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A geographical cluster of progressive supranuclear palsy in northern France

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Abstract

Objective: To describe a cluster of progressive supranuclear palsy (PSP) in northern France. PSP has not been reported in geographical, temporal, or occupational clusters. A unit of Neurology and Neurogeriatrics opened in 2005 at the Centre Hospitalier de Wattenloos, serving the population of Wattenloos and Leers (combined population 51,551) and parts of neighboring towns. For most of the 20th century, this area was a center for chromate and phosphate ore processing, textile dyeing, and tanning. Significant industrial waste persists close to residential areas.

Methods: From 2005 to 2014, 92 patients with PSP at Centre Hospitalier de Wattenloos were identified and studied. Detailed residential data were available in the medical records. Eighty cases have had magnetic resonance head scanning and 60 have died, of whom 13 have been examined neuropathologically.

Results: The ratio of observed to expected PSP incidence over the period 2005 to 2012 was 12.3 (95% confidence interval: 7.4–35.9). Mean onset age was 74.3 years. The Richardson syndrome/PSP-parkinsonism ratio was 43%/42%. Four other phenotypes each occurred in 2% to 5%. Onset was gait/balance difficulty in 52%. None of the 92 affected patients were relatives and 7 were of North African ancestry. MRI was compatible with a clinical diagnostic of PSP in all cases. Histopathologic examination confirmed neurofibrillary degeneration and tufted astrocytes in all autopsied cases. Western blots revealed a typical tau 4R doublet. The tau H1 haplotype occurred in 95.8% of cases' chromosomes.

Conclusions: We have identified a cluster of PSP in a geographical area with severe environmental contamination by industrial metals.

Progressive supranuclear palsy (PSP) is an uncommon sporadic disorder with no reports in the literature of geographical clusters. Its incidence in developed countries is approximately 1.2 per 100,000 per year and the prevalence of investigator-diagnosed cases is 5 to 6 per 100,000.

The cause is unknown but several familial clusters have now been reported.^{2,9} Olfaction, affect, and reaction time assessments revealed more frequent dysfunction among relatives of individuals with PSP than among relatives of controls.⁷

Genetic variations in *MAPT* locus are a mild risk factor for PSP.⁸ An inversion of a 900-kb span of chromosome 17 defines the H1 haplotype.^{9,11} A subhaplotype of H1 designated H1c is responsible for the association between the H1 haplotype and PSP.^{12,13}

Studies of nongenetic risk factors have found lesser educational attainment.^{14,16} Two geographical clusters of illnesses similar to PSP have been described on Guam^{17,20} and in Guadeloupe where a case-control survey²¹ revealed a strong association (odds ratio 8.3, $p < 0.001$) of Guadeloupean tauopathy with consumption of traditional medicines containing annonacin,²² a mitochondrial toxin that produces a tauopathy in a rodent model.²³

Wattrelos is a town in northern France where textile dyeing plants and tanneries operated for most of the 20th century, using arsenic and chromate from the nearby chemical plants. Arsenic and hexavalent chromium contamination have been documented in the soils of the sites of former plants in Wattrelos and Leers,²⁴ where the cluster of PSP cases described in this report live.

METHODS

Patients. Wattrelos has one hospital, the Centre Hospitalier de Wattrelos (CHW). It is the only medical facility in the town and has an acute and chronic inpatient and outpatient service. In 2005, a Department of Geriatric Neurology was established in the hospital when one of the authors (D.C.-L.) was appointed to the staff. In April 2007, she diagnosed the first patient with PSP at CHW. By July 2014, 92 patients, all of whom had fulfilled the National Institute of Neurological Disorders and Stroke–Society for PSP criteria for clinically probable PSP, had been studied.²⁵ Most patients manifested many of the additional supportive criteria for PSP including abnormal neck posture, signs of spastic face, poor or absent response of bradykinesia and axial and bulbar signs to levodopa therapy, early dysphagia and dysarthria, and early cognitive impairment with at least 2 of the following: apathy, abstract thought impairment, decreased verbal fluency, imitation behavior, or frontal release signs. Eighty-nine patients (97%) were referred by primary care physicians and 3 (3%) by neurologists or physiotherapists.

