glia that are immunoreactive for abnormally phosphorylated tau protein (AT8 antibody, black color). Photomicrographs 'h' and 'i' show neurons and glia reactive with the Gallyas silver stain (black color). The Gallyas silver stain is specific for abnormally phosphorylated tau protein. The counterstain is Neutral Red. With both stains, normal brain tissue is unstained (no black color). a) Superior temporal gyrus, showing frequent immunoreactive neurons and glia (case #1). b) Dentate nucleus of cerebellum, showing frequent immunoreactive neurons (case #2). c) Inferior frontal gyrus, showing frequent immunoreactive neurons and glia (case #3). d) Pontine nuclei, showing multiple immunoreactive neurons (case #5). e) Putamen, showing frequent immunoreactive

neurons and glia (case #4). f) Dentate nucleus, showing frequent immunoreactive neurons (case #2). g) Pontine nuclei, showing higher magnification of immunoreactive neurons (case #3). h) Superior temporal gyrus, showing a tufted astrocyte, a small neurofibrillary tangle and two coiled bodies (case #1). i) Putamen, showing two coiled bodies (case #4).

TABLE 1
Neuropathological findings of the 5 patients with incidental neuropathological PSP

	H & E Staining	Gallyas, Campbell-Switzer, and Thioflavine S Staining	Alpha-synuclein immunostaining
Case 1	<ul style="list-style-type: none"> Non-specific astrocytic gliosis was mild to moderate in the frontal lobe upper neocortical layers, mild and patchy in the amygdala and entorhinal cortex, mild to moderate in the hippocampal CA1 region. Substantia nigra showed mild to moderate loss of pigmented neurons 	<ul style="list-style-type: none"> Senile plaques absent in the neocortices; sparse focal concentrations of diffuse plaques in the temporal and parietal cortex; moderate to frequent diffuse plaques in the occipital cortex Rare to sparse to focally frequent numbers of small and large neuronal tangles, tufted astrocytes, and coiled bodies in the frontal, temporal, and parietal neocortex Frequent coiled bodies, tufted astrocytes, and thorned astrocytes in the superior temporal gyrus, and within focal areas of the frontal and parietal cortex Sparse numbers of neurofibrillary tangles (NFTs), tufted astrocytes, and thorned astrocytes in the putamen and globus pallidus; infrequent NFTs in the anterior insular cortex and anterior cingulate gyrus; rare tangles in the substantia nigra Braak and Braak neurofibrillary tangle scoring was Stage III 	<ul style="list-style-type: none"> No Lewy bodies or Lewy neurites
Case 2	<ul style="list-style-type: none"> Mild non-specific gliosis in the upper layer in the neocortical regions, as well as the amygdala, hippocampus, and entorhinal cortex. Substantia nigra and locus ceruleus were mildly depleted of pigmented neurons 	<ul style="list-style-type: none"> Moderate to frequent senile plaques (more of diffuse type); moderate density of neuritic or cored plaques; very sparse plaques in the striatum; moderate plaque densities in the thalamus. Sparse to moderately dense NFTs in the frontotemporal cortex; moderate numbers of NFTs in the substantia nigra, pons, and dentate cerebellar nuclei; moderate tangle density in the substantia nigra; rare tangles in the pontine nuclei; moderate tangles in the cerebellar dentate nucleus. Moderate to frequent densities of abnormal glia in the frontal cortex, including frequent coiled bodies, moderate densities of astrocytes with fibrous and protoplasmic morphology; rare to sparse tufted astrocytes, and rare thorned astrocytes. 	<ul style="list-style-type: none"> No Lewy bodies or Lewy neurites
Case 3	<ul style="list-style-type: none"> Non-specific gliosis which was mild in the upper neocortical areas and basal ganglia, mild to moderate in the cingulate gyrus cortex, amygdala, and CA1 region of the hippocampus, and moderate to marked in the entorhinal cortex and dentate nucleus 	<ul style="list-style-type: none"> Complete absence of senile plaques in the brain Occasional NFTs seen in the large neurons of the caudate and putamen; sparse to moderate densities of NFTs, pretangles, and tufted astrocytes in the frontal lobe, putamen, thalamus, subthalamic nucleus, globus pallidus, substantia nigra, pontine nuclei, and cerebellar dentate nucleus, with occasional 	<ul style="list-style-type: none"> Incidental Lewy bodies were found: one Lewy body each was seen in the dorsal medulla and the anterior cingulate gyrus, along with sparse Lewy bodies in the amygdala and entorhinal cortex.

