A case of atypical progressive supranuclear palsy

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Background: Progressive supranuclear palsy (PSP) is a neurodegenerative extrapyramidal syndrome. Studies have demonstrated that PSP can present clinically as an atypical dementing syndrome dominated by a progressive apraxia of speech (AOS) and aphasia.

Aim: We aimed to investigate the clinical presentation of PSP, using a comprehensive multidimensional evaluation, and the disease response to various pharmacological treatments.

Methods: A 72-year-old right-handed male, with 17 years education, who first presented with aphasia, AOS, depression, apathy, and postural instability at 69 years; a complete neuropsychological evaluation, tapping the different cognitive domains, was performed.

Results: Testing revealed a moderate global cognitive deficit (Mini-Mental State Examination test score = 20), low memory test scores (story recall, Rey’s 15-word Immediate and Delayed Recall), and poor phonemic and semantic fluency. The patient’s language was characterized by AOS, with slow speech rate, prolonged intervals between syllables and words, decreased articulatory accuracy, sound distortions, and anomia. Behavioral changes, such as depression, anxiety, apathy, and irritability, were reported. The neurological examination revealed supranuclear vertical gaze palsy, poor face miming, and a mild balance deficit. Magnetic resonance imaging showed only widespread cortical atrophy. Single photon emission computed tomography demonstrated left > right frontotemporal cortical abnormalities. After 6 months, a further neuropsychological assessment showed a progression in cognitive deficits, with additional attention deficits. The patient reported frequent falls, but the neurological deficits remained unchanged. Neuroimaging tests showed the same brain involvement.

Conclusion: Our case highlights the heterogeneity of the clinical features in this syndrome, demonstrating that atypical PSP can present as AOS and aphasia, without the classical features or involvement of the subcortical gray and brainstem region, commonly affected in typical PSP.

Keywords: pharmacological treatments, neuropsychological deficits

Introduction

Progressive supranuclear palsy (PSP) is a neurodegenerative extrapyramidal syndrome, characterized by motor symptoms, such as postural instability, rigidity, akinesia, and behavioral and cognitive symptoms. The disease is progressive, and patients have a median survival of around 6 years after onset of symptomatology, which usually occurs between 55 and 70 years of age. Both sexes are nearly equally affected, with an annual incidence of 5.3 per 100,000 inhabitants in Europe.1-3 The most common problem of PSP is postural instability and frequent falls, followed by dysarthria as the second most common symptom, and bradykinesia as the third. Visual disturbances are also early symptoms. Supranuclear gaze deficits involve either downward or upward gaze and later, horizontal gaze.4
The pathological changes are characterized by neuronal loss, with gliosis and neurofibrillary tangles in the subcortical and brainstem nuclei and the cerebellar dentate nucleus. At the first visit in our clinic, in January 2011, a general physical examination did not reveal any known pathology. A neurological examination detected hypomimic facies; impaired balance; ataxic-type gait; pyramidal-extrapyramidal hypertonia in all four limbs; reduced strength, especially on the right side; wide-base standing position; and supranuclear upgaze paresis.

Magnetic resonance imaging (MRI) showed the ventricular–cisternal system in its normal axis, normal morphology and size, and no areas of altered signal in the brain parenchyma. Diffuse cortical atrophy was present.

Single photon emission computed tomography (SPECT) showed widespread hypoperfusion of the cerebral cortex, with thinning of cortical thickness. The hypoperfusion of both hemispheres appeared more pronounced in the posterior temporal cortex, with a prevalence in the left hemisphere. Perfusion of the basal ganglia and cerebellar hemispheres was preserved.

The patient was assessed by the same neuropsychologist for all follow-ups, using a wide battery of neuropsychological tests to investigate all cognitive functions.

Materials and methods

Case description

The patient was a 72-year-old, right-handed male, with 17 years of education and no family history of a neurodegenerative disorder. He was a retired university office manager. The patient only suffered from high blood pressure and was in good health until approximately 2 years before presentation, when he was affected by a depression of mood state.

A neuropsychological evaluation performed at that time, in 2009, highlighted only an impairment in episodic memory and reduced phonemic fluency and a pathological performance in the Frontal Assessment Battery.
constructional praxis (Copying Drawing and Landmark Drawing Copy Test). Individual performance can range between 0 and 8, according to the number of test scores above the cutoff; a score of below 4 characterizes demented subjects.

