

Clinical Reasoning: A 72-year-old man with a progressive cognitive and cerebellar syndrome

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Section 1

A 72-year-old right-handed man was referred to the cognitive neurology clinic after being involuntarily committed to an inpatient psychiatry unit for 2 years. He was unable to give a coherent history, which was obtained from his wife. His birth and early development were unremarkable. He had previously held a number of jobs including working in the merchant navy for 2 years. He was unemployed before admission. He did not drink alcohol excessively and was a heavy smoker. He was fit and medically well until 5 years before the assessment, when he developed progressive balance and behavioral problems. This included an ataxic gait requiring intermittent wheelchair use, slurred speech, and poor memory. He had become increasingly irritable and aggressive with paranoid ideas of spousal infidelity.

Further history revealed a strong family history of cognitive problems. The patient's father died at age 63 years with a diagnosis of "dementia" and prominent memory loss. The patient had 2 brothers, one who died in a car crash and the other with a diagnosis of "dementia" at age 61 years. His brother's son, at the time of consultation, had a reported diagnosis of early-onset "dementia" at 54 years. These relatives were never seen by a neurologist and there was no documentation of any neurologic examination for them.

While hospitalized at inpatient psychiatry, the patient was treated with 1.5 mg a day of risperidone. He had a number of unprovoked fights with other patients. He developed weight loss from self-neglect. He was able to feed himself but needed help with all activities of daily living. There was no weakness or abnormal movements. He was otherwise medically well during this time without other organ dysfunction.

Examination of the eyes revealed frequent square-wave jerks in the primary position and jerk nystagmus bilaterally. There was a slurring dysarthria. In the limbs, tone and reflexes were normal. He had bilateral finger-to-nose dysmetria, a normal stance, and marked broad-based gait. Romberg sign was negative and there was no muscle wasting or fasciculations. There were no frontal-release signs or limb apraxia.

The patient was apathetic and did not initiate conversation. He would rapidly forget what was said to him. Addenbrooke's Cognitive Examination (revised edition) showed an overall score of 51 out of 100 with subscores attention and orientation 10/18, memory 11/28, fluency 1/14, language 24/26, and visuospatial 5/16.

Questions for consideration:

1. Where would you localize the problem?
2. What is your initial approach to investigations?

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Section 2

The patient has neurologic problems in multiple areas of the CNS. The cognitive problems would point to a lesion in the cerebrum. There are global problems but more pronounced deficits in behavior, executive function, and memory. These would point to lesions in the frontal and temporal lobes. The severity of these impairments and degree to which they impact his life suggest an underlying dementia. The speech, balance problems, and findings of nystagmus and past-pointing on examination indicate a global cerebellar lesion.

Initial investigations should be tailored to finding reversible medical problems although these would usually present with a subacute onset. A full general medication examination did not reveal any other abnormalities. Basic laboratory investigations including electrolytes, full blood count, liver enzymes, renal function, thyroid function, vitamin B₁₂, and folate were