	H & E Staining	Gallyas, Campbell-Switzer, and Thioflavine S Staining	Alpha-synuclein immunostaining
	<ul style="list-style-type: none"> Mild loss of pigmented neurons in the substantia nigra and locus ceruleus 	<p>thorned astrocytes and coiled bodies; moderate densities of NFTs and sparse to moderate densities of argyrophilic grains in the amygdala; frequent tangles and grains in the hippocampal CA1 region; sparse grains in the entorhinal cortex.</p> <ul style="list-style-type: none"> Braak and Braak neurofibrillary tangle scoring was stage V 	
Case 4	<ul style="list-style-type: none"> Mild to moderate non-specific gliosis in neocortical areas in the inferior parietal lobule; focally moderate to severe gliosis in the anterior cingulate gyrus; patchy moderate gliosis with scattered swollen eosinophilic neurons in the amygdala and entorhinal cortices Marked neuronal loss and gliosis in hippocampal CA1 region; moderate focal gliosis in the caudate No neuronal loss or gliosis in the subthalamic nucleus; no neuronal loss in the pigmented neurons of the substantia nigra or locus ceruleus 	<ul style="list-style-type: none"> Neocortical areas devoid of senile plaques except for one focus with a few diffuse plaques in the frontal lobes; rare astrocytic plaque-like formations in the frontal, temporal, and parietal neocortex; rare to sparse argyrophilic grains, neurofil threads, tufted astrocytes, and NFTs in the inferior temporal neocortex; widely scattered neurons with cytoplasmic inclusions composed of argyrophilic filaments and granules in the fusiform gyrus. All these changes were seen at much increased densities in the amygdala, entorhinal cortex, and area CA1 of the hippocampus. Rare coiled bodies in the medial temporal lobe white matter; moderate numbers of tufted astrocytes in the putamen; moderate numbers of coiled bodies were present along with sparse neuronal tangles and tufted astrocytes in the putamen 	<ul style="list-style-type: none"> No Lewy bodies or Lewy body neurites
Case 5	<ul style="list-style-type: none"> Moderate non-specific gliosis of the upper cortical areas Moderate to marked gliosis in the amygdala and entorhinal cortex; mild patchy Purkinje cell loss in the superior cerebellar vermis Occasional hypertrophic astrocytes in the caudate, and scattered pigment deposits in the putamen Marked depletion of neurons in the nucleus basalis of Meynert; marked gliosis in the hypothalamus, and focal gliosis in the thalamus Moderate depletion of pigmented neurons in the substantia nigra, while the locus ceruleus was severely depleted 	<ul style="list-style-type: none"> Occasional tangles in area CA1 of the hippocampus Sparse to moderate neuritic and cored plaques and rare NFTs in the neocortical areas, except for the inferolateral temporal cortex where there were sparse to moderate tangles Moderate tangles in the amygdala, moderate to frequent tangles in area CA1 of the hippocampus, and frequent tangles in the entorhinal cortex Occasional tangles and tufted astrocytes in the putamen; sparse to moderate tangles in the globus pallidus; moderate to frequent tangles in the subthalamic nucleus; moderate tangles in the substantia nigra Occasional tangles in the pontine nuclei and dentate nucleus of the cerebellum 	<ul style="list-style-type: none"> No Lewy bodies or Lewy body neurites

TABLE 2

Gallyas-positive PSP features density grading in possible incidental PSP versus clinical PSP; mean (SD), N.

