Clinical Reasoning: Rapidly progressive quadriparesis in a forgetful patient

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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

Figure MRI brain (fluid-attenuated inversion recovery sequence) shows high signal in the corticospinal tract (small arrows)

Although not formally measured, there was relevant sulcal enlargement, including a wide sylvian fissure (thick arrow) and widening of the right central sulcus at the lateral aspect (sequence not shown), suggestive of frontotemporal atrophy.

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 SSEP, what tests should one consider?

GO TO SECTION 2

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 nontuberculous 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

Table Differential diagnosis for progressive pyramidal weakness and cognitive problems

Differential diagnosis	Clinical characteristics	Diagnostic tests
Neurodegenerative diseases		
Amyotrophic lateral sclerosis (ALS) with frontotemporal dementia	Combination of upper and lower motor neuron signs (fasciculations) plus frontotemporal cognitive deficits	EMG shows denervation. NCS show normal motor and sensory conduction (no conduction block). MRI: high signal in corticospinal tracts and frontotemporal atrophy (but mainly used to rule out other causes). SSEPs: loss of or low amplitude. Neuropsychology suggestive of frontotemporal deficits.
Alzheimer disease (AD) with presenilin-1 (PSEN1) mutation	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	Neuropsychometric testing shows focal or lateralized cognitive deficits with early involvement of memory and learning. CT/MRI: generalized or focal atrophy. PET/SPECT: hypoperfusion/low metabolism in hippocampus, precuneus, and parietotemporal cortex (AD). Genetic testing for PSEN1 mutation.
Corticobasal degeneration (CBD), progressive supranuclear palsy (PSP)	Insidious onset, cortical dysfunction with sensory disturbance (alien hand) and apraxia, extrapyramidal dysfunction (akinetic-rigid syndrome)	Neuropsychometric testing shows focal or lateralized cognitive deficits with sparing (CBD) of memory and learning. CT/MRI: focal/asymmetric atrophy (CBD), midbrain atrophy (PSP). PET/SPECT: focal/asymmetric hypoperfusion with sparing of basal ganglia (CBD).
Wilson disease (with neurologic involvement)	Psychiatric symptoms, dementia, rigidity, and extrapyramidal features; Kayser-Fleischer corneal arcus in 50%–60% of patients; family history	Serum: ceruloplasmin level below 20 mg/dL. Urine: urinary copper excretion >100 µg over 24 hours. MRI: high T2 signal in basal ganglia, brainstem, white matter. Genetics: mutation in Wilson gene <i>ATP7B</i> on chromosome 13.
Creutzfeldt-Jakob disease	Rapidly progressive dementia, myoclonus, ataxia, pyramidal signs	MRI: high signal in putamen and head of caudate (sensitivity 83%–92%, specificity 87%–95%). CSF: positive for protein 14-3-3 (can be normal in familial forms and elevated in nonprion disease of the CNS). EEG: periodic synchronous biphasic or triphasic sharp wave complexes (sensitivity 67%, specificity 85%).
Inflammatory/autoimmune disease		
Inflammation (acute disseminated encephalomyelitis, MS)	Gradual/subacute onset of sensory and motor deficit; cerebellar, brainstem signs or myelopathy	MRI: high T2 and FLAIR signal, new lesions enhance with contrast. CSF: positive for unmatched oligoclonal bands in MS (pleocytosis or increased protein common in ADEM). Visual- and brainstem-evoked responses can be delayed.
Paraneoplastic disease		
Paraneoplastic encephalomyelitis ± anterior horn cell involvement	Subacute encephalitis with confusion, behavioral and cognitive difficulties, brainstem signs	Serum: positive anti-Ro, La, Hu, Ma2, GAD/amphiphysin, or TPO antibodies, CT thorax/abdo/pelvis, PET scan, mammogram, testicular ultrasound to identify possible primary tumor.