Clinical and imaging study. Each patient received a trial of carbidopa/levodopa with evaluations at 3 months and 6 months using the Unified Parkinson's Disease Rating Scale, MRI, videotape records, olfactory testing, Folstein Mini-Mental State Examination, and detailed neuropsychological examination for patients with Mini-Mental State Examination score >19 of 30. The neuropsychological tests comprised the Grober and Buschke test,²⁶ Frontal Assessment Battery,²⁷ Cognitive, Trail Making Test (TMT), Stroop, images description (DO 80), and praxis analysis. Eye and eyelid movements were examined. Saccades, antisaccades, pursuit, and optokinetic nystagmus (OKN) were tested at the first examination. OKN was evaluated using a handheld OKN tape. Command saccades were considered slow if the progress of the movement in response to direct the eyes to a peripheral target was perceptible to the examiner.

With assistance from family members, we recorded each residential street address since birth, occupations, job descriptions, and hobbies.

Olfactory testing was performed using the European Test of Olfactory Capacities.²⁸ A speech therapist analyzed buccofacial apraxia²⁹ and language (Boston Naming Test). Brain MRI study was performed in all patients except in the 12 with medical contraindications, in whom a CT was undertaken.

Standard protocol approvals, registrations, and patient consents. We received approval from the institutional ethical standards committee on human experimentation, and we received written informed consent from all patients (none had guardians).

Epidemiologic study. The rationale for defining the temporal limits of the cluster analysis to the period 2005 to 2012 is that before author D.C.-L. arrived at CHW in 2005, some cases with PSP would likely have been misdiagnosed. She diagnosed her first case of PSP in Wattrelos in 2007. We censored

the incidence analysis in 2012 because cases with onset since then are unlikely to have reached clinical attention to date.

To calculate the expected incidence of PSP, we used the entire population of both Wattrelos and Leers although residents of those towns have the option of seeking neurologic care at the university center in Lille and elsewhere. This may have led us to underestimate the PSP incidence in those 2 towns despite the reports of neurologists in nearby towns that they saw little or no PSP. We obtained population data for 2006 and 2011 and used the mean of these figures to make our calculations. For the expected incidence, we averaged the results of all 4 formal studies of PSP frequency to date,¹⁻⁴ arriving at a figure of approximately 1.2 cases per 100,000 per year. We did not age-adjust because the proportion of the Wattrelos-Leers population aged 60 years and older is similar to that in the areas studied in the 4 surveys.

Pathologic study. Thirteen postmortem brains were obtained with consent from the patients' families. The left half was fixed in formaldehyde and the right was frozen at -80°C for biochemical and genetic study. Microscopic examination was performed on paraffin-embedded material after staining with hematoxylin and eosin, ubiquitin, α -synuclein, Gallyas silver, and anti-tau (polyclonal antibody; Dako, Carpinteria, CA; raised against the C-terminal part of the recombinant human protein, including the 4 repeats).