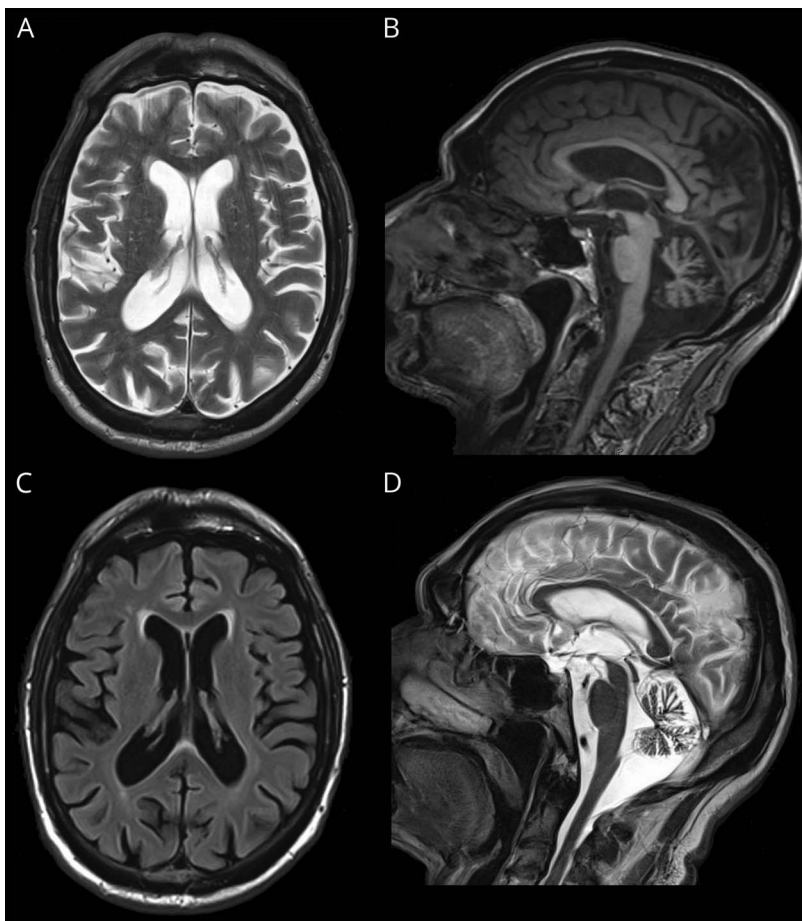
normal. Autoantibodies and a screen for antineuronal antibodies was normal. The patient had a normal HIV test and syphilis screen. A chest radiograph was normal. The patient underwent cerebral imaging with 1.5T MRI (T1- and T2-weighted sequences including T2 fluid-attenuated inversion recovery), which based on neuroradiologic review showed mild cortical and white matter cerebral atrophy (in no specific distribution) according to the global cortical atrophy rating scale and severe global cerebellar atrophy (figure).

Combined cerebellar and cognitive dysfunction can be caused by metabolic or genetic conditions and a family history may provide key insight into the mode of transmission. As there are consecutive generations involved, an autosomal dominant mode of transmission was suspected.

Question for consideration:

1. What would you consider in the differential diagnosis?

Figure Structural MRI scan sequences



Structural 1.5T MRI scans. (A) A T2-weighted axial section shows global central cerebral atrophy with opening of the sulci and mild ventricular enlargement. (B) A T1-weighted sagittal section shows severe cerebellar atrophy. (C) A T2 fluid-attenuated inversion recovery axial section shows mild periventricular small vessel disease near the anterior horn of the lateral ventricles. (D) A T2-weighted cerebellar sagittal section shows severe cerebellar atrophy.

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Section 3

The patient has a cognitive and cerebellar syndrome of insidious onset. Taken together, these findings are most commonly encountered with metabolic problems such as alcohol excess, Wernicke encephalopathy, or nutritional and hormonal imbalances such as hypothyroidism. However, the patient neither had the collateral history to fit this nor a supportive biochemical profile. Infectious etiologies such as HIV and syphilis were considered but there were no additional features such as general medical and biochemical abnormalities. HIV can cause a cerebellar ataxia due to opportunistic infections and although tertiary syphilis can rarely cause a pancerebellar syndrome, it is also accompanied by sensory ataxia due to posterior column disease, eye signs (such as an Argyll-Robertson pupil, uveitis, and/or keratitis) and “lightning-like” pains affecting the back and abdomen, which were lacking in our patient. Granule cell neuronopathy due to reactivation of JC virus is another condition that can cause a progressive cerebellar ataxia but our patient was not immunocompromised. Immune-mediated problems with or without an associated cancer may present with cerebellar and cognitive symptoms and the spectrum of these diseases is expanding. However, one would expect a subacute onset over weeks to months with an immune-mediated condition. If autoimmune etiologies are suspected, CSF examination may be useful as it may indicate a lymphocytic pleocytosis or elevated protein. Our patient had a normal CSF profile with no cells and normal glucose and protein values. Syndromes associated with anti-GAD, GABA_B, and glial fibrillary acid protein (GFAP) antibodies may cause a cognitive and cerebellar syndrome, but they are usually associated with additional clues such as MRI changes and CSF abnormalities. The clinical course may include seizures and cortical hyperintensities in the case of anti-GAD, a

meningitic syndrome in GABA_B encephalitis, or cord abnormalities and meningeal contrast enhancement with anti-GFAP syndrome.¹ Paraneoplastic cerebellar syndromes can be associated with anti-Yo, anti-Hu, and anti-Ri antibodies but these were negative.² In cases with a shorter history of clinical progression lasting weeks to a few months, assessment for occult solid organ malignancy with CT scan of the chest, abdomen, and pelvis and/or a whole body PET CT scan may be useful. A PET CT scan showed no evidence of malignancy in our patient.

