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Progressive supranuclear palsy and primary lateral sclerosis secondary to globular glial tauopathy: a case report and a practical theoretical framework for the clinical prediction of this rare pathological entity.

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Abstract

Globular glial tauopathy (GGT) is a rare 4-repeat (4R) tauopathy characterized by the accumulation of 4R-tau globular inclusions in neurons and, to a higher extent, astrocytes and oligodendroglial cells. Several clinical phenotypes have been associated with GGT pathology, making the prediction of this rare pathological entity difficult. We report the case of a patient who presented with eye-movement abnormities and gait instability symptoms reminiscent of progressive supranuclear palsy-Richardson's syndrome (PSP-RS), who later developed severe upper motor neuron signs consistent with a diagnosis of primary lateral sclerosis (PLS). Neuropathological assessment revealed a neuropathological diagnosis of GGT type III. We argue that retrospectively, this pathological substrate could have been foreseen based on the concurrence of atypical features such as severe corticospinal degeneration, which is uncommon in the early stages of pure PSP-RS, and marked supranuclear gaze palsy features, which are uncommon in motor neuron disease with TDP-43 proteinopathy. A theoretical framework is proposed to help clinicians correctly predict the rare pathological substrate of GGT in subjects with coexistent features of PSP-RS and PLS on the sole basis of clinical findings.

Keywords

Globular glial tauopathy; primary lateral sclerosis; frontotemporal dementia; progressive supranuclear palsy; neuropathology

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Introduction

Frontotemporal lobar degenerations (FTLDs) are neurodegenerative diseases predominately affecting the frontal and temporal lobes of the brain, associated with progressive changes in behaviour, language, and executive function. Patients may develop motor deficits consistent with parkinsonism and/or motor neuron disease (Bang, Spina, & Miller, 2015). FTLDs are classified into neuropathological subtypes according to the main protein that accumulates in the brain of affected individuals. The three most common of which are TDP-43, tau and FUS, as well as on the basis of the cellular and morphological characteristics of these inclusions (Mackenzie et al., 2010). FTLD may present clinically as behavioral variant frontotemporal dementia (bvFTD), primary progressive aphasia (PPA), corticobasal syndrome and progressive supranuclear palsy (PSP). Because of the extensive anatomical, pathological and clinical overlap between the various FTLD subtypes, the prediction of a specific neuropathological substrate in vivo, given any clinical presentation, remains complex (Perry et al., 2017).

Globular glial tauopathy (GGT) is a rare FTLD subtype characterized by the presence of tau-immunoreactive globular inclusions in astrocytes and oligodendrocytes. The inclusions are composed by hyperphosphorylated tau isoforms containing four microtubule binding domain repeats, making GGT a 4-repeat (4R)-tauopathy (Ahmed et al., 2013). GGT is more commonly observed as a sporadic disease, though cases associated with mutations in the *microtubule associated protein (MAPT)* tau gene have been reported (Ferrer et al., 2014; Tacik et al., 2015; Tacik et al., 2017; Zarranz et al., 2005). Pathologically, GGT is classified into three distinct subtypes (Ahmed et al., 2013). This neuropathological variability constitutes the basis of the heterogeneous clinical presentation of GGT which includes bvFTD, nonfluent variant PPA, semantic variant PPA, and primary lateral sclerosis (PLS) among others, together with a variable extent of extrapyramidal motor features (Ahmed et al., 2013; Burrell et al., 2016; Ferrer et al., 2014; Graff-Radford et al., 2016; Kim et al., 2017; Zarranz et al., 2005). Subsequently, predicting a neuropathological diagnosis of GGT based on clinical manifestations proves challenging. In addition, prediction of pathology could be particularly difficult in patients with PLS, because of the shared selective vulnerability of the motor cortex and corticospinal tracts in GGT, PSP pathology and motor neuron disease (MND) secondary to TDP-43 pathology (Ahmed et al., 2013; Josephs et al., 2006; Neumann et al., 2006).

PLS is a clinical syndrome under the umbrella spectrum of motor neuron diseases, characterized by early predominant upper motor neuron degeneration with weakness, spasticity, and absence of symptoms of lower motor neuron degeneration during the first four years of disease course (Gordon et al., 2006). The definition of PLS as a distinct clinicopathological entity from amyotrophic lateral sclerosis (ALS) is controversial, since a large proportion of PLS patient eventually develop signs of LMN disease later in the disease course. Nevertheless, a clinical diagnosis of PLS may be predictive of a slow disease progression (D'Amico et al., 2013).