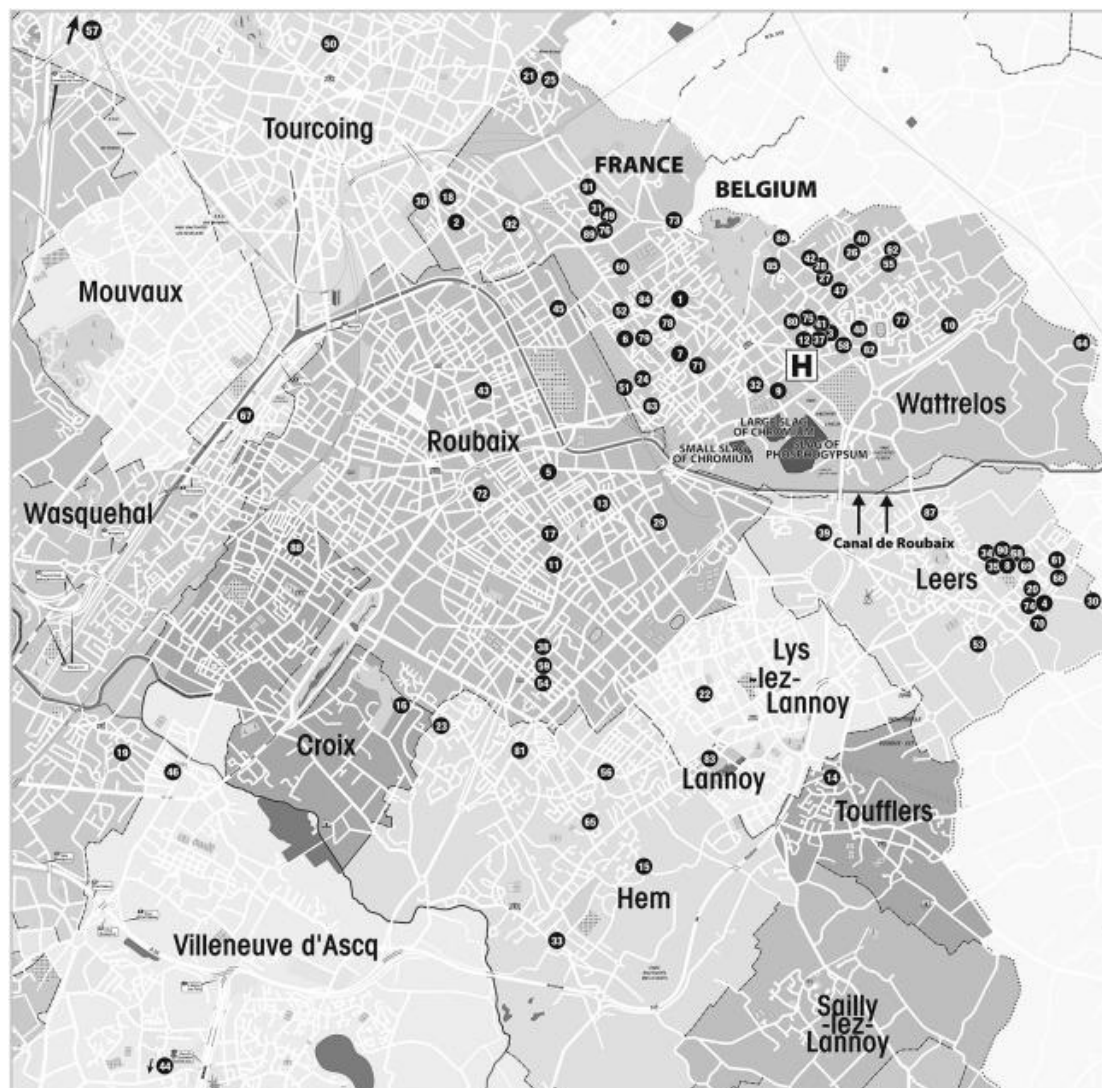
Biochemical study. Frozen brain samples from the mesencephalon and Brodmann areas (BAs) 4, 10, and 18 were processed as previously described.³⁰ Brain homogenates containing 30 μg of total proteins were loaded on sodium dodecyl sulfate–polyacrylamide gel electrophoresis. Western blot analysis was processed using anti-pSer396, a monoclonal antibody against phosphorylated serine 396 on tau proteins (dilution 1:10,000; Invitrogen, Carlsbad, CA). Phosphorylation-independent antibody anti-tau Cter, directed against the last amino acids of tau sequence, was also used at the dilution of 1:10,000.³¹

Molecular genetic study. DNA was prepared from frontal and occipital cortices by phenol-chloroform extraction. *MAPT* H1/H2 genotyping was performed on brain samples using the 238–base pair insertion/deletion polymorphism in intron 9 as described by Baker et al.⁹ Genotyping of SNP rs42557 was performed by standard PCR reaction and sequencing on an ABI 3130XL DNA analyzer (Applied Biosystems, Foster City, CA). Primers are available upon request.

