Amyotrophic Lateral Sclerosis–Plus Syndrome With TAR DNA-Binding Protein-43 Pathology

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Background: Amyotrophic lateral sclerosis (ALS)–Plus syndromes meet clinical criteria for ALS but also include 1 or more additional features such as dementia, geographic clustering, extrapyramidal signs, objective sensory loss, autonomic dysfunction, cerebellar degeneration, or ocular motility disturbance.

Methods: We performed a whole-brain and spinal cord pathologic analysis in a patient with an ALS-Plus syndrome that included repetitive behaviors along with extrapyramidal and supranuclear ocular motility disturbances resembling the clinical phenotype of progressive supranuclear palsy.

Results: There was motoneuron cell loss and degeneration of the corticospinal tracts. Bunina bodies were present. TAR DNA-binding protein-43 pathology was diffuse. Significant tau pathology was absent.

Conclusions: TAR DNA-binding protein-43 disorders can produce a clinical spectrum of neurodegeneration that includes ALS, frontotemporal lobar degeneration, and ALS with frontotemporal lobar degeneration. The present case illustrates that isolated TAR DNA-binding protein-43 disorders can produce an ALS-Plus syndrome with extrapyramidal features and supranuclear gaze palsy resembling progressive supranuclear palsy.


THE DIAGNOSIS OF AMYOTROPHIC lateral sclerosis (ALS) requires the presence of progressive upper and lower motor neuron symptoms and signs. The additional features of sensory disturbance, autonomic dysfunction, extrapyramidal features, ocular motility abnormalities, dementia, cerebellar dysfunction and/or geographic clustering are considered to exclude the diagnosis of classic ALS and when present define the ALS-Plus syndrome. The following case is an example of ALS-Plus with neuropathology that is remarkably similar in distribution and extent to that which has been reported in sporadic ALS.

REPORT OF A CASE

A 66-year-old man had dysarthria for 1 1/2 years and dysphagia for 1 year before seeking medical attention. Clinical examination revealed that he had anarthria and marked difficulty swallowing liquids and solids and had lost 17 lb (to convert pounds to kilograms, multiply by 0.45). He was drooling and had difficulty with excessive pharyngeal secretions. One year previously, uncontrollable laughing developed. Concurrent with this, he developed a personality change that was manifested as apathetic, disinterested behavior, which was unusual for him, and he began to obsessively pace, climb and descend stairs, and open and close windows and doors. Three months before being seen, he developed progressive hand weakness and intrinsic hand muscle atrophy, greater on the left side than the right side, and diffuse muscular twitching in the arms, legs, and trunk. Two months previously, he developed a slow, stiff, unsteady gait and began to fall backward. In addition, he noted difficulty in voluntarily closing his eyes and an inability to voluntarily gaze, which was greater in the vertical than the horizontal direction. He did not report dyspnea or orthopnea; however, he did have frequent sleep arousal and excessive daytime sleepiness. He did not have pain, tremor, sensory disturbance, or bowel or bladder problems. He denied other medical history. His mother had developed dementia at the age of 60 years, which manifested as personality change and unusual behavior that included physical violence. Family history was otherwise normal.

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The patient was a thin, ill-appearing man in no acute distress. Forced vital capacity was 60% of predicted. He was awake, alert, and anarthric and could appropriately respond to yes/no questions and follow commands. He was able to pick out the name of objects from a written list. His writing was illegible. He blinked to visual threat. Pupils were 3 to 4 mm in diameter and reactive to light and near vision. He had a prominent stare with eyelid retraction and a surprised look. He blinked infrequently. Horizontal and vertical pursuit movements were interrupted and slow. Horizontal and vertical saccades were slow and hypometric. Downgaze was more affected than upgaze. He was unable to suppress head turning with attempted lateral gaze. The vertical and horizontal oculocephalic reflex was normal. Square wave jerks on fixation were noted. His mouth was held open; there was weakness of the masseter and pterygoid muscles, with masseter atrophy. The face was masked with upper and lower facial diparesis and prominent facial reflexes. He was unable to voluntarily close his eyes on command. Mental fasciculations were present. The palate elevated poorly but was midline. The sternocleidomastoid muscles and tongue were weak, atrophic, and fasciculating. Rapid tongue movements were slowed. Power was Medical Research Council (MRC) grade 5 in the deltoid, biceps, and triceps muscles but MRC grade 4 in the right and left finger extensor and hand intrinsic muscles. There was atrophy of the hand intrinsic muscles. Leg power was MRC grade 5; he was able to rise from a chair without using his hands, and heel and toe walking was normal. Large-amplitude fasciculations were noted throughout the arms, hands, chest, thighs, calves, forearms, and abdominal wall. Tone was more rigid in the legs than the arms, without tremor or cogwheeling. Rapid movements were slowed in the hands and feet with reduced amplitude. Bradykinesia was present. Walking was slow with a narrow base, small steps, and absent arm swing. Turning was poor, with multiple steps. Retropulsion was prominent. There was no limb apraxia or alien hand. Sensory and cerebellar examinations yielded normal findings. There was jaw clonus. Reflexes were 3 of 4 in the arms and legs, greater on the left side than the right side, with bilateral Hoffman sign and crossed adduction. Cutaneous abdominal reflexes were absent. Toes were extensor (the so-called Babinski sign) bilaterally. Snout, glabellar, and palmpalatal reflexes were present.