We report the case of a patient who developed clinical features suggestive of both PSP Richardson's syndrome (PSP-RS) and PLS, and had GGT pathology on autopsy. We discuss

in detail the aspects of his clinical presentation and highlight those features that might have helped to predict his underlying pathology in vivo. We propose a theoretical framework to facilitate the antemortem recognition of this rare pathological entity in patients with FTD syndromes.

Case presentation

An 83-year-old right-handed man presented to the UCSF Memory and Aging Center clinic with 6 years of progressive imbalance and falls. At age 77, he reported difficulties with vision and gait instability. One year later, he developed bilateral foot drop and cramps in his legs. Later that same year, he began complaining of right arm weakness and difficulties with fine movements, and began falling approximately once a month. At age 81, he complained of weakness in the right leg, dysphagia and dysarthria, and developed a facial stare. He began falling once a week and started using a walker. A year later, he was hospitalized after a fall and began using a wheelchair. By the age of 83, he was no longer able to write or use utensils. He had developed dystonia and involuntary movements of the right arm. Behavioral and cognitive changes developed contextually to the motor deficits and included impulsivity, diminished judgement, difficulties with thought expression, grammar and spelling, and dysprosody.

Neurological examination at age 83 showed a procerus sign and hypomimia. Speech was characterized by frequent phonemic distortions and paraphasic errors. Square wave jerks were present along with delayed saccade initiation and slow velocities on horizontal gaze, and diminished vertical gaze. Muscle tone was increased axially in an extrapyramidal fashion, in the right upper extremity with combined pyramidal and extrapyramidal features, and at the right lower extremity with extrapyramidal feature. Fine movements of the right hand were impaired, but segmental strength was otherwise full and muscle stretch reflexes (MSRs) were normal. No fasciculations or Babinski sign were noted. He required assistance to stand up from a chair. Laboratory work-up including cerebral spinal fluid (CSF) and serological evaluation for various etiologies was normal. He was diagnosed with PSP-RS on the basis of his early impairment of eye-movement abnormalities and frequent falls (Litvan et al., 1996).

A year later, ideomotor apraxia was noted in his left hand (right hand untestable) and right leg. Decreased muscle bulk was noted at the right first dorsal interosseous and abductor pollicis brevis. Rare fasciculations were reported in the upper chest, forearms and anterior thighs, but they were not observed in subsequent examinations and are thoughts to have been related to transient treatment with pyridostigmine which was suggested to the patient as potential treatment of his weakness by a local clinician. Right arm segmental strength was 3/5 at triceps and biceps, 1/5 at wrist extensors and flexors and intrinsic hand muscles. Right leg strength was 3/5 in the hamstrings, 1/5 in quadriceps, gastrocnemius and tibilias anterior. Strength was also 1/5 at the left tibialis anterior. MSRs were 3+ in the arms and 2+ at the legs. A jaw jerk reflex was noted. Rapid alternating movements were impaired in all four extremities, more so on the right. Later, his speech became incomprehensible and he developed difficulties with saccades initiation in all directions. He died of pneumonia at age 85.

His medical history included prostate cancer, paroxysmal atrial flutter, hypertension and hearing loss. His medications included benazepril, metoprolol, thiamine, and aspirin. He was treated with pyridostigmine for a few years during the disease course with mild, though unsustained improvement. He experienced a near drowning accident at the age of 12. He never smoked or used illicit drugs and occasionally drank alcohol. He suffered multiple head traumas due to falls beginning at the age of 78. His family history was remarkable for his father who died of an intracranial aneurysmal bleed at the age of 59. His mother and two of his brothers died of cancer.