The strong family history in our patient suggests a genetic cause. There are many cerebellar syndromes associated with dementia. Common genetic ataxias such as Friedreich ataxia and autosomal recessive spastic ataxia of Charlevoix-Saguenay present in younger patients and are not usually associated with progressive cognitive deficits. The latter may be encountered in other conditions presenting with ataxia such as fragile X tremor-associated syndrome (FXTAS), cerebrotendinous xanthomatosis (CTX), and Niemann-Pick type C (NPC).^{3,4} MRI findings help to narrow the differential further and distinguish these conditions. FXTAS and CTX are usually associated with characteristic white matter changes in the posterior fossa and NPC may show callosal thinning and cerebellar atrophy. The severe cerebellar atrophy present in our patient may point towards spinocerebellar ataxias (SCAs). SCA-2, -3, and -17 may present with a cerebellar as well as a cognitive syndrome. Biochemical and genetic tests (expansion repeat testing for SCAs and a next-generation sequencing ataxia panel) for all of these conditions were negative in our patient.

Question for consideration:

1. Which additional genetic tests would you consider in someone with a dementia and a cerebellar syndrome?

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Section 4

A cerebellar syndrome is not typically seen in patients with classic Alzheimer disease, frontotemporal dementia (FTD), or dementia with Lewy bodies. In contrast, multiple system atrophy can present with a cerebellar syndrome but cognitive symptoms are not prominent in this condition and in our patient there are no other supportive symptoms such as REM behavior disorder and extrapyramidal signs. In this case, testing for the following mutations known to cause autosomal dominant forms of dementia were negative: amyloid precursor protein (*APP*), presenilin 1 and 2, microtubule-associated protein tau (*MAPT*), and progranulin (*PGRN*).^{5,6} The patient also underwent testing for an abnormal expansion of the *C9orf72* gene, which is tested separately from the genes included in most panels. Testing for *C9orf72* demonstrated an abnormal repeat size confirming a diagnosis of *C9orf72*-related behavioral variant FTD.

Discussion

Expansion of the GGGGCC hexanucleotide repeat in the *C9orf72* gene is the most common genetic cause of FTD and amyotrophic lateral sclerosis (ALS).⁷ A phenotype of behavioral-variant FTD is the most common presentation followed by motor-neuron disease. There is also a known overlap of these conditions (e.g., FTD and ALS). The clinical phenotype may also include extrapyramidal symptoms but cerebellar ataxia has not been described previously. The presence of psychosis is well-described in association with *C9orf72* and paranoid delusions were an important feature in our patient's history.⁷ The age at onset varies between 43 and 68 years. There is an autosomal dominant mode of transmission. A third of new cases do not have a family history of any neurologic disorder. MRI findings may include frontal, temporal, and parietal cortex atrophy and thinning of the thalamus and cerebellum. Histopathologically, TDP-43 deposition is usually found in affected sites. There are no treatments available but clinical trials are ongoing for potential therapies.

Cerebellar atrophy has been described as part of *C9orf72*-related FTD but prominent clinical ataxia as demonstrated here has not been described previously.⁸ Cerebellar atrophy is global with the lobule VIIa-Crus I being preferentially affected. The cerebellar vermis may be atrophied in FTD due to *MAPT* mutations. Other genetic FTD syndromes (e.g., *PGRN*) have relative sparing of the cerebellum.

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Disclosure

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

Appendix Authors

Name	Location	Contribution
Meher Lad, MBBS, MRCP	Newcastle University, UK	Concept and drafting of manuscript
Timothy D. Griffiths, MD, FmedSci	Newcastle University, UK	Patient care, concept, revision of manuscript

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