CLINICAL AND LABORATORY INVESTIGATIONS

Magnetic resonance images of the brain demonstrated diffuse atrophy with increased signal in the corticospinal tracts. Nerve conduction was normal. An electromyogram demonstrated acute and ongoing partial denervation in multiple muscles of the left arm and leg, the tongue, and the thoracic paraspinal region. The spinal cord was normal. Complete blood cell count was normal, as were electrolyte, anti-GM1 antibody, and creatine phosphokinase concentrations. Liver function studies, thyroid function studies, serum heavy metal screening, serum protein electrophoresis, and urine protein electrophoresis yielded normal results.

CLINICAL COURSE

The patient refused riluzole therapy. A gastrostomy tube was inserted 2 weeks after presentation. One month later, worsening dyspnea and orthopnea developed, and forced vital capacity decreased to 38% of predicted. Noninvasive positive-pressure ventilatory assistance was instituted. The patient declined long-term mechanical ventilatory assistance, and hospice care was instituted. Two months after the initial presentation, the patient died of respiratory failure.

POSTMORTEM EXAMINATION

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POSTMORTEM EXAMINATION

NEUROPATHOLOGIC FINDINGS

The brain, spinal cord, and spinal roots were macroscopically normal. The substantia nigra was normally pigmented. The cervical and thoracic spinal cord demonstrated corticospinal tract degeneration with myelin staining. Axonal spheroids positive for α-synuclein antibody indicative of interrupted axonal transport were seen in the corticospinal tract. There was no other pathologic immunoreactivity for α-synuclein or Lewy body pathology elsewhere in the brain. Mild to moderate loss of motoneurons in the anterior horns was noted. Bunina bodies as well as TAR DNA-binding protein-43 (TDP-43)–positive cytoplasmic skein and Lewy body–like and punctate cytoplasmic inclusions were noted in some remaining motoneurons. Neuronal cytoplasmic TDP-43 inclusions and glial cytoplasmic inclusions were present in the motor cortex. Extensive neuronal and glial TDP-43 inclusions were also noted in the midbrain, hippocampus, globus pallidus, hypoglossal nucleus, substantial nigra, and caudate/putamen area. (Figure 1) A semi-quantitative pathologic scale (0, none; 0.25, rare; 1, mild; 2, moderate; and 3, severe) was used to score TDP-43 pathology in each brain region (Figure 2). Tau immunohistochemistry showed isolated and rare neurofibrillary tangles, which were limited to the entorhinal cortex (Braak and Braak stage 1), likely the result of normal aging.

GENETIC FINDINGS

Mutations in the progranulin (GRN) (OMIM 138945) and TDP-43 (TARDBP) (OMIM 605078) genes were excluded using DNA sequencing. The DNA was extracted from brain tissue using an automated extractor according to the manufacturer’s protocol (M48 workstation; Qiagen GmbH, Hilden, Germany). DNA sequencing of the GRN and TARDBP genes was performed as previously described.1,2

COMMENT

This 66-year-old man had a rapidly progressive upper and lower motoneuron disorder culminating in death after 20 months as a result of neuromuscular respiratory failure. Symptoms began in the bulbar musculature and progressed and spread to include limb and respiratory muscles. Supranuclear ocular motility and extrapyrami-
Dal abnormalities developed without sensory or autonomic dysfunction. He manifested an apathetic, disinhibited personality with motor stereotypies. Mental status examination was hampered by anarthria and limb weakness; however, severe memory or language impairment was not noted. Magnetic resonance images demonstrated increased signal in the corticospinal tract. An electromyelogram demonstrated evidence of a diffuse lower motor neuron process.