Neuropsychological testing

Formal neuropsychological testing (Kramer et al., 2003) at age 84 (Table 1), revealed significant multiple-domain cognitive impairment. Language difficulties were observed. His speech had a “musical quality.” Several phonological and paraphasic errors on formal testing of repetition. Verbal agility was markedly impaired, and there was evidence of word-finding difficulties, and mild semantic loss. Performance on tests of memory showed poor learning, and delayed recall in the average range. On executive function testing, he was prone to errors and lost set. Visuospatial and constructional skills were impacted by motor deficits. Clinical dementia rating (CDR) score was 0.5. The patient repeated neuropsychological testing 8 months later. At that time, his speech had further deteriorated to the point that he was only able to communicate through nodding or knocking on the table. A modified trail making test showed diminished psychomotor speed and reduced accuracy. Performance on memory and confrontation naming was perceived as stable. CDR score remained 0.5.

Neurodiagnostics and genetic testing

The patient underwent a whole-body FDG-PET/CT at age 82, which showed no evidence of occult neoplasm. An EMG at age 83 revealed absent compound muscle action potentials (CMAP) in the right peroneal and tibial muscle groups. The right median nerve showed reduced CMAP amplitude. Poor activation of motor unit action potentials (MUAPs) in nearly every muscle assessed was reported. A low density of fibrillation potentials in the right tibialis anterior and gastrocnemius muscles were noted. Sensory studies showed absent bilateral sural nerve potentials and right superficial peroneal potential. The impression of the study was severe suprasegmental weakness of the right, upper more than lower, extremities, and evidence of axonal sensorimotor polyneuropathy at lower extremities which might have contributed to patient’s balance deficit. An MRI of the brain without contrast was performed at age 84 and showed moderate dorsolateral-predominant frontoparietal volume loss, worse on the left, and severe midbrain atrophy. FLAIR hyperintensity was observed in the periventricular and subcortical white matter, particularly in correspondence with areas of greater cortical atrophy, as well as in the basis pontis (Figure 1). Analysis of dementia-related risk genotypes revealed ApoE genotype E3/E3 and an H1/H1 *MAPT* haplotype. Pathogenic mutations in the *MAPT, GRN, C9ORF72, TARDBP, FUS, APP, PSEN1, PSEN2* genes and the *TREM2* R47H mutation were not found. The participant was enrolled in an ongoing research project on 4-repeat tauopathies at UCSF for which he provided written informed consent in accordance with the Declaration of Helsinki.

Neuropathological evaluation

The brain and the spinal cord were collected at autopsy. The fresh brain weighed 1273 grams and showed mild atrophy of the prefrontal and superior temporal regions. Macroscopically, there was atrophy and discoloration of the left globus pallidus internus, and bilateral atrophy of the subthalamic nuclei. The dentate nucleus and the brainstem were also atrophic. Blocks for histological purposes were submitted from the left cerebral hemisphere, right half of the cerebellum, the brainstem and the spinal cord. Microscopic evaluation showed superficial microvacuolation in the frontoparietal, superior temporal and insular cortices. Astrogliosis was prominent in the inferior frontal gyrus, subgenual cingulate cortex and superior frontal sulcus. Severe gliosis was seen in the amygdala, globus pallidus, dentate nucleus and the entire brainstem. Neuronal loss (higher than 50% but lower than 75%) was observed in the globus pallidus, substantia nigra, locus ceruleus, and hypoglossal nucleus. Axonal spheroids and asymmetric corticospinal tract degeneration were observed in the medulla and spinal cord. Anterior horns motor neurons were normal in number and morphology.

Immunohistochemistry for phosphorylated tau (CP13) showed fibrillary and diffuse/granular tau neuronal cytoplasmic inclusions were seen in the subgenual cingulate cortex, ventral striatum, hippocampus, dentate nucleus, substantia nigra, midbrain tectum, periaqueductal grey, oculomotor nucleus, and locus ceruleus, as well as to a lesser extent in the prefrontal, temporal, pericentral, angular and insular cortices, putamen, amygdala and thalamus. Globose tangles were seen in remaining neurons of the subthalamic nucleus.

