Pearls and Oy-sters: CSF1R-Related Leukoencephalopathy With Spinal Cord Lesions Mimicking Multiple Sclerosis

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Abstract:

CSF1R-related leukoencephalopathy is an autosomal dominant neurological disorder causing microglial dysfunction with a wide range of neurologic complications, including motor dysfunction, dementia and seizures. This case report highlights an unusual presentation of CSF1R-related leukoencephalopathy with radiographic spinal cord involvement initially diagnosed as multiple sclerosis. The case highlights the importance of considering adult-onset neurogenetic disorders in the setting of white matter disease. Genetic testing provides a confirmatory diagnosis for an expanding number of adult-onset leukoencephalopathies and informs therapeutic decision-making.
Pearls:

- *CSF1R*-related leukoencephalopathy is an autosomal dominant adult-onset neurodegenerative disorder that can present with white matter and spinal cord lesions and therefore may be mistaken for multiple sclerosis (MS).
- Persistent foci of diffusion restriction on brain MRI are common in *CSF1R*-related leukoencephalopathy, and help differentiate this entity from MS.

Oy-sters:

- Rapidly progressive dementia is a highly atypical presentation for MS, and alternative diagnoses need to be considered.
- Radiographic spinal cord involvement is an uncommon feature of *CSF1R*-related leukoencephalopathy. Cord lesions in the presence of white matter hyperintensities should not deter from genetic evaluation in the proper clinical context.

Case Report

A 46-year-old female presented with a two-year history of cognitive decline. Initial symptoms included transient right arm numbness as well as word-finding difficulties, impulse dysregulation, left-right confusion, bradykinesia, and difficulty following multistep commands. Serial administration of the Montreal Cognitive Assessment revealed decline from 25/30 to 11/30 over a one-year period. Neuropsychological testing revealed moderate impairments in verbal and visual memory, visuospatial skills and executive function. She lost the ability to drive, cook, manage finances, and live independently. Additionally, she endorsed worsening balance,
chronic headaches and urinary frequency without incontinence. She was previously healthy and had no family history of neurodegenerative disorders.

Initial neurologic examination was notable for impaired orientation, attention, short-term memory and visuospatial functioning. There was evidence of cerebellar dysfunction with impaired smooth pursuit, bilateral dysmetria and imbalance, as well as parkinsonism characterized by cogwheel rigidity at the wrists, shuffling gait, and bradykinesia. She demonstrated sensory impairment with a positive Romberg test and diminished bilateral lower extremity proprioception.

Neuroimaging with and without contrast showed extensive non-enhancing predominantly periventricular white matter lesions in the brain and short-segment spinal cord lesions. She was treated for a presumed progressive form of multiple sclerosis (MS) with siponimod. As her neurologic condition continued to decline rapidly, she was referred to the NYU Multiple Sclerosis Comprehensive Care Center for a second opinion. Repeat neuroimaging showed extensive bilateral periventricular and callosal T2/FLAIR (Fluid Attenuation Inversion Recovery) hyperintensities, corpus callosum thinning, and an incidental posterior fossa arachnoid cyst (Figure 1). Unexpectedly, MRI revealed bifrontal periventricular foci of restricted diffusion that were also present on brain MRI from one year prior. Spinal cord MRI (Figure 2) revealed right lateral cord lesions at C2-3 and mid-C3 levels. Cerebrospinal fluid analysis disclosed elevated protein, but otherwise normal cell count, two matched oligoclonal bands (OCBs), as well as normal IgG index and synthesis rate. Vitamin B12, folate, and 25-hydroxy vitamin D were within normal limits and serologic testing for infectious and autoimmune causes was
unrevealing. Paraneoplastic antibody testing was not performed. Routine electroencephalogram was normal.

