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

Author(s):
Dimitra Khalil Chaity, MuDr; Conor Fearon, MRCPI, PhD; Michael Alexander, MRCPI; John Walsh, MRCPI; Neil Austin, PhD; James O Byrne, MRCPI, PhD; Gregory Pastores, MD; Aine Merwick, MRCPI, PhD; Muhammad Saif, MRCP UK; Sean O Dowd, MRCPI, MD

Corresponding Author:
Dimitra Khalil Chaity, dr.d.khalil13@gmail.com

Affiliation Information for All Authors:
1. Department of Neurology, The Mater Misericordiae University Hospital, Dublin, Ireland; 2. Academic Unit of Neurology, Trinity College Dublin, Ireland; 3. Department of Neurophysiology, Tallaght University Hospital, Dublin, Ireland; 4. Department of Neuroradiology, Tallaght University Hospital; 5. Department of Neuropsychology, The Mater Misericordiae University Hospital, Dublin, Ireland; 6. National Centre for Inherited Metabolic Disorders Adult Service, The Mater Misericordiae University Hospital, Dublin, Ireland; 7. Department of Neurology, Cork University Hospital, Cork, Ireland; 8. Department of Hematology, Manchester Royal Infirmary, United Kingdom

Neurology® Published Ahead of Print articles have been peer reviewed and accepted for publication. This manuscript will be published in its final form after copyediting, page composition, and review of proofs. Errors that could affect the content may be corrected during these processes.

Copyright © 2022 American Academy of Neurology. Unauthorized reproduction of this article is prohibited
Equal Author Contribution:
Dr. Conor Fearon contributed equally to this work.

Contributions:
Dimitra Khalil Chaity: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data
Conor Fearon: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data
Michael Alexander: Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data
John Walsh: Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data
Neil Austin: Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data
James O Byrne: Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data
Gregory Pastores: Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data
Aine Merwick: Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data
Muhammad Saif: Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data
Sean O Dowd: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data

Figure Count:
1

Table Count:
1

Search Terms:

Acknowledgment:
I would like to thank all the authors specially Dr. O Dowd and Dr. Fearon for their critical review and intellectual support.
Abstract

Metachromatic Leukodystrophy (MLD) is a rare inherited lysosomal disorder. The condition progresses relentlessly, with severe disability typically established within 6 to 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. Neurological examination revealed intermittent dystonic posturing of the right upper and lower limb when walking. 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 arylsulphatase 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. Haematopoietic stem cell transplantation (HSCT) was offered following discussion with experts. The male sibling died of multiple complications post-HSCT. The index patient is now 24 months post 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.

Section 1

A 23-year-old woman presented with a 3-year progressive history of forgetfulness, unsteady gait, and falls. She had no past 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 three with a brother aged 20, and a sister aged 12; both were reported to be well. There was no other family history of neurological disease or premature death. She did not drink, smoke, or use recreational drugs.

Neurological 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. Romberg’s test was negative. She scored 70/100 on Addenbrooke’s Cognitive Examination Version 3 with salient frontal and executive dysfunction. MRI Brain 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?
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), neurogenetic disorders (heredo-degenerative, metabolic disorders etc.) must be considered. Initial laboratory work-up 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 aetiology, a genetically mediated disorder, including a mitochondrial cytopathy or metabolic process, was suspected.

Questions for consideration

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

Section 3

Given the apparent absence of a family history in our case, an autosomal recessive process was considered. Differential diagnosis of leukodystrophies are broad (Table) and after considering them, serum amino acid profile, very long chain fatty acids, vitamin A & E, arylsulfatase A, cholestanol and urinary organic acids were ordered. Lysosomal enzyme testing showed low arylsulphatase and elevated urinary sulfatides. Nerve conduction studies demonstrated a mild to moderate length-dependent large fibre, sensory-predominant, demyelinating polyneuropathy. 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 MRI brain demonstrated an MLD score of 21. Her other siblings were tested with consent; her brother harboured the same mutation. He acknowledged mild attentional deficits in the preceding months but no other symptoms. He had mild fronto-executive deficits on cognitive testing and MRI Brain and neurophysiology findings were similar to those of his sister.

Question for consideration

1. What are the management options?
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 to 30 years, although typically individuals reach maximum disability within 6 to 14 years following symptoms onset (although there is variability in outcome) (4). After consulting expert opinion in Ireland and the UK, hematopoietic stem cell transplantation (HSCT) was offered to the siblings. The extensive risk profile was discussed; detailed serial capacity assessments were completed prior to 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 haemorrhage. Our 23-year-old female patient subsequently received HSCT. Status epilepticus complicated the immediate post-transplant phase, but she stabilized quickly and is now 24 months post HSCT. Both cognitive and motor function have stabilised.