We added other cognitive tests to this test battery, with the aim of obtaining a more complete and exhaustive neuropsychological profile assessing all cognitive functions (memory, language, attention, and executive functions).

**Memory**

Three additional tests were administered in order to assess memory functions more comprehensively: the Corsi block-tapping test and digit span test, respectively, for visuospatial and verbal short-term memory, and the story recall test for the evaluation of episodic memory.

**Language**

To assess language functioning, we used the Aachener Aphasie Test, comprising six subtests: spontaneous speech, token test, repetition, written language, naming, and comprehension; and a semantic verbal fluency test.

**Attention**

To assess attention deficits we used the Alertness test from the German Testbatterie zur Aufmerksamkeitsprüfung or Test for Attentional Performance (TAP).

This test measures reaction time (RT) with or without a warning signal (tone). In the test, a cross appears in the middle of the computer screen, and the subject has to press a button as rapidly as possible. The order of block presentation is ABBA, in which A is the block without a tone and B is the block with a warning signal. A total of 80 trials were presented. The three parameters evaluated are: reaction times, number of omissions, and the index of phasic alertness.

**Executive functions**

We assessed various aspects of executive abilities, such as shifting, interference inhibition, reasoning, and planning.

The Trail Making Test (TMT) was used to explore visual–conceptual and visual–motor tracking.

The Stroop test measured the ability to control and inhibit the automatic response.

**Depression assessment**

We used a short version (15 items) of the Geriatric Depression Scale (GDS) to evaluate the possible presence of depression. The GDS questions are answered by stating “yes” or “no.” This simplicity enables the scale to be used with individuals who are ill or moderately cognitively impaired. A score higher than 5 is indicative of depression.

**Psychiatric evaluation**

Neuropsychiatric symptoms were evaluated using the Neuropsychiatric Inventory (NPI). Twelve behavioral domains are evaluated in this test: delusions, hallucinations, agitation/aggression, dysphoria, anxiety, euphoria, apathy, disinhibition, irritability/lability, aberrant motor activity, nighttime behavioral disturbances, and appetite/eating disorders.

The NPI is comprised of screening questions used to ask the caregiver whether the patient’s behavior has changed since the onset of dementia and if so, whether the altered behavior was present during the last month.

The Italian version of the NPI was validated by Binetti et al in Alzheimer’s disease patients and has demonstrated comparable psychometric properties.

**Functional assessment**

Functional autonomy was evaluated using the basic Activities of Daily Living (ADL) scale and the Instrumental Activities of Daily Living (IADL) scale. These are two indices of functional dependence; the ADL scale measures the patient’s abilities in basic self-care tasks, such as feeding, bathing, walking and transferring, maintaining continence, etc; whereas the IADL scale explores instrumental activities, including telephoning, outdoor mobility and grocery shopping, travelling, taking medicines, managing money, housekeeping, preparing meals, and laundry.

**Results**

Tables 1–4 summarize the patient data for each test. The patient’s score and the cutoff in the standardization sample for each test are shown. For the attention test of the TAP battery, the medians of reaction times are shown.

At diagnosis, the patient showed a severe depression of mood state, with dysarthric language and an impairment of cognitive functioning characterized by memory deficits, reduced phonemic and semantic fluency, and deficits in abstract reasoning. The reaction times were mildly slow.

Neurologically, gait ataxic disturbances, balance deficits, and supranuclear upgaze paresis were already present. No falls were reported.

As regards behavioral symptoms, an interview with relatives revealed depression, anxiety, apathy, irritability, and sleep disorders.
As to functional independence, the patient was autonomous in activities of daily living, such as basic self-care tasks but needed help with instrumental activities.

After the evaluation the patient began pharmacological treatment with rivastigmine 6 mg daily for 6 months and paroxetine 20 mg daily.

At the first follow-up visit, after 6 months from diagnosis, he showed a further impairment of cognitive deficits and of balance disturbances, with bradykinesia. The patient appeared to relatives to be less anxious, depressed, and apathetic but also more dependent on others for simple daily living activities, such as feeding and bathing. However, the patient himself complained of sadness and depression, although he still showed interest in his life.