In view of the individual’s atypical presentation, including rapidly progressive dementia with largely preserved motor function, parkinsonian features, lack of CSF-restricted OCBs, and persistent restricted diffusion on MRI, she was referred for neurogenetic evaluation. A next-generation sequencing panel of 446 genes associated with leukodystrophies and genetic leukoencephalopathies (Invitae Corporation, San Francisco, CA) identified a heterozygous pathogenic variant in \( CSF1R \) c.2330 G>A p.(Arg777Gln), associated with \( CSF1R \)-related leukoencephalopathy. Siponimod was discontinued and she was referred for physical, occupational and speech therapy. She was referred for consultation for hematopoietic stem cell transplantation, but the risks were felt to outweigh the perceived benefits.

**Discussion**

\( CSF1R \)-related leukoencephalopathy, also known as adult-onset leukoencephalopathy with axonal spheroids and pigmented glia, is an autosomal dominant neurodegenerative disorder which presents with progressive behavioral and cognitive dysfunction, followed by motor impairment. Symptoms include dementia, seizures, spastic paraplegia, parkinsonism, dystonia, and personality and behavioral changes.\(^1\) The mean age of onset is in the fourth or fifth decade, with the average disease duration of 6.8 years.\(^2\)
The diagnosis should be suspected in individuals with early-onset, rapidly progressive dementia and suggestive neuroimaging findings. Deep and subcortical lesions, often asymmetrically distributed and predominantly involving frontal white matter are common.\textsuperscript{3} Atrophy of the corpus callosum and foci of diffusion restriction are highly suggestive of a \textit{CSF1R}-related leukoencephalopathy.\textsuperscript{4} Diagnosis is confirmed by identification of a heterozygous disease-causing mutation in \textit{CSF1R}. The causative gene encodes a tyrosine kinase growth factor receptor for colony-stimulating factor-1 and is expressed in brain microglia. Both loss-of-function and dominant negative effects have been proposed mechanisms of disease, leading to defects in microglial signaling and impaired microglia activation.\textsuperscript{5,6} Pathological hallmarks of this disease are pigmented macrophages and axonal spheroids.\textsuperscript{7}

In women, motor symptoms may predominate in early stages of the disease, which may cause diagnostic confusion with MS.\textsuperscript{2} Misdiagnosis can lead to improper use of immunotherapy as in our case. Thus, a high index of suspicion for \textit{CSF1R}-related leukoencephalopathy is required when red flags are present, such as progression of cognitive deficits out of proportion to motor deficits.\textsuperscript{2,6}

Characteristic brain MRI findings (Figure 1) include diffuse parenchymal volume loss and cerebral white matter T2/FLAIR hyperintensities with involvement of the corpus callosum. T2/FLAIR hyperintensities have a predilection for frontal and parietal regions, initially in a patchy distribution and later in a more confluent pattern, as was seen in our patient.\textsuperscript{6} Abnormal signal in the corticospinal tracts at the level of the posterior internal capsule or brainstem can also be seen.\textsuperscript{8} Interestingly, foci of diffusion restriction in the deep white matter seen in \textit{CSF1R}-
related leukoencephalopathy may persist for prolonged periods as illustrated by our case; and it has been suggested that they reflect edema within myelin rather than acute ischemia.\(^6\) Deep white matter calcifications have been described on CT.\(^8\) In this case, her cognitive decline, including difficulties with executive functioning and visuospatial skills, may be explained by the frontoparietal white matter involvement. This may also disrupt sensory and motor circuits involving the cortex, giving rise to her complex neurological presentation including parkinsonism and cerebellar dysfunction without basal ganglia or cerebellar lesions.\(^3\)

Although spinal cord involvement has only been reported in a few cases of CSF1R-related leukoencephalopathy, a systematic study of spinal cord findings in this disorder has not been undertaken to date.\(^9\) Lesions may involve the lateral corticospinal tracts and diffusion restriction may be present in the spinal cord lesions as well.\(^9,\,10\) In our case, spinal cord MRI was remarkable for short-segment focal hyperintensities in the right lateral cord at C2-3 and mid-C3 levels (Figure 2). Such spinal lesions are highly characteristic of MS, and likely contributed to misdiagnosis in our case. It is important to note that their presence does not negate the possibility of a genetic leukoencephalopathy.\(^11\)

Although CSF1R-related leukoencephalopathy is usually inherited from an affected parent, sporadic cases have been reported. The absence of family history does not preclude this diagnosis, as in this case.