The patient met El Escorial criteria for clinically definite ALS. The extrapyramidal and ocular motility findings are reminiscent of progressive supranuclear palsy (PSP). Hyperintensity of the corticospinal tracts on magnetic resonance images is an occasional finding in ALS and has been reported in atypical primary lateral sclerosis. The personality change and motor stereotypies are characteristic of frontotemporal lobar degeneration (FTLD) and lesions of the orbitofrontal, ventral striatal, basal forebrain, and anterior temporal connections. Frontotemporal lobar degeneration may occur in ALS and in PSP. The ALS-Plus syndromes meet clinical criteria for ALS but also include 1 or more other features such as dementia, geographic clustering, extrapyramidal signs, objective sensory loss, autonomic dysfunction, cerebellar degeneration, or ocular motility disturbance. The combination of ALS, FTLD, and PSP-like features are consistent with the diagnosis of an ALS-Plus syndrome.

The neuropathologic findings demonstrating Bunina bodies, loss of motoneurons, and corticospinal tract degeneration are consistent with the diagnosis of ALS. There was also diffuse TDP-43 pathology. TAR DNA-binding protein-43 has been identified as a major disease-associated protein in FTLD characterized by ubiquitin inclusions and in sporadic ALS with and without FTLD. In ALS, TDP-43 pathology is often diffusely distributed. Thus, it is not surprising that the present case of ALS-Plus syndrome was associated with TDP-43 proteinopathy in the brain and spinal cord motor regions and in other brain regions closely associated with behavioral change and extrapyramidal disorders.

Sporadic PSP is characterized by the presence of tau-positive inclusions and may demonstrate corticospinal tract degeneration in atypical cases. Mutations in the GRN gene have been reported to cause diffuse TDP-43 proteinopathy manifesting as FTLD, associated in some patients with atypical parkinsonism including features of PSP or corticobasoganglionic degeneration without ALS. A search for GRN mutations in 272 patients with sporadic ALS, 40 with familial ALS, and 49 with ALS-FTLD yielded missense mutations of uncertain significance in 1 patient with limb-onset sporadic ALS and 1 with ALS-FTLD. It is notable that our patient’s mother had dementia suggestive of FTLD. A GRN mutation was not identified in our patient. Although he did not have the clinical features of corticobasoganglionic degeneration, a unique predominantly glial TDP-43 pathology with staining of astrocytic plaquelike structures and coiled bodies with biochemical changes of TDP-43 similar to that seen in FTLD with ubiquitin inclusions has been reported in up to 15.4% of patients with corticobasoganglionic degeneration. Both TDP-43 and tau pathologic

Figure 2. Extent and distribution of TAR DNA-binding protein-43 pathology. SN indicates substantia nigra. For disease severity, 1 is mild; 2, moderate; and 3, severe.
features are present in Pacific Island geographic clusters of ALS, that is, parkinsonism-dementia complex. 26 Mutations in the TDP-43 gene have been reported in both familial and sporadic ALS. 1-3,27,28 However, our patient was not found to carry a mutation of the TDP-43 gene.

This case report suggests the possibility that the extent and distribution of TDP-43 proteinopathy may determine clinical features. Confirming this will require pathologic analysis of a large number of ALS-Plus cases. While the most frequent manifestation may be ALS with or without cognitive impairment or dementia, the present case suggests that isolated TDP-43 proteinopathy can also produce an extrapyramidal disorder with supranuclear gaze paresis like that seen in PSP. Further studies are needed to determine whether isolated TDP-43 pathology can produce ALS-Plus syndromes with other features. This case also highlights the clinical overlap between tau and TDP-43 proteinopathies. Frontotemporal dementia occurs in PSP, FTLD, and corticobasal ganglionic degeneration and also in ALS with or without FTLD. While supranuclear gaze abnormalities have often been clinically linked to presumed tau pathology, this case and previous reports of atypical PSP in patients with GRN mutations suggest that such assumptions may be flawed and perhaps particularly so when there is a clinical or pathologic indication of associated upper or lower motoneuron degeneration.

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