RESULTS

Epidemiologic data. We compiled a detailed clinical database of the 92 patients identified since 2007 as having PSP and living in Wattrelos, Leers, and nearby towns. The incidence of PSP elsewhere is 1.2 cases/10⁵/y.¹⁻⁴ The population of Wattrelos in 2011 was 41,538.³² The catchment area for its hospital includes all of that town and most of Leers, immediately to the southeast, with a 2011 population of 9,343,³³ and smaller parts of other towns. Of the 92 incident PSP cases, 62 were living in Wattrelos or Leers at the time of diagnosis and experienced symptom onset between January 1, 2005, and December 31, 2012.

The geography of the cluster appears to be limited largely to Wattrelos and Leers. Inquiries of neurologists at the University of Lille, the closest referral center, revealed only the expected very low frequency of patients with PSP. The places of residence of the 92 patients at the time of PSP onset appear in the [figure](#) along with the hospital where they were diagnosed, the slag heaps, and the canal that receives runoff from the heaps. The numbers correspond to the patients' names in alphabetical order.



Figure

Places of residence of the 92 patients at the time of PSP onset

Map showing the places of residence of the 92 patients at the time of PSP onset, along with the hospital where they were diagnosed, the slag heaps, and the canal that receives runoff from the heaps. The numbers correspond to the patients' names in alphabetical order. PSP = progressive supranuclear palsy.

The total population of Wattrelos and Leers averaged between 2006 and 2011 was 51,511. This gave an at-risk figure for the 8-year observation period of 412,088 person-years, for an expected absolute number of PSP cases of 4.95 over that period. As the observed number of incident cases was 62, the observed to expected (O/E) ratio is 12.3. The 95% confidence interval of the O/E ratio may be estimated by comparison with the interval of 2 to 10 for the prevalence figure (approximately 6 per 100,000) on which the incidence figures were calculated. This would give an interval of 0.4 to 2.0 for the incidence figure of 1.2/100,000/y and yield a 95% confidence interval for the O/E ratio of 7.4 to 35.9.

Clinical features of the patients. For the 92 patients ascertained from April 2007 to July 2014, the male to female sex ratio was 1.11, with 43 women. The mean age at onset was 74.3 years (SD 7.89, range 50–93) (women, 75.9 years; men, 71.9 years). Onset age differed slightly between PSP in this cluster and sporadic PSP in New Jersey³⁴ (67, SD 7.3 years) but was similar to the onset age in the UK study.² The fraction of the population aged 60 years and older does not differ between Wattrelos (16.6%) and other studies. For the 60 patients known to be deceased, disease duration was 5.74 years (SD 2.2, range 2–12). At the first examination, phenotypic variants included Richardson syndrome in

30 patients (33%), PSP-parkinsonism in 49 (53%), progressive aphasia with PSP in 2 (2%), speech apraxia with PSP in 5 (5.4%), pure akinesia with gait freezing (PAGF) in 3 (3%), and frontotemporal dementia with PSP in 3 (3%).

The first symptom was gait or balance problems in 52%, very close to the 60% in the literature for PSP, axial and/or symmetric parkinsonism in 21%, cognitive decline in 14%, speech disorders in 8%, tremor in 2%, and visual difficulties in 1%. Eighty-nine percent reported falls at the first examination. Seventy-seven percent of patients experienced backward falls. All patients had prominent body bradykinesia and axial rigidity. Twenty percent had rest tremor. At first examination, vertical saccadic eye movements were slow in 85%, and down gaze was absent in 15%. Fifteen percent had square wave jerks.