Diagnosis of CSF1R-related leukoencephalopathy has significant implications for risk of recurrence, in view of 50% likelihood of inheritance for offspring. At-risk family members
should be encouraged to review their family history with a genetic counselor and decide whether they would like to pursue genetic testing. In our case, the individual did not have prior pregnancies. Both of her siblings chose to undergo genetic testing and were not found to possess the pathogenic variant.

There are no curative therapies for CSF1R-related leukoencephalopathy at present. However, hematopoietic stem cell transplantation showed evidence of stabilizing disease in six of seven individuals in a recent case series.\textsuperscript{12} Additionally, antibodies designed to rescue loss of function in CSF1R by activating TREM2 have shown promise in cellular models.\textsuperscript{13} Symptom management through physical, occupational, speech-language and cognitive rehabilitation should be considered for all patients. Anti-seizure medications and psychopharmacology may also be needed.\textsuperscript{3}

Distinguishing CSF1R-related leukoencephalopathy from MS is of obvious importance, but not straightforward in practice. When considering the diagnosis of MS, one should first consider if the clinical history and examination are suggestive of a typical demyelinating event, i.e. temporal evolution of symptoms and their localization suggest inflammation along a myelinated white matter tract, or of a progressive ‘myelopathy plus’ syndrome.\textsuperscript{14} A key red flag for MS in our case was rapid cognitive decline early on in the course, out of proportion to the motor symptoms. The patient’s brain MRI revealed numerous periventricular white matter changes (‘Dawson finger’ configuration, Figure 1B) as well as midbrain and spinal cord lesions, but lacked lesions in other MS-typical locations including cortical/juxtacortical regions, anterior temporal lobes, pons or cerebellum (Figure 1, A-F). Restricted diffusion as seen in our patient (Figure 1, G- H) is rare in
MS and is only seen in the acute phase. The matched OCBs suggest systemic rather than CSF-restricted inflammation, which also argues against MS. Although disease onset in one’s forties is more than a decade older than the mean age of onset of relapsing MS, it is not atypical in primary progressive MS. Because of findings atypical for MS across clinical history, neuroimaging and laboratory data, a search for an alternative diagnosis was indicated.

Our case illustrates both typical and rare clinical and neuroimaging features on the expanding spectrum of CSF1R-related leukoencephalopathy, and highlights the importance of differentiating it from more common adult-onset neurologic disorders, such as MS. Correct diagnosis of CSF1R-related leukoencephalopathy is important not only for the patient, but for at-risk relatives as well.

References


Figure 1. MRI Brain. FLAIR (A-C, E, F), T2WI (D), DWI (G) and ADC (H) sequences.

Extensive, patchy and confluent white matter hyperintensities in the periventricular white matter with frontal and parietal predominance (A and B). Note some of the lesions in a triangular configuration perpendicular to the ventricle resembling a Dawson finger (arrow on B). Severe atrophy and FLAIR hyperintensity is noted in the corpus callosum (arrow on C). Lesions along the corticospinal tracts are better appreciated on coronal T2WI (arrows on D). Mild volume loss and hyperintensity on the left cerebral peduncle corresponding to the left corticospinal tract (arrow on E). Note lack of additional lesions in brainstem or inferior temporal lobes (E and F). Areas of restricted diffusion are present in the periventricular white matter (arrows on G and H). Incidental notice of mega cisterna magna and cavum velum interpositum (A, E and F).
Figure 2. MRI Cervical spine.

Axial (A and B) and sagittal (C) T2WI of the cervical spine show focal peripheral hyperintense lesions in the right lateral cord at C2-C3 (arrow on A) and mid C3 levels (arrow on B). The C2-3 lesion is faintly seen on the sagittal sequence (arrow on C). The mid C3 lesion was not seen on sagittal images.
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