Discussion:

Metachromatic leukodystrophy is a rare lysosomal storage disorder, leading to 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, i.e. oligodendrocytes and Schwann cells. The storage of sulfatides results in progressive demyelination of the central and peripheral nervous system.

There are three clinical forms: late-infantile, juvenile, and adult onset. European data suggests 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, MRI brain typically reveals bilateral confluent periventricular white matter change with frontal predominance and may spare perivenular myelin in early stage. This results in a classic ‘tigroid’ pattern- which is absent in our case, likely due to the stage at which the case presented, although a small study showed that ‘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-fibres 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 pseudo-deficiency. In this scenario, urinary sulfatide excretion can distinguish MLD from pseudo-deficiency.

Currently, no curative treatment is available for MLD. Three treatment modalities have attracted attention in recent years: hematopoietic stem cell transplantation (HSCT), enzyme replacement
therapy (ERT) and gene therapy. HSCT is widely accepted as a treatment option in early-stage MLD. Neuropathological 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 is supported by HSCT leading to improvement by preserving myelin. Little or no response is reported in peripheral neuropathy (11, 12). Patients from two 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 non-transplanted 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 makes 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 versus novel treatments with potential for very significant morbidity or mortality.

References:


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 corpus callosum.
<table>
<thead>
<tr>
<th>Inheritance Pattern: Autosomal Dominant</th>
<th>MRI findings</th>
<th>Clinical Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult-onset autosomal dominant leukodystrophy (<em>LMNB1</em>)</td>
<td>WM hyperintensity of the subcortical, deep cerebral, cerebellar peduncles, the pyramidal tracts and brainstem</td>
<td>Early autonomic dysfunction such as orthostatic hypotension, urinary incontinence, constipation and erectile dysfunction, cerebellar and pyramidal signs</td>
</tr>
<tr>
<td>Alexander disease (<em>GFAP</em>)</td>
<td>Frontal predominant leukoencephalopathy. Atrophy of the cervical cord and medulla. Pons is usually preserved and abnormalities in spinal cord (tadpole sign)</td>
<td>Bulbar/pseudobulbar palsy, palatal myoclonus, spasticity, ataxia, cognitive decline, dysautonomia</td>
</tr>
<tr>
<td>Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (<em>NOTCH3</em>)</td>
<td>Abnormal signal in anterior temporal lobe, periventricular WM, and external capsule.</td>
<td>Migraine with aura, TIAs/recurrent stroke, depression, cognitive decline.</td>
</tr>
<tr>
<td>Cerebral leukodystrophy with retinal vasculopathy (<em>TREX1</em>)</td>
<td>Leukoencephalopathy (frontotemporal, diffuse, periventricular), cerebral atrophy, calcifications, contrast enhancement</td>
<td>Retinal abnormalities, Raynaud’s phenomenon, migraine</td>
</tr>
<tr>
<td>Hereditary diffuse leukoencephalopathy with axonal spheroids and pigmented glia (<em>CSF1R</em>)</td>
<td>Periventricular and frontoparietal WM hyperintensity +/- microcalcifications, punctate diffusion restriction and corpus callosum involvement</td>
<td>Levodopa unresponsive parkinsonism, spasticity, ataxia, dementia, psychiatric changes</td>
</tr>
<tr>
<td>Hypomyelinating leukodystrophy with atrophy of the basal ganglia and cerebellum (<em>TUBB4A</em>)</td>
<td>Atrophy of basal ganglia and cerebellum, hypomyelination</td>
<td>Typically, childhood onset, microcephaly, nystagmus, ataxia, spasticity, dystonia</td>
</tr>
<tr>
<td>Small vessel disease with ocular abnormalities (<em>COL4A1</em>)</td>
<td>Diffuse abnormality with dilated perivascular spaces and microhaemorrhages</td>
<td>Ocular/retinal abnormalities</td>
</tr>
</tbody>
</table>