Continued

Table	Continued	
Differential diagnosis	Clinical characteristics	Diagnostic tests
Nutritional/metabolic deficiencies		
Vitamin B₁₂ deficiency	Subacute combined degeneration of the cord, dementia, encephalopathy, sensory polyneuropathy	Serum: B ₁₂ levels low.
Folate deficiency	Subacute combined degeneration of the cord-like picture	Serum: folate levels low.
Hypothyroidism	Cognitive slowing and dementia, fatigue, constipation, cold intolerance	Serum: TSH high or low, fT4 and fT3 low.
Adult-onset metachromatic leukodystrophy	Autosomal recessive, presents with dementia or psychiatric features, pyramidal signs, speech problems, ataxia	Serum: deficiency of arylsulfatase A.
Adult-onset hexosaminidase A deficiency	Autosomal recessive, variable clinical features even within same family, can present with spinal muscular atrophy or early-onset ALS features (wasting, weakness, fasciculations, upper motor neuron signs), dysarthria, and cognitive impairment	Assay of hexosaminidase A enzymatic activity; if decreased: molecular genetic testing for HEXA mutations.
Adult polyglucosan body disease	Autosomal recessive, progressive upper and lower motor neuron signs with gait difficulty, mild cognitive impairment, neurogenic bladder dysfunction	MRI: progressive white matter changes (paraventricular, subcortical, and as far as the craniocervical junction). NCS/EMG: lumbosacral axonal polyradiculoneuropathy. Sural nerve biopsy: typical polyglucosans within nerve tubes. Low glycogen branching enzyme (GBE) activity in skin fibroblast cultures and GBE1 mutations on molecular genetic testing.
Infectious causes		
HIV	AIDS dementia complex in advanced disease; myelopathy due to IRIS or JC virus infection	Serum: HIV serology, CD4 count, viral titer, check for concomitant hepatitis coinfection.
Syphilis	Delirium and dementia; myelopathy and sensory neuropathy	Serum: VDRL/TPHA test.
Chronic Lyme disease	Lyme encephalopathy or (rarely) chronic encephalomyelitis with spastic paraparesis, cranial neuropathies, and cognitive impairment; arthritis; acrodermatitis chronica atrophicans	Serum/CSF: high titer of anti- <i>Borrelia burgdorferi</i> IgM or IgG (ELISA followed by a Western blot) or isolation of <i>B burgdorferi</i> from clinical specimen.
Whipple disease	Migratory arthralgia, diarrhea, abdominal pain; cognitive dysfunction, oculomasticatory myorhythmia, gaze palsy; multiple neurologic symptoms possible	Demonstration of <i>Tropheryma whippelii</i> on small-bowel biopsy (periodic acid-Schiff-positive macrophages). MRI/CT may show high signal lesions in CNS disease. PCR of CSF, brain tissue, and peripheral blood possible.
Toxic causes		
Heavy metal poisoning (lead, mercury, cadmium, thallium)	Acute confusion, dementia	Serum: lead and mercury levels.

Abbreviations: ADEM = acute disseminated encephalomyelitis; FLAIR = fluid-attenuated inversion recovery; GAD = glutamic acid decarboxylase; Ig = immunoglobulin; IRIS = immune reconstitution inflammatory syndrome; MS = multiple sclerosis; NCS = nerve conduction studies; SSEP = somatosensory evoked potential; TPHA = *Treponema pallidum* hemagglutination assay; TPO = thyroid peroxidase; TSH = thyroid-stimulating hormone; VDRL = Venereal Disease Research Laboratory.

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?

GO TO SECTION 3

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).¹ 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^{2,3} are recognized features in 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* hexanucleotide mutation. This is the most common mutation identified so far in familial ALS.⁵ 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).⁴ Recent studies have suggested that the most common mutation in familial ALS may be a hexanucleotide repeat expansion in *C9orf72*⁵ with a frequency of approximately 40%,^{6,7} and 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.⁸ In patients with ALS-FTD, the hexanucleotide GGGGCC is

present in 700–1,600 copies.⁸ 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.⁸ 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.⁹ Clinically, patients with the *C9orf72* repeat expansion also have a recognizable phenotype,⁷ 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.⁷

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 database¹⁰ 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 Mantoan Ritter: 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. Meriel McEntagart: 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, study supervision.

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DISCLOSURE

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