The patient’s relatives reported the onset of great difficulty in his building management, a task that he had previously carried out without any problems.

A further SPECT showed widespread hypoperfusion of the cerebral cortex, with thinning of the cortical thickness. The hypoperfusion of both hemispheres in the frontal and temporal cortices appeared more pronounced than earlier. Perfusion of the basal ganglia and cerebellar hemispheres was preserved.

The results of neuropsychological evaluation showed a further worsening of cognitive performance, above all of memory, attention, and language, with the patient demonstrating anomia, and semantic and verbal paraphasic errors.

Table 1 The patient’s scores and cutoff score of the cognitive tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Diagnosis</th>
<th>1 FU</th>
<th>2 FU</th>
<th>3 FU</th>
<th>4 FU</th>
<th>Cutoff score</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMSE</td>
<td>17.7*</td>
<td>18.7*</td>
<td>22.7*</td>
<td>24.7</td>
<td>18.7*</td>
<td>≥24</td>
</tr>
<tr>
<td>GDS</td>
<td>14*</td>
<td>15*</td>
<td>15*</td>
<td>15*</td>
<td>15*</td>
<td>≥5</td>
</tr>
<tr>
<td>ADL</td>
<td>0/6</td>
<td>3/6</td>
<td>3/6</td>
<td>4/6</td>
<td>5/6</td>
<td></td>
</tr>
<tr>
<td>IADL</td>
<td>4/5</td>
<td>4/5</td>
<td>4/5</td>
<td>5/5</td>
<td>5/5</td>
<td></td>
</tr>
<tr>
<td>NPI</td>
<td>25</td>
<td>13</td>
<td>18</td>
<td>18</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>MDB</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rey’s 15-word immediate recall</td>
<td>21.3*</td>
<td>14.3*</td>
<td>20.3*</td>
<td>16.3*</td>
<td>16.3*</td>
<td>≥28.53</td>
</tr>
<tr>
<td>Rey’s 15-word delayed recall</td>
<td>3.8*</td>
<td>2.4*</td>
<td>0*</td>
<td>2.4*</td>
<td>1.4*</td>
<td>≤4.69</td>
</tr>
<tr>
<td>Immediate visual memory</td>
<td>18.2</td>
<td>18.5</td>
<td>20.5</td>
<td>18.5</td>
<td>17.5</td>
<td>≤13.85</td>
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<tr>
<td>Phonological verbal fluency</td>
<td>−1.5*</td>
<td>−0.7*</td>
<td>1.3*</td>
<td>−2.7*</td>
<td>0.3*</td>
<td>≤17.35</td>
</tr>
<tr>
<td>Sentence construction</td>
<td>15.7</td>
<td>18.5</td>
<td>13.5</td>
<td>13.5</td>
<td>NA</td>
<td>≤8.72</td>
</tr>
<tr>
<td>Copying drawings</td>
<td>8.4</td>
<td>8.6</td>
<td>5.6*</td>
<td>6.6*</td>
<td>5.6*</td>
<td>≤7.18</td>
</tr>
<tr>
<td>Landmark Drawing Copy Test</td>
<td>66.3</td>
<td>68.7</td>
<td>67.7</td>
<td>59.7*</td>
<td>64.7</td>
<td>≤61.85</td>
</tr>
<tr>
<td>Raven’s colored progressive matrices</td>
<td>15.4*</td>
<td>11.1*</td>
<td>10.1*</td>
<td>11.1*</td>
<td>15.1*</td>
<td>≤18.96</td>
</tr>
</tbody>
</table>

Note: *Pathological score.

Abbreviations: ADL, Activities of Daily Living scale; FU, follow-up; GDS, Geriatric Depression scale; IADL, Instrumental Activities of Daily Living scale; MDB, Mental Deterioration Battery; MMSE, Mini–Mental State Examination test; NA, not available; NPI, Neuropsychiatric Inventory.