As the disease progressed (3 years' follow-up), the ratio of phenotypic variants changed, and 40 patients (43%) had Richardson syndrome while 39 patients (42%) had PSP-parkinsonism. At the late stage of the disease, all patients fulfilled ocular motor criteria for PSP with restriction of vertical eye motion higher than 50% and slow vertical saccadic eye movements. Forty-three patients had complete vertical gaze palsy as demonstrated in the video on the *Neurology*® Web site at Neurology.org.

In patients with Richardson syndrome, eyelid symptoms, including eyelid apraxia and blink frequency below 1/min were present in all patients after 3 years of disease progression. In PSP-parkinsonism, eyelid motion was reduced but preserved, and blepharospasm was more common and seen in 5 patients. Fifty-six patients had eyelid apraxia (61%), 40 with Richardson syndrome (100%) and 16 with PSP-parkinsonism (40%). OKN quick phases were absent in all patients and antisaccades were impaired in all patients.

Only one patient experienced a significant and sustained response to carbidopa/levodopa, with a 40% improvement in the Unified Parkinson's Disease Rating Scale, during 3 years. The lack of levodopa responsiveness was obvious in all cases but one.

This cluster differs in its distribution of PSP's major clinical subtypes, Richardson syndrome and PSP-parkinsonism (43%:42% vs 54%:32%,³⁵ respectively).

Thirteen patients to date have come to autopsy, 9 with Richardson syndrome (66%), 2 with speech apraxia (15%), one with PSP-parkinsonism, and one with PAGF.

Initial cognitive testing showed impaired episodic memory in 84 patients (91%) and biographic memory in 76 patients (83%). The Frontal Assessment Battery was performed in 47 patients, with mean score (of best possible 18) of 10.3 (SD 3.88). We administered the Grober and Buschke test to the 28 patients able to perform it. It showed reduced free recall (mean: 6.5 words/16; SD 2.5) and preserved cued remembering (mean: 14.5/16; SD 2). The mean results for TMT A was 83 seconds (SD 34; below 50th percentile) and for TMT B was 241 seconds (SD 120; 25th percentile 25). Patients had a mean of 2 errors on the Stroop test. Olfactory testing showed severe hyposmia in all patients, with a mean identification of 5 smells out of 16.

None of our patients or surviving relatives endorsed a family history of PSP. Family history of neurologic disorders was claimed by 13 patients (14%): dementia in 9 (10%) and parkinsonism in 4 (4%). Seven (8%) of our patients were of North African ethnic origin and were born in Algeria.

MRI was performed in 80 patients (87%). T1-weighted axial images showed midbrain atrophy in all cases, with loss of convexity of the lateral margin of the midbrain tegmentum, and widened interpeduncular angle. Thinning of the tectum and atrophy of the superior colliculi were common. A hummingbird sign was obvious in patients with Richardson syndrome, with normal pontine diameter.

Pathology. All 13 autopsied cases satisfied neuropathologic criteria for definite PSP.³⁶ Macroscopic examination showed global atrophy disproportionately affecting brainstem. Microscopic study ([table](#)) showed severe neuronal loss involving substantia nigra and locus coeruleus. AD2 antibody showed diffuse tau protein deposits. Globoid neurofibrillary tangles and tufted astrocytes were prominent in the substantia nigra, subthalamic nucleus, locus coeruleus, midbrain tegmentum, cerebellar nuclei,

cerebellar cortex, pallidum, and bulb. Neurofibrillary tangles were less abundant in entorhinal, temporal, and primary motor cortices. Tau deposits were less abundant in the subthalamic nucleus in 2 patients with PSP-parkinsonism and PAGE.

