RESIDENT & FELLOW SECTION

Clinical Reasoning: A 23-Year-Old Woman Presenting With Cognitive Impairment and Gait Disturbance

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Abstract

Metachromatic leukodystrophy (MLD) is a rare inherited lysosomal disorder. The condition progresses relentlessly, with severe disability typically established within 6–14 years of symptom onset. There is no cure, and limited treatment options are available to slow disease progression. We describe the case of a 23-year-old woman with forgetfulness, unsteady gait, and falls. Neurologic examination revealed intermittent dystonic posturing of the right upper and lower limb when walking. The Addenbrooke's Cognitive Examination (ACE) score was 70/100. MRI sequences demonstrated frontal-predominant atrophy and extensive white matter hyperintensity. Differential diagnoses such as autoimmune, inflammatory, and neoplastic diseases were excluded, and a genetic diagnosis was considered. Lysosomal enzyme testing showed low arylsulfatase with elevated urinary sulfatides, and genetic testing revealed a homozygous pathogenic mutation in the *ARSA* gene securing a diagnosis of adult-onset MLD. A male sibling also had early cognitive impairment and was found to have the same mutation. Hematopoietic stem cell transplantation (HSCT) was offered after discussion with experts. The male sibling died of multiple complications after HSCT. The index patient is now 24 months after HSCT, and disease progression has halted. This case highlights the challenges in the accurate diagnosis of adult-onset leukoencephalopathies and explores potential treatment strategies. A stepwise approach to the differential diagnosis of white matter diseases is demonstrated. HSCT may be an effective treatment, but the significant complication rate needs to be carefully considered.

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Glossary

ACE = Addenbrooke's Cognitive Examination; **HSCT** = hematopoietic stem cell transplantation; **MLD** = metachromatic leukodystrophy.

Section 1

A 23-year-old woman presented with a 3-year progressive history of forgetfulness, unsteady gait, and falls. She had no medical history.

She was the product of a normal delivery, with normal developmental milestones. Until her late teens, she played field sports capably and was an accomplished dancer. Academically, she was consistently in the middle range of her classes and completed a higher diploma in business management.

After college, she struggled in an administrative office job, which surprised her parents, and was made redundant. Thereafter, she undertook a retail job in a clothing store. She also had difficulties there in operating cashier tills and IT systems. She was gifted a car for her 21st birthday but could not learn the appropriate sequencing to drive safely and abandoned the effort after several months. Her mother described that the patient often lost items irretrievably and frequently repeated herself. She needed constant reminders to bring personal items with her.

Her sporting and dancing prowess declined, and she incurred numerous falls, which she attributed to clumsiness. Sleep quality was good, but she felt fatigued by day. She denied low mood but became less talkative and withdrawn.

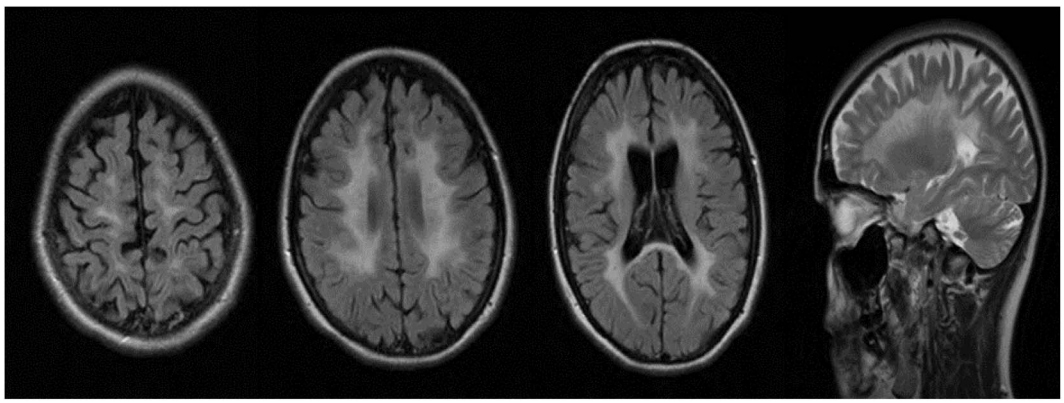
She was the oldest of a kinship of 3, with a brother aged 20 years and a sister aged 12 years; both were reported to be well. There was no other family history of neurologic disease or premature death. She did not drink, smoke, or use recreational drugs.