Table 2 The patient’s scores and cutoff score of the other cognitive tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Diagnosis</th>
<th>1 FU</th>
<th>2 FU</th>
<th>3 FU</th>
<th>4 FU</th>
<th>Cutoff score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digit span</td>
<td>4.5</td>
<td>4.5</td>
<td>4.5</td>
<td>3.5*</td>
<td>3.5*</td>
<td>≤3.5</td>
</tr>
<tr>
<td>Vissuospatial span</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>≤3.5</td>
</tr>
<tr>
<td>Prose memory</td>
<td>0*</td>
<td>0*</td>
<td>0.35*</td>
<td>−0.75*</td>
<td>0*</td>
<td>≤4.5</td>
</tr>
<tr>
<td>Semantic verbal fluency</td>
<td>3.75*</td>
<td>2.5*</td>
<td>3.25*</td>
<td>0.75*</td>
<td>1*</td>
<td>≤7</td>
</tr>
<tr>
<td>Naming (AAT)</td>
<td>7*</td>
<td>7*</td>
<td>7*</td>
<td>7*</td>
<td>6*</td>
<td>≤8</td>
</tr>
<tr>
<td>Attentive matrices</td>
<td>34.75</td>
<td>29.25*</td>
<td>24.25*</td>
<td>19.25*</td>
<td>19.75*</td>
<td>≤30</td>
</tr>
<tr>
<td>Alertness (RT without warning)</td>
<td>390*</td>
<td>406*</td>
<td>615*</td>
<td>NA</td>
<td>NA</td>
<td>≥327</td>
</tr>
<tr>
<td>Alertness (RT with warning)</td>
<td>379*</td>
<td>374*</td>
<td>573*</td>
<td>NA</td>
<td>NA</td>
<td>≥307</td>
</tr>
<tr>
<td>Phasic index</td>
<td>0.028</td>
<td>0.083</td>
<td>0.070</td>
<td>–</td>
<td>–</td>
<td>≥−0.11</td>
</tr>
</tbody>
</table>

Note: *Pathological score.

Abbreviations: AAT, Aachener Aphasie test; FU, follow-up; NA, not available; RT, reaction time.
The language examination using Aachener Aphasie Test (AAT) showed, at that time, a mild nonfluent, Broca-like aphasial like language deficits, which were most evident in expression and were characterized by word retrieval difficulties and anomia, and some semantic paraphasias. His conversational/narrative speech was characterized by a slow speech rate, prolonged intervals between syllables and words, and decreased articulatory accuracy with increased speaking rate. These are all characteristics of AOS. His prosody was also abnormal. He also displayed word repetition, characterized by phonemic substitution; his comprehension was better than expression, but the patient had more difficulty with the syntactically complex sentences. He printed dictated words and sentences adequately, such as words and phrases read aloud.

The early clinical and neuropsychological manifestations in this case were consistent with PSP syndrome, even if the neuroradiological data were unusual in regard to the usual involvement of the subcortical gray and brainstem region reported in the literature.

It was decided to change the pharmacological therapy, substituting paroxetine with 50 mg of sertraline, daily. Sertraline hydrochloride is an antidepressant of the selective serotonin reuptake inhibitor (SSRI) class and is also a dopamine reuptake inhibitor. Moreover, a combination of melevodopa (l-dopa methylester, a highly soluble prodrug of l-dopa) plus carbidopa in an effervescent tablet formulation (CHF 1512; Sirio Pharma Co, Ltd, Shantou, People’s Republic of China) and zolpidem, a nonbenzodiazepine hypnotic drug (with an imidazopyridine structure that binds to the GABA-benzodiazepine receptor complex found in high density in basal ganglia), were prescribed.

After 6 months, a new multidimensional evaluation showed a rather stable situation, both in cognitive and functional aspects. The pharmacological therapy with rivastigmine, sertraline, levodopa, and zolpidem was confirmed.

The onset of a spastic smile and psychomotor slowing led to the patient requesting a return visit. The assessment identified an impairment of the patient’s functional autonomy, both in simple and instrumental daily activities, and in executive functions, as demonstrated by the phonological and semantic verbal fluency tests and the patient’s inability to perform the TMT and the Stroop Test. A new drug, memantine, at a daily dose of 20 mg, was added to the therapy.

After 6 months of treatment with memantine, the neuropsychiatric symptomatology was reduced in our patient, although moderate depression and mild irritability continued. As regards cognitive functions, the patient’s spontaneous speech had become poor, telegraphic, and echolalic; compared with the previous language assessment, we observed a further impairment of sentence comprehension and repetition, with more severe difficulty with phrases and syntax.

