Clinical Reasoning: Rapidly progressive quadriplegia in a forgetful patient

SECTION 1
A 50-year-old right-handed retired family business manager developed progressive left-sided weakness over 5 days after a mechanical fall. She remembered catching her foot on the carpet and falling down a flight of stairs, followed by severe neck pain over C4-C5 and inability to get up for nearly an hour. Over the subsequent month her symptoms progressed and she presented to the hospital with an asymmetric spastic paraparesis, loss of pinprick sensation in her arms and legs, loss of vibration sense to both hips, and double incontinence.

MRI of the patient’s cervical spine revealed severe cervical canal stenosis but no cord abnormality, while brain MRI showed high signal in the corticospinal tract bilaterally (figure). Somatosensory evoked potentials (SSEPs) were of low amplitude but not delayed. The patient stabilized on a rehabilitation ward and was discharged home independent and continent but with some frequency of micturition.

When reviewed in clinic 2 months later, the patient had significantly deteriorated, was wheelchair-bound, and complained of memory deterioration, slurred speech, coughing on free fluids, and new right-sided weakness. The patient’s medical history included unexplained collapses with a postictal confusional period of 30 minutes since age 14 years. Her mother died of dementia at age 68 and her brother of a stroke at age 50. She was an ex-smoker of 20 cigarettes per day and rarely consumed alcohol.

On cognitive assessment using the Addenbrooke’s Cognitive Assessment–Revised, the patient scored 67/100, losing points for attention; poor category and letter fluency; memory, naming, and abstract reasoning; writing; and constructional ability. She also had behavioral changes: she was disinhibited and emotionally labile (pseudobulbar affect with pathologic smiling and laughter). She had become disorganized with housework and was unable to reason in a 2-step strategy (such as making decisions about her own care). She was concrete in her ways and did not want any change. She had dysarthria with mild nasal escape and a spastic quadriparesis with pyramidal weakness (worse on the left and in her upper limbs), sustained ankle clonus, and hyperreflexia. Sensory examination was normal.

Questions for consideration:
1. What is the differential diagnosis in a patient with pyramidal weakness and cognitive problems?
2. In view of her imaging results and abnormal SEP, what tests should one consider?
SECTION 2
In a patient with chronic progressive motor symptoms and cognitive problems, the differential diagnosis includes inflammatory, infectious (e.g., HIV, Lyme disease, Whipple disease, neurosyphilis, and non-tuberculous mycobacterial infection), metabolic/toxic, neurodegenerative, and paraneoplastic causes (table). An initial screen should include a full blood count with differential, urea and electrolytes (including corrected calcium and phosphate concentrations), liver function tests, amylase, and C-reactive protein, which were normal in our patient. Normal thyroid function tests and vitamin B12 levels ruled out hypothyroidism and B12 deficiency as a metabolic cause of her symptoms. She had a slightly low folate level of 3.0 μg/L (normal range 5–10 μg/L). Ferritin, lead, cadmium, and thallium levels were measured to exclude toxic causes of encephalopathy and motor symptoms and were normal. Serologic investigations for inflammatory diseases, including serum angiotensin-converting enzyme, rheumatoid factor, antineutrophil cytoplasmic antibodies, immunoglobulins, and serum protein electrophoresis, were normal or negative.

CSF analysis revealed a normal cell count, normal cellularity, and no growth after 48 hours incubation, ruling out an active inflammatory process. CSF glucose and the CSF glucose/serum glucose ratio were normal. Oligoclonal bands were negative and CSF protein was marginally elevated at 0.71 g/L.

A paraneoplastic syndrome was also considered. CT of thorax, abdomen, and pelvis only showed a few calcified nodules within both hemithoraces, consistent with previous granulomatous infection. Bilateral mammograms were unremarkable. In view of the rapid progression of the patient’s symptoms, an MRI of her brain was repeated with gadolinium administration, showing once again the high signal in the corticospinal tracts and asymmetrical bilateral frontotemporal atrophy (figure). She declined a body PET-CT.

In view of the patient’s previous history suggesting seizures and to ensure her cognitive problems were not due to underlying ictal phenomena, an EEG was

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<td><strong>Clinical characteristics</strong></td>
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<td>Amyotrophic lateral sclerosis (ALS) with frontotemporal dementia</td>
<td>Combination of upper and lower motor neuron signs (fasciculations) plus frontotemporal cognitive deficits</td>
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<tr>
<td>Alzheimer disease (AD) with presenilin-1 (PSEN1) mutation</td>
<td>Autosomal dominantly inherited syndrome of AD-type dementia; onset in early 50s is typical; associated with heterogeneous neurologic symptoms including spastic paraparesis (which is a strong indicator for PSEN1 mutation), seizures, and myoclonus</td>
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<td>Corticobasal degeneration (CBD), progressive supranuclear palsy (PSP)</td>
<td>Insidious onset, cortical dysfunction with sensory disturbance (alien hand) and apraxia, extrapyramidal dysfunction (akinetic-rigid syndrome)</td>
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<tr>
<td>Wilson disease (with neurologic involvement)</td>
<td>Psychiatric symptoms, dementia, rigidity, and extrapyramidal features; Kayser-Fleischer corneal arcus in 50%–60% of patients; family history</td>
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<tr>
<td>Creutzfeldt-Jakob disease</td>
<td>Rapidly progressive dementia, myoclonus, ataxia, pyramidal signs</td>
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<td>Inflammatory/autoimmune disease</td>
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<tr>
<td>Inflammation (acute disseminated encephalomyelitis, MS)</td>
<td>Gradual/subacute onset of sensory and motor deficit; cerebellar, brainstem signs or myelopathy</td>
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<tr>
<td>Paraneoplastic disease</td>
<td></td>
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<tr>
<td>Paraneoplastic encephalomyelitis ± anterior horn cell involvement</td>
<td>Subacute encephalitis with confusion, behavioral and cognitive difficulties, brainstem signs</td>
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performed. This showed diffuse theta waves, suggestive of a mild nonspecific cerebral dysfunction. EMG showed evidence of widespread chronic partial denervation with active changes in all 4 limbs and respiratory muscles. In view of the rapidly progressive course of the illness, the abnormalities were interpreted in keeping with a diagnosis of motor neuron disease, possibly with associated frontotemporal dementia.

