Cerebellar ataxia in progressive supranuclear palsy : a clinico-pathological case report

Cerebellar ataxia in progressive supranuclear palsy: a clinico-pathological case report

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Abstract

Several clinical subtypes of progressive supranuclear palsy (PSP) have been described. We present a PSP patient with predominant cerebellar ataxia (PSP-C) and a pathologically confirmed PSP diagnosis. Cerebellar ataxia was observed at disease onset in this patient of European descent. The patient developed a symmetric akinetic-rigid syndrome with supranuclear gaze palsy later in the disease. Dopamine transporter imaging was abnormal and magnetic resonance imaging showed evidence of mesencephalic atrophy and moderate cerebellar atrophy. Post-mortem examination revealed tau-positive pathology in a classical topography for PSP. The initial presentation of PSP-C can show overlapping features with late-onset cerebellar ataxia syndromes. Early falls, absence of autonomic dysfunction and presence of supranuclear gaze palsy in the first years after symptom onset can serve as clinical signs to distinguish PSP-C from late-onset spinocerebellar ataxias, idiopathic late-onset cerebellar ataxia and multiple system atrophy.

Introduction

Several clinical subtypes of progressive supranuclear palsy (PSP) have been described, including PSP-RS (PSP-Richardson's syndrome), PSP-P (PSP-parkinsonism), PSP-PGF (PSP-progressive gait freezing), PSP-PNFA (PSP-progressive non-fluent aphasia) and PSP-bvFTD (PSP-behavioural variant of frontotemporal dementia) [1]. Cerebellar involvement as initial clinical presentation was reported in a minority of PSP patients in previous studies, and seems to be more prevalent in Asian than in Western countries [2-5].

Case report

We present a patient of European descent with cerebellar ataxia at disease onset and a pathologically confirmed PSP diagnosis. Familial history was unremarkable for neurological disorders. This female patient developed truncal ataxia and gait impairment at age 60. The neurological examination did not show any signs suggestive for sensory ataxia. During clinical follow-up, progressive impairment of the postural reflexes was noted, with recurrent falls, starting at age 61. A symmetric and mainly axial hypokinetic-rigid syndrome became evident in the following years. The extrapyramidal symptoms were not responsive to levodopa therapy (200mg levodopa/50mg benserazide t.i.d.). Clinical examination at age 63 revealed a wide-based gait with postural instability and retropulsion. The patient showed severe hypomimia with procerus sign, severe dysarthria, brisk tendon reflexes in four limbs and bilateral extensor plantar responses. Hypometric voluntary saccades were initially observed at disease onset, evolving to vertical supranuclear gaze paralysis at age 64, which was more pronounced for downgaze. A formal cognitive assessment is not available, but major cognitive impairment was not observed. Finally, severe dysphagia and weight loss led to percutaneous endoscopic gastrostomy placement at age 64. Due to the severe swallowing dysfunction, the patient suffered from recurrent aspiration pneumonia and died at age 65. Magnetic resonance imaging of the brain showed midbrain atrophy and moderate cerebellar atrophy (Figure 1). Dopamine transporter imaging (123-I-ioflupane SPECT scan) was abnormal with severely reduced striatal tracer uptake bilaterally (Figure 1). Molecular-genetic testing for spinocerebellar ataxias types 1, 2, 3, 6 and 7 was negative. For the post-mortem examination, the brain was embedded in paraffin after fixation in 10% buffered formalin. Macroscopic examination showed mesencephalic atrophy and mild cerebellar atrophy. Sections from the frontal and temporal lobes, hippocampal region, striatum, subthalamic nucleus, brainstem, area striata and cerebellum were prepared. Immunohistochemical analysis for hyperphosphorylated tau-protein, beta-amyloid, ubiquitin, TDP-43 and p62 proteins was performed. The main abnormalities of the microscopic examination consisted of globose neurofibrillary tangles (NFT), neuritic threads, tufted astrocytes (TUFA), coiled

bodies (CB), neuronal loss and gliosis (Figure 1 and Table 1). The cerebellar dentate nucleus, formatio reticularis, substantia nigra pars compacta and subthalamic nucleus were the most severely affected areas. The pallidum was less affected, with more severe atrophy of the internal pallidum. The iso- and allocortical regions were relatively spared with minimal tau-positive pathology. The dentate nucleus was very severely affected with grumose neuronal degeneration; numerous CBs and globose NFT were observed. There was a mild loss of Purkinje cells, with sparse tau-immunoreactive inclusions in the Purkinje cells. Ubiquitin staining did not show any evidence of Lewy body pathology. Several senile plaques of the diffuse type were present, but not of the neuritic type. Flame-shaped tangles were absent. The findings in the amyloid staining were compatible with Alzheimer's disease neuropathologic changes A2B0C0. TDP-43 inclusions were absent. The neuropathological findings are compatible with a definite diagnosis of PSP.