The patient’s wife had noticed a frequent cough when he drank and sometimes during a meal. A videofluoroscopic examination showed moderate dysphagia.

**Discussion**

A spectrum of clinical syndromes and neurodegenerative disorders must be considered in a patient who presents with these neuropsychological and clinical symptoms. Frontotemporal dementia, progressive nonfluent aphasia, and corticobasal degeneration (CBD) all represent syndromes...
reflecting asymmetric cortical dysfunction.\textsuperscript{38} PSP has been associated with CBD syndrome.\textsuperscript{39} Dementia with Lewy bodies rarely presents as an asymmetrical cortical degeneration syndrome.\textsuperscript{40}

We tested a wide range of cognitive functions in this patient and the response of his disease to all the drugs available for this pathology.

The early clinical and neuropsychological manifestations were the most consistent with PSP syndrome. He exhibited gait impairment and supranuclear gaze palsy, typical of PSP. The overlap of PSP with CBD has been increasingly recognized lately. Our patient did not present limb apraxia, asymmetric extrapyramidal syndrome, alien limb behavior, myoclonus, or cortical sensory loss, all typical findings of CBD.

Our patient showed depression of mood state as the first symptom of the pathology. Moreover, this was resistant to all pharmacological treatment as the patient continued to be depressed at all follow-up visits, as shown by the GDS scores.

Most published reports\textsuperscript{41,42} on behavior in PSP patients have been single case studies and have emphasized symptoms related to depression, psychosis, or obsessive features. Borroni et al,\textsuperscript{8} in a sample of 24 PSP patients, found a high frequency of depression, anxiety, sleep, and eating disorders. More recently, Fukui et al\textsuperscript{43} studied 74 PSP patients, observing a relatively high incidence (24\%) of obsessive–compulsive symptoms. These are frequent but under recognized neuropsychiatric symptoms of dementia in PSP, probably due to a dysfunction of the fronto–caudate–thalamus–cerebellum circuit.

Unlike the results of Litvan et al,\textsuperscript{13} which indicated apathy as the dominant behavioral change in PSP, the main behavioral symptom in our case was depression. The apathy that the patient showed in the early stage of disease was replaced by an unmistakable depression.

Depressive symptoms can appear as an initial manifestation of an incipient cognitive change or can be interpreted as a risk factor for cognitive decline, or can be a concomitant disease, possibly the result of an awareness of cognitive difficulties, as suggested by previous authors.\textsuperscript{43,44}

With regard to cognitive functions, only a mild executive deficit was found in the patient at the first neuropsychological examination performed following the onset of the depression.

Functional imaging studies of PSP patients show a deafferentation of the frontal lobes. The frontal lobes have reduced perfusion despite limited local pathological changes. The metabolic deficits are found in areas disconnected from the prominent subcortical pathology of PSP.

There are five frontal subcortical circuits, originating in the supplementary motor area, frontal eye fields, dorsolateral prefrontal cortex, orbitofrontal cortex, and anterior cingulated cortex. These circuits unite regions of the frontal lobe with the striatum, globus pallidus, and thalamus in functional systems that mediate motor activities, eye movements, cognition, and behavior. In PSP, all five circuits are impaired.\textsuperscript{15,45}

MRI of our patient showed no involvement of either the frontal areas or of the subcortical structures. Moreover, the first SPECT imaging performed showed a hypoperfusion in both temporal posterior hemispheres, although moderate depression and mild cognitive symptoms were evident. Only the second SPECT scan showed a reduced perfusion of both frontal lobes.

As suggested in the literature,\textsuperscript{46} there is a worsening of executive functions only in the later stages of disease when the frontal structures are more involved, while the onset of neuropsychiatric disorders are independent of cognitive deficits, due to the dysfunction of different subcortical circuits.

The peculiarity of our case is the lack of an obvious involvement of subcortical structures, as the MRI and SPECT images showed, even in the phase of disease during which the patient showed obvious motor deficits.