Table

Anatomical pathologic findings in the 13 autopsied cases from the Wattlelos/Leers PSP cluster

Anatomical pathologic findings in the 13 autopsied cases from the Wattlelos/Leers PSP cluster														
Patient no.														
Quantity of tau protein	1	2	3	4	5	6	7	8	9	10	11	12	13	
RS	RS	RS	PAGF	RS	RS	PSP-P	RS	RS	RS	RS	RS	AOS	AOS	
(BA4)	++	++	+	+	+	+	++	++	++	++	++	+++	+++	
(9)	+	++	+	+	+	++	++	++	++	++	+	+++	+++	
B)	0	0	0	0	0	++	+	+	0	0	+	+	++	
	0	++	0	0	0	+	0	0	0	++	0	++	++	
	+	+	+	+	+	+++	+++, grains	+	+	+	+	+	++++, grains	
	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+	+++	
	+++	++	++	+	++	+	+	+++	++	+	+	+	+++	
	+	+	++	++	+++	+	++	++	+	+++	+	+	+++	
	+	+	+	+	+	0	+	++	+	+	+	0	+++	
	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+	+++	
	+++	+++	+++	+++	+++	++	+++	+++	+++	+++	+++	+	+++	
	+++	+++	+++	++	++	++	++	++	++	+++	+++	+	+++	
	+++	+++	+++	+++	++	++	+++	+++	+++	+++	+++	+	+++	
	++	++	+++	+	+	+	+	+	+	+	+	+	++	
(bellum)	+++	++	++	+	++	++	+	+++	+	+++	++	+	+++	
se/5)	0	0	1	2	0	3	0	3	2	0	3	2	4	
	0	0	0	0	0	0	0	0	0	0	0	0	0	
Lacunes white matter; pons														
AD neuritic plaques														
Micro-lacunes in basal ganglia														
Moderate CAA and arteriosclerosis														
AD neuritic plaques														
PSP = progressive supranuclear palsy; PSP-disease; AOS = apraxia of speech; BA = Brodmann area; CAA = cerebral amyloid angiopathy; PAGF = pure akinesia with gait freezing; PSP = progressive supranuclear palsy; PSP-RS = Richardson syndrome.														
burden in the 15 major areas involved in PSP from 0 to +++ (0 = absent; + = mild; ++ = moderate; +++ = severe).														
/oid and α-synuclein burden from 0 to 3.														

Open in a separate window

In 2 patients with PSP and speech apraxia phenotype, neurofibrillary tangles were prominent in motor cortex and fronto-opercular cortex. In one patient with mild cognitive impairment, neurofibrillary tangles involved mainly the subcortical areas. Moderate β -amyloid deposition was observed in hippocampal cortex and frontal and motor cortex in older patients. It was observed in 8 brains (61%): moderate in 1 (8%) and more pronounced in 7 (53%). No brain revealed α -synuclein staining.

Vascular lesions were additionally seen in 3 patients (23%), and consisted of vascular lacunes, which appeared as hyperintensities in the white matter on fluid-attenuated inversion recovery MRI sequences, in 2 patients. The extent, intensity, and location of those lesions do not suggest that they would explain the neurologic findings that supported the diagnosis of PSP. One patient had a contraindication to MRI and correlations with pathology were not available.

Biochemical results. Immunoblotting analysis of the different affected brain regions (mesencephalon and primary motor cortex [BA4]) of the first 12 autopsied PSP cases revealed, using the phosphorylation-dependent antibody anti-pSer396, the typical tau electrophoretic profile consisting of a main doublet at 64 and 69 kDa. However, heterogeneity in the signal intensity was observed among the different brain regions. Occipital cortex was never affected whereas frontal areas (BA10) were differentially affected among PSP cases. These findings were consistent with neuropathologic data obtained with AD2 antibodies (the latter is similar to pSer396 antibody).

Genetic results. Of the 24 chromosome 17s in the first 12 autopsied cases, 23 (96%) bore the H1 haplotype. The frequency of allele A of SNP rs242557 occurred in 66.7%. All of the frequencies are similar to those previously described in PSP^{10,13} with an overrepresentation of the H1 haplotype and H1c subhaplotype.

DISCUSSION

Investigations to date suggest that this cluster of PSP is centered on Watrelos and Leers, with very few patients living more than a few kilometers away. Some of the patients who died or discontinued medical care at CHW before the arrival of the first author at the hospital are likely to have been misdiagnosed as Parkinson disease or diffuse cerebrovascular disease.