Discussion

Similar to the initial clinical presentation in the majority of PSP-C patients with a pathologically confirmed diagnosis, truncal ataxia and cerebellar gait impairment were the presenting symptoms in our patient [5]. Specific diagnostic criteria for the PSP-C subtype are not provided within the Movement Disorder Society (MDS) clinical diagnostic criteria for PSP, and the presence of prominent appendicular ataxia is mentioned as a mandatory exclusion criterion [1]. Shimohata and coworkers have proposed clinical diagnostic criteria for PSP-C, but validation in larger patient series is needed [6]. According to these criteria, a diagnosis of probable PSP-C requires: A) a slowly progressive course, B) onset age > 40 years, C) supranuclear gaze palsy, D) truncal and limb ataxia within two years after symptom onset, and E) postural instability with falls within two years after symptom onset. Dysautonomia and the presence of a hot-cross bun sign on brain MRI are considered exclusion criteria for a PSP-C diagnosis. We can conclude that our patient fulfills these diagnostic criteria for probable PSP-C.

The clinical phenotype of PSP-C can resemble a late-onset cerebellar ataxia syndrome and therefore overlapping clinical features with spinocerebellar ataxias or with the cerebellar subtype of multiple system atrophy (MSA-C) can be observed. In a series of 134 clinically diagnosed MSA patients, 15 patients received a definite pathological diagnosis of PSP [7]. Cerebellar ataxia was reported as initial symptomatology in three of these PSP patients, suggesting a clinical diagnosis of PSP-C. In a retrospective study, patients with late-onset cerebellar ataxia rather developed pathologically confirmed PSP-C than pathologically proven MSA-C, in absence of severe autonomic dysfunction and when vertical supranuclear gaze palsy and falls were present within 2 years of disease onset [3]. Koga and coworkers reported 5 PSP-C patients in a population of 1085 autopsy-confirmed PSP patients,

confirming the low prevalence of this PSP subtype [4]. The pathological features of PSP-C patients were not significantly different from the other PSP patients in this large autopsy series. The dentate nucleus in our patient was severely affected with tau-positive pathology. Prominent cerebellar symptoms in PSP patients were associated with more pronounced neuronal loss and tau-positive inclusions in the dentate nucleus in a Japanese autopsy study [2], but not in the Mayo Clinic brain bank study [4].

In line with previous studies, we confirm that cerebellar ataxia can be an initial presentation of PSP. The absence of prominent dysautonomia, early falls and the subsequent development of supranuclear gaze palsy can guide the clinician to the diagnosis of PSP-C. Midbrain atrophy and prominent cerebellar abnormalities on brain MRI can be absent in the initial disease stages, but will eventually develop in later stages in most patients. Our clinico-pathological case report can assist clinicians in the complex differential diagnosis of late-onset cerebellar ataxia and adds to the evidence of presence of the rare PSP-C phenotype in the European population. In the further development of clinical diagnostic criteria for PSP-C, we would suggest to give more weight to the presence of cerebellar ataxia together with supranuclear gaze palsy, in first two years after disease onset. An early diagnosis of atypical PSP phenotypes is highly relevant for future clinical studies with novel tau-based therapies.

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Figure caption

Figure 1: Progressive supranuclear palsy with cerebellar ataxia (PSP-C)

Upper-left: 123-I-ioflupane SPECT scan, showing bilateral reduced striatal tracer uptake

Upper-right: Magnetic resonance imaging (MRI), T2-weighted image: mesencephalic atrophy and moderate vermian and cerebellar atrophy.

Lower-left: Microscopic pathological examination: *A)* AT8 staining (monoclonal antibody for phospho-tau): Frontal cortex and subcortical white matter contain tufted astrocytes (arrow), oligodendroglial coiled bodies (double arrow) and neuritic threads (arrowhead). *B)* AT8 staining: Subthalamic nucleus is severely affected with globose neurofibrillary tangles (arrow) and neuritic threads (arrowhead). *C)* AT8 staining: Substantia nigra. The pigmented neurons contain many globose neurofibrillary tangles (arrow) and neuritic threads (arrowhead). *D)* AT8 staining: Abundant globose neurofibrillary tangles (arrow) and neuritic threads (arrowhead) in the pontine nuclei. *E)* AT8 staining: Dentate nucleus. Globose neurofibrillary tangles (arrow) and neuritic threads (arrowhead) in the dentate nucleus. *F)* Hematoxylin Eosin: Dentate nucleus. The grumose degeneration with swelling of the axons in the dentate gyrus is easily seen. (arrow).

Lower-right: Magnetic resonance imaging (MRI), T1-weighted mid-sagittal image, showing mesencephalic atrophy (humming bird sign) and moderate cerebellar atrophy

Declarations

Ethical compliance statement

The authors confirm that the approval of an institutional review board was not required for this work. Informed consent from the patient was obtained for the inclusion of clinical data in scientific publications. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

Authors' contributions

1. Research project: A. Conception, B. Organization, C. Execution;

2. Manuscript Preparation: A. Writing of the first draft, B. Review and Critique.

DC: 1A, 1B, 1C, 2A, 2B; AS: 1B, 1C, 2B; SC: 1B, 1C, 2B; PMP: 1B, 1C, 2B; JB: 1B, 1C, 2B

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