With regard to neuropsychological characteristics, our results are in accordance with the literature. At the first stage of the disease, our patient showed a mild deficit in verbal phonemic fluency and in long-term memory, and slow reaction times. In fact, one study has reported that letter fluency tends to be more severely affected than category fluency.\textsuperscript{47}

The short-term memory is considered to be relatively well preserved in PSP.\textsuperscript{48} Other authors\textsuperscript{49,50} have demonstrated the prolonged reaction times and a cognitive slowing independent of the motor function. As to language, repeated studies\textsuperscript{12–14} have demonstrated the nonfluent aphasias in this neurodegenerative disorder, such as an impairment of oral and written comprehension, also found by Podoll et al\textsuperscript{51} in five patients with PSP.

Certainly the disorder of speech and communication in PSP can take different forms. Dysarthria is the most common, but dysprosody, aphonias, stuttering, palilalia, and echolalia, as well as abnormal loquacity have also been described.\textsuperscript{52,53}

To date, there is no approved treatment for PSP. Treatment with levodopa\textsuperscript{54} may alleviate some motor symptoms, such as bradykinesia and rigidity, but only 20\%–40\% of PSP patients respond to it. Levodopa can be combined with other
therapies, such as serotonergic drugs, which improve depressive symptoms but which are ineffective in the treatment of cognitive and other symptoms.

The cholinergic system is impaired in PSP, as evidenced by a decrease in choline acetyltransferase activity in the basal ganglia and by a loss of mesencephalic cholinergic nuclei. This cholinergic deficit may explain the cognitive dysfunction. Donepezil is a centrally acting cholinesterase inhibitor that prolongs the action of acetylcholine in residual cholinergic neurons. Fabbri et al investigated the efficacy and tolerability of donepezil in six PSP patients and found no significant changes in cognitive deficits or in autonomy in daily living activities.

In contrast to other cholinesterase inhibitors, rivastigmine inhibits both acetylcholinesterase and butyrylcholinesterase and, in a small number of patients, produces a slight improvement in cognitive symptoms.

In 12 patients with PSP, Foster et al found a loss of interneurons containing benzodiazepine/GABA receptors, primarily in the anterior cingulated cortex, together with a deafferentation of the cerebral cortex from distant brain regions. Treatment with GABA agonists could be useful in PSP patients. Zolpidem is a GABA agonist of the benzodiazepine BZ1 subtype receptor and has been used in a small number of patients with PSP. Cotter et al found a sustained improvement in motor and ocular symptoms in a patient with PSP who was treated with controlled-release zolpidem over a period of 6 months.

Memantine is a new medication that acts on the glutamatergic system by blocking the N-methyl-D-aspartate (NMDA)-type glutamate receptors.

This medicine is used for the treatment of moderate to severe dementia of the Alzheimer type. Recent evidence has suggested that memantine is safe and might confer some cognitive improvement for individuals with dementia in Parkinson’s disease and dementia with Lewy bodies. There are no studies on memantine treatment in patients with PSP.

Recently, Gold et al investigated the use of davunetide, an advanced product in PSP. This is a novel neuroprotective peptide that is thought to impact neuronal integrity and cell survival through the stabilization of microtubules.

The studies on the efficacy and tolerability of pharmacological treatments in PSP patients have not provided any positive results. Our data also confirmed the inefficacy of available drugs, even in combination. Perhaps the aspect of associations between various therapies was not considered in the literature. This is a further point provided by our case. However, we investigated the efficacy of memantine in our patient with PSP and concluded that there was no significant slowing of disease progression, probably due to the stage of pathology.

A limitation of this study is that it involved a single case, and there was no control group. Moreover, we did not confirm the diagnosis, considering the lack of neuropathological findings. This weakness did not allow the achievement of any statistically significant data.

It could be interesting to investigate the use of memantine in a large group of patients and in the early stages of disease. Future strategies to treat PSP will require larger and prospective studies with multicenter trials.

**Conclusion**

In conclusion, in PSP patients, depression can represent a first symptom before an overt onset of disease. Moreover, the lack of involvement of the subcortical structures, as shown with MRI, even when the patient had a severe motor impairment, was an important and particular aspect of our case and is necessary to consider when diagnosing this neurodegenerative disease in other patients.

**Disclosure**

The authors report no conflicts of interest in this work.

**References**