By then, the patient had developed prominent fasciculations in upper and lower limbs and had a forced vital capacity of 0.9 L. Early morning arterial blood gas analysis showed a pO₂ of 9.73 kPa and a pCO₂ of 9.84 kPa, with a base excess of 3.4 mmol/L.

Questions for consideration:
1. What is your diagnosis?
2. How would you interpret the MRI findings?
3. What further tests could you consider to investigate the cause of her disease?
SECTION 3

The combination of clinical and electrophysiologic evidence of progressive lower and upper motor neuron signs in 2 segments, in the absence of any other relevant disease process, fulfills the El Escorial criteria for clinically probable amyotrophic lateral sclerosis (ALS). Additionally, our patient had cognitive problems, which were confirmed as predominantly frontotemporal on formal neuropsychological assessment. The combination of these 2 clinical syndromes supported a diagnosis of ALS–frontotemporal dementia (ALS-FTD). Her MRI and SSEP findings strongly supported the diagnosis, as prominence of the corticospinal tracts on MRI and low amplitude or loss of SSEPs are recognized features of ALS. Frontotemporal atrophy on MRI supported the diagnosis of FTD. Another neurodegenerative condition that can present with spasticity and dementia is corticobasal degeneration, where SSEPs are typically delayed rather than of low amplitude or lost, as in this case. Of note, the transient sensory symptoms the patient had originally presented with and that had resolved were thought to be related to soft tissue injury and her cervical stenosis.

As rapidly progressive ALS has occasionally been reported as a paraneoplastic syndrome, we tested for the following tumor markers and paraneoplastic antibodies, which were all reported as not significantly raised or negative: carcinoma antigen (CA) 15-3; CA 19-9; CA 125; carcinoembryonic antigen (CEA); α-fetoprotein; antibodies against Hu, amphiphysin, Ri, and CV2.1; and neuronal and thyroid microsomal antibodies. The patient tested weakly positive for Purkinje cell (Yo) antibodies on immunoblot.

In view of the patient’s family history of dementia and her presentation with combined ALS and FTD, we tested her for the recently described C9orf72 repeat expansion. This is the most common mutation identified so far in familial ALS. Southern blotting confirmed C9orf72 hexanucleotide (GGGGCC) expansion in the pathogenic range. She died shortly after discharge home on riluzole and had not consented to a postmortem.

DISCUSSION

ALS is familial in 5%–10% of cases. Up to 50% of patients with ALS also develop cognitive impairment, while 5%–15% are diagnosed with dementia, most commonly of the frontotemporal type (ALS-FTD complex). Recent studies have suggested that the most common mutation in familial ALS may be a hexanucleotide repeat expansion in C9orf72 with a frequency of approximately 40%, also present in up to 13% of apparently sporadic ALS-FTD. The hexanucleotide GGGGCC is normally present in 2–23 copies in the noncoding region of gene C9orf72 on chromosome 9 and the C9orf72 RNA transcripts are present in 3 alternatively spliced variants. In patients with ALS-FTD, the hexanucleotide GGGGCC is present in 700–1,600 copies.

While the exact pathogenic mechanism is unknown, it is thought that the high number of repeats disrupts the alternative splicing of the C9orf72 transcripts and leads to RNA accumulation in the nucleus. This may, in turn, lead to dysfunction of RNA binding proteins and cellular functions. Histopathologically, both transactive response DNA binding protein of 43 kDa (TDP-43) and p62-positive neuronal inclusions have been shown in the cerebral and cerebellar cortex of patients with the hexanucleotide repeat expansion. Clinically, patients with the C9orf72 repeat expansion also have a recognizable phenotype, comprising a family history of dementia or ALS, an earlier age at onset, evidence of cognitive impairment, and, in many instances, a rapid disease progression.

Had the C9orf72 hexanucleotide repeats been in the normal range, our genetic testing strategy would have been directed, in order, at testing for mutations in the TARDBP, FUS, and SOD1 gene, as mode of inheritance and clinical presentation would fit with our patient’s, although for FUS and SOD1 gene mutations the clinical presentation is usually more toward the ALS part of the spectrum and the mean age at onset tends to be earlier.

Although the pathogenetic mechanisms are not fully understood, the C9orf72 repeat expansion may become a pharmacogenetic target for presymptomatic carriers. Further research and a recently founded online gene database will keep us informed on new insights into the pathogenetic mechanisms and penetrance of this and other mutations causing familial ALS-FTD.

AUTHOR CONTRIBUTIONS

Laura Mannoon Riter: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and final approval, acquisition of data, study supervision. Jeremy D. Isaacs: drafting/revising the manuscript, accepts responsibility for conduct of research and final approval, acquisition of data. John Philip O’Dwyer: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and final approval, acquisition of data. John Philip O’Dwyer: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and final approval, acquisition of data, study supervision.

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DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

REFERENCES


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