Neurologic examination revealed normal cranial nerves, normal tone, power, reflexes, and sensation. Her gait was predominantly characterized by dystonic posturing of her right leg and foot with more subtle posturing of her right upper limb while walking. She could not tandem gait. The Romberg test was negative. She scored 70/100 on Addenbrooke's Cognitive Examination Version 3 with salient frontal and executive dysfunction. Brain MRI revealed widespread periventricular and deep white matter signal changes with involvement of the corticospinal tracts and brainstem. There was associated white matter atrophy with ventriculomegaly, significant atrophy in the corpus callosum, and cerebellar atrophy (Figure).

Questions for Consideration:

1. What is the differential diagnosis?
2. What are the next steps in evaluation?

Figure Axial FLAIR and Sagittal T2 MRI Sequences Showing Frontal-Predominant Atrophy and Extensive White Matter Hyperintensity



There is also appreciable hyperintensity and atrophy involving the corpus callosum.

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Section 2

The differential diagnosis for cognitive impairment and gait disturbance with white matter changes is broad. Several etiologic categories including inflammatory/autoimmune (less likely given the tempo of progression in this case), infectious (less likely given the absence of other infectious symptoms and more chronic temporal course), neoplastic (less likely due to pace of progression), and neurogenetic disorders (heredodegenerative and metabolic disorders) must be considered. Initial laboratory workup included complete blood count, erythrocyte sedimentation rate, renal/liver/bone/thyroid indices, creatinine kinase, serum protein electrophoresis, lactate, vitamin B12, folate, serum copper and ceruloplasmin, HIV and syphilis serology, antinuclear antibody, ANCA, antiphospholipid antibodies, and an extensive paraneoplastic antibody panel, all of which were normal or negative. CSF analysis including cytology was normal; oligoclonal bands were negative. EEG did not show any epileptiform activity. As initial bloodwork and an entirely normal CSF militated against a neuroinflammatory, infectious, or paraneoplastic etiology, a genetically mediated disorder, including a mitochondrial cytopathy or metabolic process, was suspected.

Questions for Consideration:

1. How does this information affect the differential diagnosis?
2. What additional investigations need to be considered?

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Section 3

Given the apparent absence of a family history in our case, an autosomal recessive process was considered. The differential diagnosis of leukodystrophies is broad (Table), and after considering them, serum amino acid profile, very long chain fatty acids, vitamins A and E, arylsulfatase A, cholestanol, and urinary organic acids were ordered. Lysosomal enzyme testing showed low arylsulfatase and elevated urinary sulfatides. Nerve conduction studies demonstrated a mild to moderate length-dependent large fiber, sensory-predominant, demyelinating polyneuropathy. The metabolic disease genetic panel revealed a homozygous pathogenic mutation in the *ARSA* gene; c.1283C>T (Pro428Leu), confirming the diagnosis of metachromatic leukodystrophy (MLD). Re-evaluation of the brain MRI demonstrated an MLD score of 21. Her other siblings were tested with consent; her brother harbored the same mutation. He acknowledged mild attentional deficits in the preceding months but no other symptoms. He had mild frontoexecutive deficits on cognitive testing, and brain MRI and neurophysiology findings were similar to those of his sister.

Question for Consideration:

1. What are the management options?

Table Differential Diagnosis of Leukodystrophies[1,2]