Abundant tau-immunoreactive (tau-ir) globular astrocytic inclusions were observed predominately in the superior frontal sulcus, inferior frontal gyrus, primary motor cortex, subgenual cingulate cortex, and temporal cortices. These astrocytes showed punctate, dot-like or globular appearance of tau-ir inclusions in proximal process as opposed to the bushy appearance of tufted astrocytes of PSP (Figure 2 A–B). Abundant tau-ir neuropil threads were seen in the inferior frontal gyrus, precentral cortex, substantia nigra, tectum and median raphe. A large number of tau-ir oligodendroglial coiled bodies were predominately seen in the cerebral cortex and subcortical white matter of the superior frontal sulcus, primary motor cortex inferior frontal gyrus, temporal cortices, and insula cortex as well as in the capsula extrema, fimbria, and in the globus pallidus, substantia nigra, tectum, and periaqueductal grey. In the peri-Rolandic region, these inclusions were abundant in the corticospinal tract and rare in the adjacent white matter of the primary sensory cortex (Figure 2C). The majority of these inclusions showed the characteristic globular appearance of globular oligodendroglial inclusions (GOI) with the inclusion diameter being greater than the diameter of oligodendroglial nuclei (Figure 2D) (Ahmed et al., 2013). These inclusions did not stain with 3-repeat (RD3) tau antibodies. Taken together these findings were consistent with a primary neuropathological diagnosis of globular glial tauopathy (GGT) type III (Ahmed et al., 2013). There was no evidence of aging-related tau astrogliopathy (ARTAG) (Kovacs et al., 2016).

Immunohistochemistry (IHC) for phosphorylated tau (CP13) and 3-repeat tau (RD3) showed neurofibrillary tangle pathology of Alzheimer’s disease in the entorhinal cortex and

hippocampus (Braak stage 2). Beta-amyloid IHC showed amyloid plaque pathology restricted to the neocortex and hippocampus (Thal phase 2). These findings were consistent with an incidental diagnosis of low Alzheimer's Disease Neuropathological Changes (ADNC) A1, B1, C3. TDP-43 IHC in the anterior cingulate cortex, inferior temporal gyrus, amygdala, hippocampus, entorhinal cortex, and spinal cord, as well as alpha-synuclein IHC in the cingulate cortex, middle frontal gyrus, amygdala, hippocampus, entorhinal cortex, and brainstem showed no inclusions (Montine et al., 2012).

Vascular pathology was limited to moderate atherosclerosis of the circle of Willis and basilar artery. There was no evidence of arteriolosclerosis.

Discussion:

We report the case of a patient who developed progressive gait instability and vision complaints at age 77, followed by progressive corticospinal deficits with right-predominant weakness and spasticity, and dysarthria leading to mutism. Eye-movement abnormalities suggestive of PSP-RS such as a stare, hypomimia, square-wave jerks, slow saccades and diminished vertical gaze developed slowly and became severe only late in the disease course. Oculomotor deficits are consistent with the severe degeneration of the frontal eye fields (superior frontal sulcus), which is congruous with the supranuclear localization of these deficits. Behavioral changes such as impulsivity and diminished judgement, along with language deficits such as agrammatism, phonemic distortion and dysprosody were also observed. Lastly, ideomotor apraxia was noted in the left upper extremity, spared by corticospinal weakness, in the late disease stage. The patient was diagnosed with PSP-RS based on his early complaints of postural deficits with tendency to fall, and difficulties with vision, clinical observation of eye-movement abnormality and axial rigidity, and history of recurrent falls, likely secondary to PSP pathology (Litvan et al., 1996).

While patient's initial lower extremity weakness with bilateral foot drop might have been secondary to the development of sensory-motor polyneuropathy, contextual right-hand fine movement deficits were his first symptom of corticospinal deficit at age 77. Predominant upper motor neurodegeneration is later suggested by the development of severe right extremities weakness, right upper extremity spasticity, presence of a jaw-jerk, in the absence of sustained fasciculations (only seen during brief treatment with pyridostigmine), and paucity of muscle wasting which were only observed in the right first digital interosseous and abductor pollicis brevis in the frame of comorbid median nerve neuropathy at the wrist, six years after the onset of weakness. CMAP deficits and sparse fibrillation potentials were only seen in lower extremities (with the exception of reduced CMAP of the median nerve at the wrist) and are likely to be secondary to comorbid polyneuropathy. These findings are consistent with the clinical definition of PLS, and are supported by the complete lack of lower motor neuron degeneration and TDP-43 proteinopathy at autopsy.

