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Received Date : 22-Jan-2017

Revised Date : 01-Feb-2017

Accepted Date : 02-Feb-2017

Article type : Scientific Correspondence

Article title: Frontotemporal lobar degeneration-TDP with 'multiple system atrophy phenocopy syndrome'

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Keywords: Multiple system atrophy; Frontotemporal Lobar Degeneration; TDP-43;

Running title: FTLD-TDP presenting as MSA

Abbreviations:

MSA - Multiple system atrophy

MSA-P - Parkinsonian-type MSA

MSA-C - Cerebellar-type MSA

FTLD – Frontotemporal lobar degeneration

FTD - Frontotemporal dementia

MND – Motor neuron disease

NCI - Neuronal **cytoplasmic** inclusion

Multiple system atrophy (MSA) is a neurodegenerative disorder presenting with parkinsonism, cerebellar involvement, autonomic dysfunction and pyramidal signs (1). Two main clinical subtypes of MSA are recognized**:** a parkinsonian-type (MSA-P) associated with predominant nigrostriatal degeneration and a cerebellar-type (MSA-C) with predominant olivopontocerebellar atrophy. A 'definite' diagnosis requires pathological confirmation with demonstration of glial cytoplasmic inclusions comprising alpha-synuclein protein aggregates (1). **Here we** present a patient with an MSA-P clinical phenotype and a novel pathological profile of frontotemporal lobar degeneration (FTLD).

A Caucasian man developed erectile dysfunction at age 50 years. Two years later, he experienced gait difficulties and had recurrent falls. Parkinsonism was found and he was started on levodopa (1000mg/day), with slight improvement. Around age 55, constipation, dysarthria and occasional dysphagia to liquids appeared. Later that year, his wife described laryngeal stridor during sleep. Soon urinary symptoms appeared, including increased frequency, nocturia, and urgency, later

followed by urinary incontinence and recurrent urinary infections. He never had symptoms suggestive of postural hypotension. Progressively the patient became more dependent and unable to walk without support.

There was **no relevant medical or family history** including family history of parkinsonism, frontotemporal dementia or motor neuron disease.

Neurological examination at age 56 revealed saccadic ocular pursuit movements, severe dysarthria, slightly asymmetric parkinsonism without tremor, and a dystonic posture of the left arm. He had global hyperreflexia and normal plantar reflex. At this time he was unable to walk. Cognition was normal and showed no cortical sensory loss. Ropinirole, amantadine and baclofen were tried without significant benefit. By the age of 57, a gastrostomy tube was inserted because of severe dysphagia. Progressively, muscle wasting and a spastic tetraparesis became evident. With dedicated nursing care, the patient survived **a** further 9 years and died at age 66. Throughout the 16-year disease course there were no signs of cognitive or behavioural dysfunction. Although formal evaluation of cognition was never performed, a letter typed by the patient himself at a late stage of his disease discussing the functional impact of the symptoms attests to good verbal fluency and abstract reasoning.

In view of the presentation a clinical diagnosis of probable MSA-P was made. Brain MRI at age 55 showed global cortico-subcortical atrophy with no lobar predominance and absence of putaminal atrophy, putaminal signal intensity change or pontocerebellar atrophy. Cervical MRI, electromyography and a vesicoprostatic echography at age 56 were normal.

Post-mortem neuropathological examination revealed a 1272g brain, with frontal atrophy, involving both cortex and subcortical white matter **(Fig1A-B).** The corpus callosum was uniformly thin. The hippocampus was moderately atrophic and the amygdala showed severe atrophy. The thalamus and basal ganglia were also markedly atrophic, with softening and greyish discoloration of the putamen bilaterally (**Fig1B**). The substantia nigra was preserved. There was no brainstem or cerebellar atrophy.

Histological examination of the anterior frontal region showed mild spongiosis in the superficial cortical layers. TDP43 and p62 immunohistochemistry highlighted scattered neuronal **cytoplasmic** inclusions (NCIs) and short dystrophic neurites (**Fig1H**). Tau, beta-amyloid and alpha-synuclein immunohistochemical preparations were entirely negative. There were moderate numbers of TDP43-immunoreactive NCIs in the granule cell layer of the dentate fascia (Fig**1I**). **Both putamen and**

caudate nucleus were severely atrophic, the latter showing severe astrogliosis and vacuolation of the neuropil with only very occasional surviving neurons **(Fig1D and E)**. TDP43 and p62 immunohistochemistry highlighted sparse NCIs and threads/neurites in the caudate nucleus and putamen **(Fig.1D-G).** The substantia nigra presented a slight decrease of the normal neuronal density and there were no Lewy bodies. There was severe astrogliosis in the corticospinal tract and pallor of the cerebral peduncles and pyramids in the medulla (Fig1.C). The neuronal cell population of the motor nucleus of the Vth cranial nerve and the nucleus of the XIIth cranial nerve was preserved, and no Bunina bodies were seen. There was moderate loss of Purkinje cells in the cerebellar cortex.

In conclusion, the findings were consistent with a TDP43 proteinopathy (FTLD-TDP type A), with a remarkably severe degeneration of the striatum and mild involvement of the cerebellar cortex. There was also evidence of upper motor neuron involvement.