Names of disease	MRI findings	Clinical findings
Inheritance Pattern: Autosomal Dominant		
Adult-onset autosomal dominant leukodystrophy (*LMNB1*)	WM hyperintensity of the subcortical, deep cerebral, cerebellar peduncles, the pyramidal tracts, and brainstem	Early autonomic dysfunction such as orthostatic hypotension, urinary incontinence, constipation and erectile dysfunction, cerebellar, and pyramidal signs
Alexander disease (*GFAP*)	Frontal-predominant leukoencephalopathy. Atrophy of the cervical cord and medulla. Pons is usually preserved and abnormalities in the spinal cord (tadpole sign)	Bulbar/pseudobulbar palsy, palatal myoclonus, spasticity, ataxia, cognitive decline, and dysautonomia
Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (*NOTCH3*)	Abnormal signal in the anterior temporal lobe, periventricular WM, and external capsule	Migraine with aura, TIAs/recurrent stroke, depression, and cognitive decline
Cerebral leukodystrophy with retinal vasculopathy (*TREX1*)	Leukoencephalopathy (frontotemporal, diffuse, and periventricular), cerebral atrophy, calcifications, and contrast enhancement	Retinal abnormalities, Raynaud's phenomenon, and migraine
Hereditary diffuse leukoencephalopathy with axonal spheroids and pigmented glia (*CSF1R*)	Periventricular and frontoparietal WM hyperintensity ± microcalcifications, punctate diffusion restriction, and corpus callosum involvement	Levodopa-unresponsive parkinsonism, spasticity, ataxia, dementia, and psychiatric changes
Hypomyelinating leukodystrophy with atrophy of the basal ganglia and cerebellum (*TUBB4A*)	Atrophy of the basal ganglia and cerebellum and hypomyelination	Typical childhood onset, microcephaly, nystagmus, ataxia, spasticity, and dystonia
Small vessel disease with ocular abnormalities (*COL4A1*)	Diffuse abnormality with dilated perivascular spaces and microhemorrhages	Ocular/retinal abnormalities
Inheritance Pattern: Autosomal Recessive		
4H syndrome (*POLR3A/POLR3B*)	Hypomyelination	Hypogonadotropic hypogonadism and dental abnormalities
AARS2-related leukodystrophy (*AARS2*)	Symmetrical WM signal change in the frontoparietal WM, corpus callosum, and pyramidal tracts	Levodopa-unresponsive parkinsonism, spasticity, ataxia, cognitive decline, pyramidal signs, premature ovarian failure in females, and psychiatric changes
Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (*HTRA1*)	Abnormal signal in the anterior temporal lobe	Parkinsonism, upper motor neuron signs, alopecia, back pain with spondylosis deformans, and dementia
Cerebrotendinous xanthomatosis (*CYP27A*)	Bilateral hyperintensity of the dentate nuclei and surrounding WM, cerebral and cerebellar atrophy, and white mater lesions of the spinal cord	Ataxia, tendon xanthomas and thickening, chronic diarrhea, cataracts, intellectual disability, autism, dementia, psychiatric problems, and seizures
Gordon Holmes syndrome (*RNF216*)	Diffuse leukoencephalopathy with cerebellar atrophy	Hypogonadotropic hypogonadism, cognitive decline, and ataxia
Homocystinuria (*CBS*)	Diffuse WM abnormality	Intellectual disability, psychiatric disability, epilepsy, marfanoid, pulmonary and cerebrovascular thromboembolic events, dislocation of the optic lenses, and osteoporosis

Continued

Table Differential Diagnosis of Leukodystrophies[1,2] *(continued)*

Names of disease	MRI findings	Clinical findings
Inheritance Pattern: Autosomal Recessive		
Krabbe disease (*GALC*, *PSAP*)	Hyperintensity of corticospinal tracts from the cortex to cerebral peduncles and optic radiation	Infantile form: severe developmental regression with seizures and hearing and vision loss Juvenile/adult form: spasticity, ataxia, visual loss cognitive impairment, seizures, and demyelinating peripheral neuropathy
Leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation (*DARS2*)	Extensive WM changes with multiple long tract involvement, including spinal cord	Spasticity, slowly progressive ataxia, and dorsal column loss
mtDNA mutations	Stroke-like lesions, confluent WM hyperintensity, and ±basal ganglia abnormalities	Multisystem disorder: short stature, sensorineural deafness, exercise intolerance, migraine, cardiac defects, stroke-like episodes, cortical blindness, lactic acidosis, myoclonus, and ataxia
Metachromatic leukodystrophy (*ARSA*)	Symmetrical periventricular WM lesions "tigroid" pattern and cortical atrophy	Gait abnormalities, ataxia, hypotonia, peripheral neuropathy, and dementia with behavioral abnormalities
Methylenetetrahydrofolate reductase deficiency (*MTHFR*)	Periventricular WM and frontal lobes	Recurrent stroke, seizures, and cognitive decline
Vanishing white matter disease (*EIF2B1-5*)	Cystic degeneration of the WM	Ataxia, spasticity, psychiatric features, premature ovarian failure, seizures, and cognitive decline
Inheritance Pattern: X-linked		
Pelizaeus-Merzbacher disease (*PLP1*)	Hypomyelination and pattern resembles the "tigroid" pattern	Slowly progressive spastic paraplegia, prominent head tremor, and cognitive decline
X-linked adrenoleukodystrophy (*ABCD1*)	Parieto-occipital WM hyperintensity, splenium of the corpus callosum, and occasionally frontal involvement	Progressive spastic paraparesis, sensory ataxia, sphincter dysfunction, impotence, rapid cognitive and neurologic decline, dementia, seizures, and hypoadrenalism

Abbreviation: WM = white matter.