Post-mortem neuropathological assessment revealed a pathological diagnosis of globular glial tauopathy (GGT) (Ahmed et al., 2013) which was the neuropathological substrate of both PSP-RS and PLS-related clinical findings in this patient. This is a different pathological background than the one recently described in a patient with comorbid PSP-RS and ALS

clinical findings secondary to coexistent PSP and TDP-43 motor neuron neuropathology (Fujita et al., 2019). Pathologically, GGT is classified into three distinct subtypes: type I with predominant frontotemporal involvement; type II with predominant involvement of the primary motor cortex and corticospinal tract degeneration; type III with mixed features between type I and II (Ahmed et al., 2013). This neuropathological variability constitutes the basis of the heterogeneous clinical presentation of GGT

The neuropathological substrate of GGT has been associated with various clinical phenotypes including Alzheimer's type dementia (Gelpi, Cullel, Navarro-Otano, & Lladó, 2013; SantaCruz et al., 2015), bvFTD (Clark et al., 2015; Kovacs et al., 2008), FTD-MND (Ahmed et al., 2011; Hasegawa et al., 2018; Takeuchi et al., 2016; Zarranz et al., 2005), atypical parkinsonism (Piao et al., 2005), PSP (Josephs et al., 2006), CBS (Ohara et al., 2002; Sakai et al., 2006; Tan et al., 2004), nonfluent variant PPA (Ferrer et al., 2003; Kim et al., 2017), and semantic variant PPA (Graff-Radford et al., 2016). In addition, primary cortex and the corticospinal tract are particularly vulnerable to GGT, particularly type II and III, thus making PLS a likely clinical presentation of this pathological entity. This is in line with the early reports of cases of atypical PSP with corticospinal degeneration, later unified under the same neuropathological spectrum of GGT (Josephs et al., 2006).

Clinical prediction of GGT is difficult because of its rarity, the association of this neuropathological entity with multiple distinct clinical syndromes and the overlapping regional vulnerability with several neuropathological substrates of other diseases, particularly other tauopathies, TDP-43 proteinopathies and FUS proteinopathies. This patient was diagnosed in vivo with PSP-RS on the basis of Litvan et al.'s research diagnostic criteria (Litvan et al., 1996). His clinical presentation was however peculiar, and characterized by the presence of atypical features. We argue that these features may be useful for the *in vivo* prediction of GGT neuropathology in patients with PSP-RS and concomitant upper motor neuron deficits, and for the addition of GGT to the differential pathological diagnosis of those patient, which includes PSP pathology, corticobasal degeneration (CBD) and TDP-43 type A and B neuropathology (Mackenzie et al., 2011). First, the early and severe features of corticospinal deficits seen in this patient are uncommon in the majority of cases with underlying PSP pathology, and represent mandatory exclusion criteria in the most recently published clinical diagnostic criteria for PSP-RS (Höglinger et al., 2017). Second, while spasticity can be seen in patients with CBD, it occurs in less than one third of CBD patients in the early disease stages (Armstrong et al., 2013). In addition, our patient did not develop relevant features of cortical sensory motor dysfunction until the late disease stage, though some of these features might have been difficult to assess in view of concomitant and severe corticospinal findings. Eye-movement abnormalities consistent with supranuclear gaze palsy are uncharacteristic of primary lateral sclerosis secondary to FTLD with TDP-43 inclusions (Proudfoot et al., 2016). Extensive white matter FLAIR hyperintensities were observed in regions that corresponded to areas with highest severity of GGT pathology burden and white matter rarefaction, in the absence of small-vessel ischemic disease. These findings, atypical for PSP, are therefore potential imaging biomarkers of GGT pathology.

We propose that a pathological substrate of GGT, particularly subtype III, should be taken into consideration in all patients with atypical PSP-RS clinical presentation with coexistent and early-onset development of marked upper motor neuron signs. A pathological diagnosis of GGT should also be considered in all patients with severe clinical features of PLS, and concomitant supranuclear gaze palsy. A diagnostic decision-tree (Figure 3) is proposed in order to provide clinicians with a theoretical framework aimed to the correct prediction of this rare neuropathological entity in vivo. This framework requires further investigation and verification in larger cohorts of patients with GGT pathology.