To the best of our knowledge, this is the first reported case of a patient with an MSA-P phenotype due to FTLD-TDP pathology. It also represents a remarkably long disease duration for MSA. The usual disease duration of MSA is 6-9 years, with a few **cases having a reported disease duration longer than 15 years** (2).

FTLD encompasses a group of heterogeneous disorders and the canonical clinical presentations include language disorders, semantic dementia and behavioural disturbances in variable combinations, reflecting the preferential involvement of the frontal or temporal lobes. From a neuropathological perspective, FTLD can be subdivided into FTLD-tau, FTLD-TDP43 and FTLD-FUS (3). FTLD-TDP43 pathology is found in about half of the behavioural variant of frontotemporal dementia (FTD) cases, and represents the most frequent pathology found in FTD associated with motor neuron disease (MND) and in semantic dementia (3).

Reports on diagnostic accuracy of MSA after pathological confirmation vary between 62 and 86% (4); the most frequent misdiagnoses are Lewy body dementia, Parkinson´s disease and progressive supranuclear palsy; a smaller portion of false positives include corticobasal degeneration and cerebrovascular disease (4). Our patient had no record of cognitive deterioration so there was no suspicion of FTLD in life.

There is some limited evidence that MSA and FTD may share some clinical features. Cognitive deterioration, particularly regarding executive dysfunction, seems to be present in up to 32% of MSA patients (5). Frontotemporal lobar atrophy has also been demonstrated in MRI studies in these patients (5). Conversely, parkinsonism may be present in some frontotemporal dementia cases (3). Curiously, a few cases of patients with an FTD phenotype have been found to have mixed

pathological findings of both FTLD and MSA (6). Clinically, these patients presented with progressive non-fluent aphasia, behavioural variant FTD or corticobasal syndrome. Pathologically, they displayed the typical alpha-synuclein positive glial cytoplasmic inclusions of MSA. However, they also showed significant frontotemporal atrophy and cortical and limbic accumulation of neuronal inclusions, where alpha-synuclein was found (6). These cases have been termed "atypical MSA" and demonstrate that MSA and FTLD pathological features may coexist.

Another potential association between the two diseases relates to C9orf72. A wide range of clinical presentations such as cerebellar ataxia, parkinsonism or corticobasal syndrome have been associated with C9orf72 repeat expansions (7). A few of these families have been described containing both MSA and motor neuron disease patients (7). However, in this patient, despite the fact that no genetic testing was performed, the typical C9orf72 pathological signature (TDP43 negative/p62 positive cerebellar inclusions) was absent.

A unique aspect of this case is the remarkable severity of striatal degeneration found. Large cohorts of FTLD brains usually display variable degrees of frontal and temporal atrophy, less severe involvement of premotor and parietal areas, and relative sparing of grey matter structures **(8)**. More recently, however, the striatum and related connections have been emerging as relevant players in FTD progression and presentation **(9)**. Basal ganglia atrophy has been described as a finding in patients with intermediate severity disease (stage 2/4) in a small cohort of patients **(10)**. Studies with voxel based morphometry magnetic resonance imaging analysis have also described the same pattern of striatal atrophy in patients with pathologically confirmed FTLD **(9)**. Recent work has demonstrated axonal damage and loss of efferent neurons in the striatum of FTD and MND-FTD patients with TDP43 pathology **(11)**. TDP-43 also tends to accumulate in basal ganglia structures, particularly in the putamen **(11)**. Nonetheless, in a study examining brains from 29 MSA patients, the presence of TDP-43 was minimal, making it highly unlikely that TDP43 has a crucial role in MSA pathophysiology **(12**). In this patient, the particular involvement of the striatum probably contributed to the peculiar clinical phenotype. This case of FTLD-TDP type A adds to the spectrum of pathologies that can be clinically misdiagnosed as MSA-P.

Acknowledgments:

The authors thank Inês Reis for histological and immunohistochemistry technical assistance and José Ferreira for the help in editing the manuscript figures.

Author contributions:

ALS and RT wrote the manuscript.

NQ, MP and MM have participated in the medical follow-up of the patient.

RT, MP and TR have participated in the brain autopsy and neuropathological evaluation.

RT acquired histological images and made the figures.

ALS, RT, NQ, TR, MP and MM reviewed and approved the manuscript.

Ethical Approval: This work has been approved by the Ethical Committee of the Portuguese Brain Bank.

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Figure legend:

Figure 1. **Brain** macroscopic **(A-B)** and histologic findings **(C-I)**

Coronal slices showing enlarged ventricles, cortical atrophy and prominent basal ganglia atrophy and discoloration (A and B). Histology showing reduction in bulk and significant pallor of the bulbar pyramids (C). Severe putamen neuron loss, vacuolation and gliosis, with sparse TDP-43 pathology and no α-synuclein (D-G). Scattered neuronal NCIs and short dystrophic neurites in frontal cortex (H) and NCIs in the granule cell layer of the dentate fascia (I).

Kluver-Barrera stain (C); Hematoxylin and eosin stain (D); Immunohistochemistry study with GFAP (E), TDP43 (F, H, I) and α-synuclein (G).