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Section 4

Metachromatic leukodystrophy (MLD) is an inherited lysosomal disorder, which is progressive and incurable.[3] In the adult form, the disease may progress over 20–30 years, although typically individuals reach maximum disability within 6–14 years after symptom onset (although there is variability in outcomes).[4] After consulting expert opinion in Ireland and the United Kingdom, hematopoietic stem cell transplantation (HSCT) was offered to the siblings. The extensive risk profile was discussed; detailed serial capacity assessments were completed before seeking informed consent. Both patients were deemed capable of making an informed decision. Transplantation was delivered in a unit with metabolic experience in Manchester, UK. The male sibling received HSCT first. Graft failure ensued with profound aplasia, and he underwent a second HSCT; unfortunately, he developed transfusion-refractory pancytopenia and died of intracranial hemorrhage. Our 23-year-old female patient subsequently received HSCT. Status epilepticus complicated the immediate posttransplant phase, but she stabilized quickly and is now 24 months after HSCT. Both cognitive and motor functions have stabilized.

Discussion

Metachromatic leukodystrophy is a rare lysosomal storage disorder, leading to the deficiency of arylsulfatase A (ASA). The prevalence of MLD is 1.0–1.8 per 160,000 worldwide.[3,5,6] Deficiency of ASA leads to accumulation of undegraded sulfatides in lysosomes, particularly in myelinating cells, that is, oligodendrocytes and Schwann cells. The storage of sulfatides results in progressive demyelination of the central and peripheral nervous system.

There are 3 clinical forms: late-infantile, juvenile, and adult onset. European data suggest that adult onset accounts for approximately 20% of presentations.[3,7] More than 150 *ARSA* mutations have been described, and c.1283C>T (p.Pro428Leu) carried by our patient is the common adult-onset variant.[3] Clinically, initial symptoms of adult-onset MLD are often psychiatric/affective, followed by a decline in intellectual capabilities and the emergence of motor symptoms.

MRI is an important diagnostic tool. In MLD, brain MRI typically reveals bilateral confluent periventricular white matter change with frontal predominance and may spare perivenular myelin in the early stage. This results in a classic "tigroid" pattern—which is absent in our case, likely because of the stage at which the case presented, although a small study showed that the "tigroid" pattern was present in only 50% of their patients with MLD. Frontal predominance and corpus callosum atrophy can also be seen early in the disease. In the late stage, there is progressive subcortical white matter extension, with involvement of U fibers and progressive atrophy.[3,8,9] These patterns can be helpful to distinguish from alternative diagnoses, for example, adult-onset autosomal dominant leukodystrophy in which MRI shows parietal predominance and X-linked adrenoleukodystrophy, which demonstrates an occipital preponderance. In mitochondrial disease, small cyst-like lesions can be seen within the abnormal white matter, involving both cerebral and cerebellar white matter as well as bilateral basal ganglia.[10]

The final diagnosis of MLD is usually achieved by combining ASA enzymatic activity quantitation and genetic analysis. It is important to highlight that low ASA activity can be seen in pseudodeficiency. In this scenario, urinary sulfatide excretion can distinguish MLD from pseudodeficiency.

Currently, no curative treatment is available for MLD. Three treatment modalities have attracted attention in recent years: HSCT, enzyme replacement therapy (ERT), and gene therapy. HSCT is widely accepted as a treatment option in early-stage MLD. Neuropathologic studies of HSCT in transplanted patients showed higher numbers of oligodendrocytes. Accumulated sulfatides were digested by donor macrophages, affording neuroprotection for oligodendrocytes. This suggests that survival, proliferation, and differentiation of oligodendrocytes are supported by HSCT leading to improvement by preserving myelin. Little or no response is reported in peripheral neuropathy.[11,12] Patients from 2 small European studies experienced graft-vs-host disease and/or rapid disease progression, but individual patients with early treatment had longer survival, with better gross motor outcome than nontransplanted controls.[13,14]

ERT in mouse models showed some reduction in sulfatide storage in peripheral tissues but has not shown beneficial effects in human subjects.[3] Gene therapy (with or without ERT) seems to be promising, but there have been no published trials in adult-onset MLD. Adeno-associated vector (AAV) gene therapy shows promise in treating leukodystrophies in animal studies. This therapeutic approach may offer a long-term correction of the mutated or missing enzymes in future.[15]

The rarity and variability of its clinical manifestations make the diagnosis of MLD difficult in adulthood. As illustrated by this case, this difficulty can be overcome using a systematic diagnostic approach. These cases also highlight the challenge that appears after diagnosis: the difficult choice between symptomatic management in the face of relentless decline vs novel treatments with potential for very significant morbidity or mortality.

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