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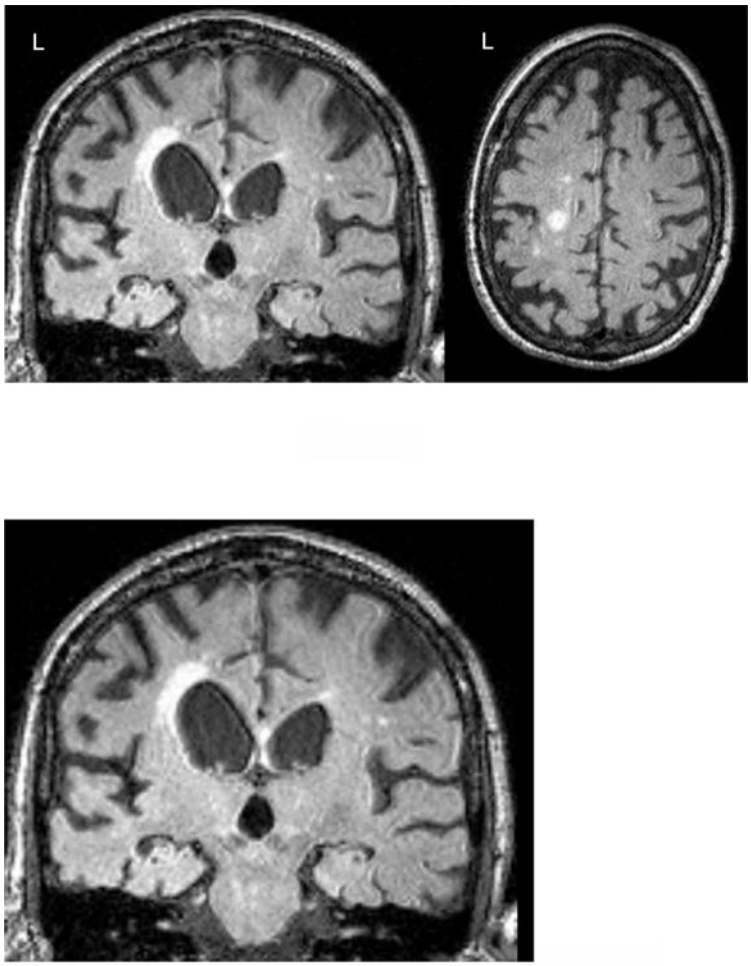

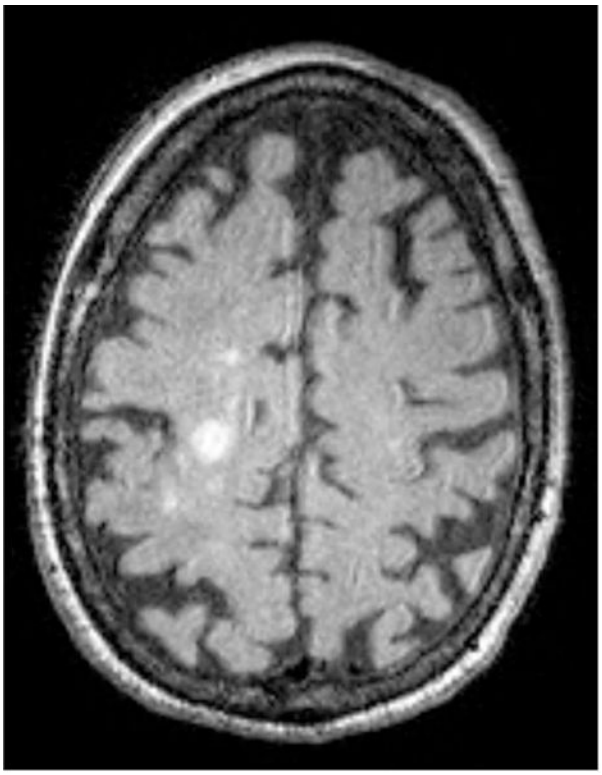

Figure 1.
Brain MRI at age 84. Coronal (left) and axial (right) T2 FLAIR images evidencing moderate dorsolateral frontoparietal volume loss, more severe in the left cerebral hemisphere, as well as subcortical and periventricular areas of white matter hyperintensities corresponding to regions with higher white matter GGT pathology at postmortem examination.