**Inheritance Pattern: Autosomal Recessive**
<table>
<thead>
<tr>
<th>Condition</th>
<th>Clinical Features</th>
<th>Genetic Basis</th>
</tr>
</thead>
<tbody>
<tr>
<td>4H syndrome ((POLR3A/POLR3B))</td>
<td>Hypomyelination</td>
<td>Hypogonadotropic hypogonadism, dental abnormalities</td>
</tr>
<tr>
<td>AARS2-related leukodystrophy ((AARS2))</td>
<td>Symmetrical WM signal change in frontoparietal WM, corpus callosum and pyramidal tracts.</td>
<td>Levodopa-unresponsive parkinsonism, spasticity, ataxia, cognitive decline, pyramidal signs, premature ovarian failure in females, psychiatric changes</td>
</tr>
<tr>
<td>Cerebral autosomal recessive cerebral arteriopathy with subcortical infarcts and leukoencephalopathy ((HTRA1))</td>
<td>Abnormal signal in anterior temporal lobe</td>
<td>Parkinsonism, upper motor neuron signs, alopecia, back pain with spondylosis deformans, dementia</td>
</tr>
<tr>
<td>Cerebrotendinous xanthomatosis ((CYP27A))</td>
<td>Bilateral hyperintensity of the dentate nuclei and surrounding WM</td>
<td>Ataxia, tendon xanthomas and thickening, chronic diarrhea, cataracts, intellectual disability, autism, dementia, psychiatric problems, and seizures.</td>
</tr>
<tr>
<td>Gordon Holmes syndrome ((RNF216))</td>
<td>Diffuse leukoencephalopathy with cerebellar atrophy</td>
<td>Hypogonadotropic hypogonadism, cognitive decline, ataxia</td>
</tr>
<tr>
<td>Homocystinuria ((CBS))</td>
<td>Diffuse WM abnormality</td>
<td>Intellectual disability, psychiatric disability, epilepsy, marfanoid, pulmonary and cerebrovascular thromboembolic events, dislocation of the optic lenses, osteoporosis.</td>
</tr>
<tr>
<td>Krabbe disease ((GALC, PSAP))</td>
<td>Hyperintensity of corticospinal tracts from the cortex to cerebral peduncles, and optic radiation</td>
<td>Infantile form: severe developmental regression with seizures, hearing and vision loss.</td>
</tr>
<tr>
<td>Juvenile/adult form: Spasticity, ataxia, visual loss cognitive impairment, seizures, demyelinating peripheral neuropathy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation ((DARS2))</td>
<td>Extensive WM changes with multiple long tract involvement, including spinal cord</td>
<td>Spasticity, slowly progressive ataxia, dorsal column loss.</td>
</tr>
<tr>
<td>mtDNA mutations</td>
<td>Stroke like lesions, confluent WM hyperintensity, +/- basal</td>
<td>Multisystem disorder: short stature, sensorineural deafness, exercise</td>
</tr>
<tr>
<td>Disorder</td>
<td>Symptoms</td>
<td>Inheritance Pattern</td>
</tr>
<tr>
<td>--------------------------------------------</td>
<td>--------------------------------------------------------------------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>Metachromatic leukodystrophy (ARSA)</td>
<td>Symmetrical periventricular WM lesions ‘tigroid’ pattern, cortical atrophy</td>
<td></td>
</tr>
<tr>
<td>Methylenetetrahydrofolate reductase deficiency (MTHFR)</td>
<td>Periventricular WM and frontal lobes</td>
<td>Recurrent stroke, seizures, cognitive decline</td>
</tr>
<tr>
<td>Vanishing white matter disease (EIF2B1-5)</td>
<td>Cystic degeneration of WM</td>
<td>Ataxia, spasticity, psychiatric features, premature ovarian failure, seizures, cognitive decline</td>
</tr>
<tr>
<td>Pelizaeus-Merzbacher disease (PLP1)</td>
<td>Hypomyelination, pattern resembles ‘tigroid’ pattern</td>
<td>Slowly progressive spastic paraplegia, prominent head tremor, cognitive decline</td>
</tr>
<tr>
<td>X linked adrenoleukodystrophy (ABCD1)</td>
<td>Parieto-occipital WM hyperintensity, splenium of the corpus callosum and occasionally frontal involvement</td>
<td>Progressive spastic paraparesis, sensory ataxia, sphincter dysfunction, impotence, rapid cognitive and neurological decline, dementia, seizures, hypoadrenalism</td>
</tr>
</tbody>
</table>

**Inheritance Pattern: X-linked**

**WM:** White matter.
Clinical Reasoning: A 23-Year-Old Woman Presenting With Cognitive Impairment and Gait Disturbance
Dimitra Khalil Chaity, Conor Fearon, Michael Alexander, et al.
Neurology published online September 13, 2022
DOI 10.1212/WNL.0000000000201373

This information is current as of September 13, 2022