	Incidental PSP	Clinical PSP	<i>P</i>	<i>P</i>_{Hochberg}^a
Frontal	1.2 (1.2), 5	1.57 (0.88), 29	.44	.88
Temporal	0.9 (1.2), 4	0.96 (0.82), 28	.88	.88
Parietal	0.60 (0.65), 5	0.88 (0.73), 30	.51	.88
Putamen	0.88 (0.85), 4	2.04 (0.64), 28	.004	.04*
Subthalamic nucleus	0.8 (1.2), 4	2.47 (0.71), 25	.002	.02*
Globus pallidus	1.25 (0.87), 4	2.44 (0.79), 28	.01	.08
Thalamus	0 (0), 3	1.7 (1.2), 17	.04	.28
Substantia nigra	1.1 (1.0), 4	1.88 (0.86), 29	.14	.70
Pons	0.38 (0.25), 4	1.20 (0.88), 24	.08	.48
Dentate nucleus	1.00 (0.91), 4	1.40 (0.63), 28	.32	.88

^a Accounting for multiple comparisons

* statistically significant

TABLE 3

Gallyas-positive PSP features density grading greater than 1.5 (grand median) in possible incidental PSP versus clinical PSP.

	Incidental PSP	Clinical PSP	P
Frontal	1/5 (20%)	12/29 (41%)	.63
Temporal	1/4 (25%)	6/28 (21%)	>.99
Parietal	0/5 (0%)	3/30 (10%)	>.99
Putamen	1/4 (25%)	20/28 (71%)	.11
Subthalamic nucleus	1/4 (25%)	21/25 (84%)	.03*
Globus pallidus	1/4 (25%)	23/28 (82%)	.04*
Thalamus	0/3 (0%)	9/17 (53%)	.22
Substantia nigra	2/4 (50%)	16/29 (55%)	>.99
Pons	0/4 (0%)	7/24 (29%)	.55
Dentate nucleus	1/4 (25%)	10/28 (36%)	>.99

* statistically significant

TABLE 4

Comparison of distribution of neuronal loss and gliosis between clinical PSP versus incidental PSP cases.

	% of Incidental PSP (n=5) with (+)gliosis/neuronal loss	% of Clinical PSP (n=32) with (+)gliosis/neuronal loss
Frontal Lobe	60%	88%
Putamen	20%	56%
Globus Pallidus	0%	31%
Subthalamic Nucleus	0%	25%
Substantia Nigra	80%	94%
Brainstem Tegmentum	80%	94%
Cerebellar Dentate Nucleus	40%	28%

TABLE 5
Comparison of pigmented neuron loss in the substantia nigra between clinical PSP and incidental PSP cases

	Incidental PSP (n = 5)	Clinical PSP (n = 32)	P
At least mild neuron loss (score > 0)	4 (80%)	30 (94%)	.36
At least moderate neuron loss (score > 1)	2 (40%)	26 (81%)	.08
Severe neuron loss (score > 2)	0 (0%)	17 (53%)	.05*
Neuron loss score; mean (SD)	1.20 (0.84)	2.28 (0.92)	.03*

* statistically significant

TABLE 6

Total plaque density grade, NFT grade, and Braak NFT stage of possible incidental versus clinical PSP cases. Mean (SD), N.

	Incidental PSP	Clinical PSP	P value
<u>Total Plaque Density Grade</u>			
Frontal	0.9 (1.2), 5	1.2 (1.3), 31	.64
Temporal	0.9 (1.3), 5	1.1 (1.3), 31	.78
Parietal	0.8 (1.2), 5	1.3 (1.3), 31	.43
<u>NFT Grade</u>			
Frontal	0.60 (0.65), 5	0.65 (0.75), 31	>.99
Temporal	0.88 (0.56), 5	0.73 (0.87), 31	.73
Parietal	0.50 (0.71), 5	0.56 (0.79), 31	.89
<u>Braak NFT Stage</u>	3.60 (0.89), 5	3.4 (1.4), 32	.86