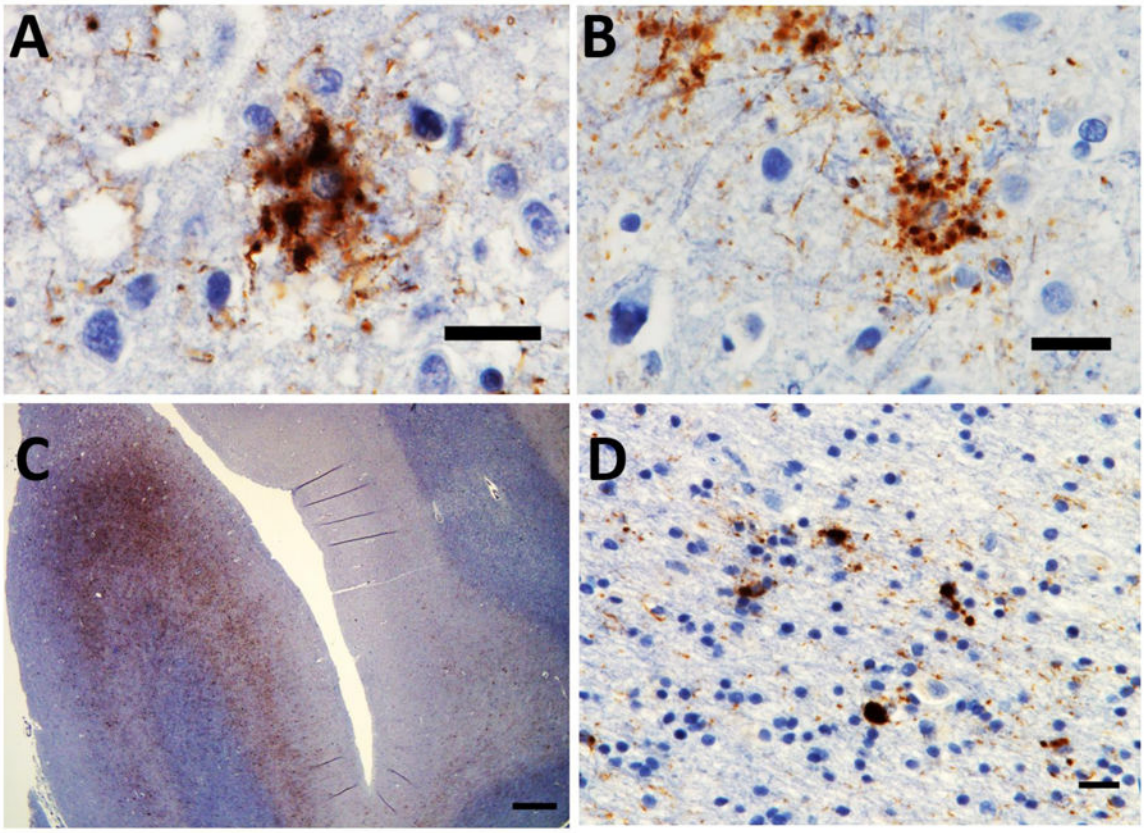

Figure 2.

(a–b) Globular astrocytic inclusions in the patient's motor cortex. (c) Abundant 4R-tau deposition is seen in the cortex and subcortical white matter of the precentral gyrus. Note the markedly lesser extent of tau deposition in the adjacent primary sensory cortex. (d) Large globular oligodendroglial inclusions in the precentral subcortical white matter are seen together with a few tau-immunoreactive neurites in the background. Immunohistochemistry for phosphorylated tau (CP13). Bars: A-B-D = 25 microns; C = 1 mm.