The distribution of the residences shows high concentration of patients in the eastern part of Leers. A planned further study will include places of residence at multiple time points preceding PSP onset and equivalent time points for controls.

The pathologic and biochemical features of the 13 autopsied cases were typical of PSP. As reported by Williams et al.,³⁵ tau burden was less important in the subthalamic nucleus in patients with PSP-parkinsonism and PAGF.

Vascular lacunes were observed in 3 cases of Richardson syndrome, but were judged to have no conclusive influence on the clinical picture with the possible exception of cognition.

The cause of the cluster will be the subject of subsequent studies. Suspicion must first be directed at the site just south of the center of Watrelos, where large heaps of spent ore (slag) from now-defunct metals extraction industry are located. Other locations in the immediate area may have been contaminated by the numerous textile-dyeing and leather-tanning plants that used metals in their processes. Many residents of the area raise fruits and vegetables in vegetable gardens and allotments for family consumption and for sale at local markets. Some plant products such as thyme commonly grown in home gardens in Watrelos³⁷ are consumed by its residents and have been found to concentrate arsenic and other toxic metals.

Arsenic, a potential neurotoxin, has been found in the soil at the sites of the former chemical plants in Watrelos²⁴ and is present in the phosphate ore formerly processed there, as described also in Pakistan.³⁸ Contamination with chromium is common in Watrelos, but we consider it to be a less likely candidate as a neurotoxin although a synergistic toxicity with arsenic is possible. Aluminum, suspected in the past of a causal link to Alzheimer disease, was not processed in this area.

A genetic founder effect must be considered. None of the patients knew of a relative with a diagnosis of PSP. The proportion with dementia or parkinsonism among family members was no greater than expected, but conclusions await a formal case-control survey. The genetic analysis of the most important genetic risk factors (haplotype H1 and subhaplotype H1c of *MAPT*) showed the expected distribution in the 12 autopsied cases. A future study should compare cases and local controls for genetic markers known to be associated with PSP and also seek still-unsuspected genomic and epigenetic etiologies using more advanced methods.

The pathology of PSP has similarities with postencephalitic parkinsonism although the clinical picture is very different. Our informal inquiries and our access to medical records failed to reveal evidence of any epidemic of encephalitis or of a history of such illness in any of the affected individuals.

If the cause of this cluster can be found, it will provide an important clue to the cause of PSP elsewhere and, by implication, a possible causative factor for other tauopathies.

Supplementary Material

Video:

[Click here to view.](#)

Accompanying Comment:

[Click here to view.](#)

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GLOSSARY

BA	Brodman area
CHW	Centre Hospitalier de Wattrelos
O/E	observed to expected
OKN	optokinetic nystagmus
PAGF	pure akinesia with gait freezing
PSP	progressive supranuclear palsy
TMT	Trail Making Test

Footnotes

Supplemental data at [Neurology.org](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4617163/)

AUTHOR CONTRIBUTIONS

D. Caparros-Lefebvre was involved in analysis and interpretation of data, drafting and revising the manuscript. L.I. Golbe was involved in analysis and interpretation of data, drafting and revising the manuscript. V. Deramecourt was involved in analysis and interpretation of data (neuropathology). C.-

A. Maurage was involved in analysis and interpretation of data (neuropathology). V. Huin was involved in analysis and interpretation of data (genotyping analysis). L. Buée was involved in analysis and interpretation of data (Western blotting). V. Buée-Scherrer was involved in analysis and interpretation of data, and revising the manuscript for intellectual content. H. Obriot was involved in analysis and interpretation of data (Western blotting). B. Sablonnière was involved in analysis and interpretation of data, and revising the manuscript for intellectual content. F. Caparros was involved in analysis of data (MRI). A.J. Lees was involved in revising the manuscript for intellectual content.

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DISCLOSURE

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