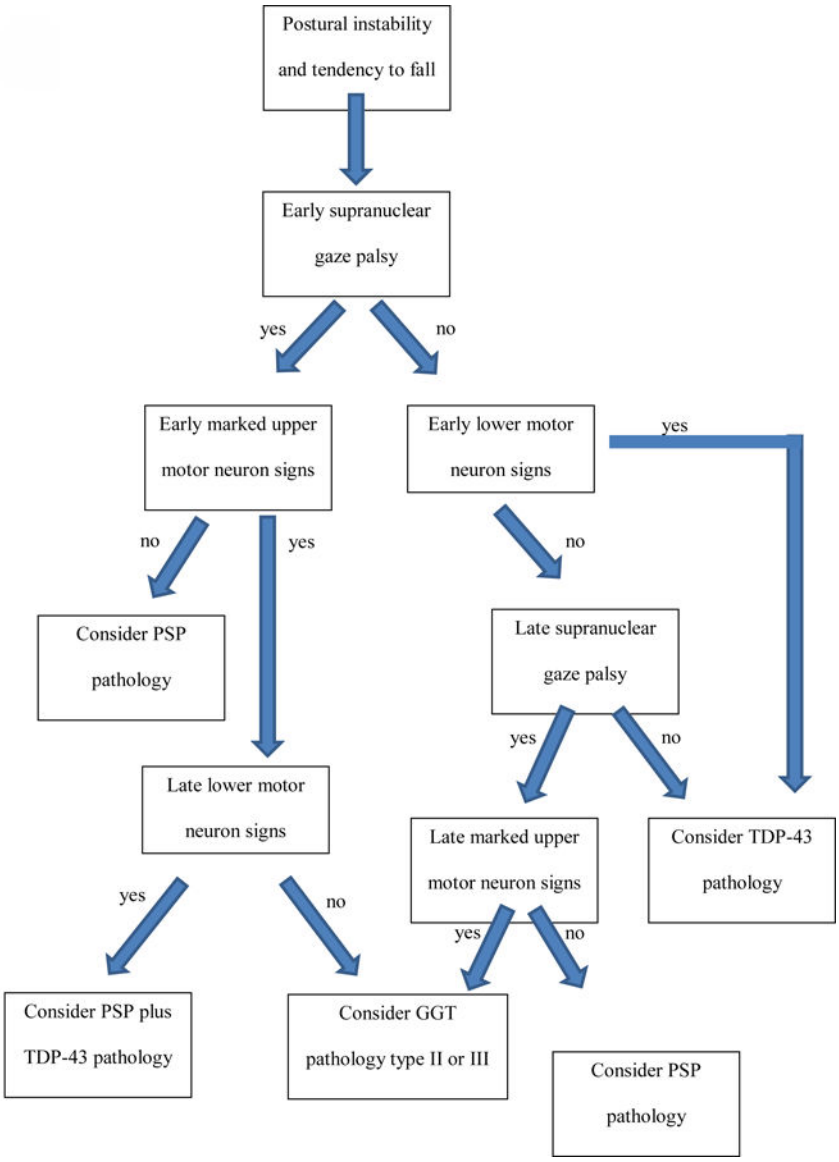

Figure 3.

Theoretical framework for clinical prediction of the underlying neuropathological substrate of primary lateral sclerosis.

Table 1.

Neuropsychological performance at baseline and 8-month follow up.

Neuropsychological test	Age 84	Age 85	Expected score, mean (SD)*
MMSE (30)	24	-	>26
GDS (30)	2	-	<9
Memory			
CVLT (9) - Encoding per trial	1, 3, 3, 4	-	5.8 (1.1), 7 (0.7), 7.4 (1.1), 8 (0.7)
CVLT (9) – recall at 30 sec	4	-	6.4 (2)
CVLT (9) – recall at 10 min	4	-	5.8 (2.9)
CVLT (9) Recognition (hits/false positives)	7/3	-	8 (1.7)
Modified Rey Osterrieth – delay recall (17)	5	5	10 (3.6)
Recognition of Modified Rey Osterrieth	Yes	-	
Language			
Modified BNT (15)	10	10	14.1 (1)
WRAT-4 – Reading (70)	47	-	41–65
Comprehension (5)	5	-	
Repetition (5)	2	-	4.6 (1)
Verbal Agility (6)	0	-	
PPVT-R (16)	13		
Visuospatial -			
Modified Rey osterrieth – copy (17)	8	6	15.6 (1)
Calculations (5)	5	-	4.8 (0.5)
VOSP (10)	8	-	8.6 (1.8)
Face perception (12)	8	-	11.4 (1)
Affect Naming (16)	12	-	12.6 (1.5)
Executive Function			
Forward/Backward Digit Span	4/4	-	6.7 (1)/5.4 (1.1)
Modified Trails Time (120 sec), lines (14), errors	>120 sec, 13, 3	>120 sec, 2, 3	41.4 sec (21.1), 14
Stroop Color Naming (words/min)	11	-	78.9 (14)
Stroop Inhibition (words/min)	5	-	46.6 (9)
Semantic Fluency (words/min)	6	-	20.6 (6.4)
Lexical (words/min)	3	-	15.6 (4.2)
Design fluency (designs/min)	5	-	9.6 (3)

* = adjusted for age and education.