Clinical Reasoning: A Young Man With Subacute Onset of Spastic Paraparesis

Author(s):
Salvatore Rossi, MD1,2; Paola Concolino, PhD3; Daniele Di Natale, MD1,2; Domizia Pasquetti, MD4; Giuseppe Maria Di Lella, MD, PhD5; Pietro Chiurazzi, MD, PhD4,6; Gabriella Silvestri, MD, PhD1,2

Affiliation Information for All Authors: 1. Dipartimento di Scienze dell’Invecchiamento, Neurologiche, Ortopediche e della Testa-Collo, UOC Neurologia, Fondazione Policlinico Universitario A. Gemelli IRCCS, L. A. Gemelli 8, 00168 Rome, Italy; 2. Dipartimento di Neuroscienze Università Cattolica del Sacro Cuore, Facoltà di Medicina e Chirurgia, L. F. Vito 1, 00168 Rome, Italy; 3. UOC Chimica, Biochimica e Biologia Molecolare Clinica - Area Diagnostica di Laboratorio, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy; 4. Istituto di Medicina Genomica, Università Cattolica del Sacro Cuore, Rome, Italy; 5. Department of Diagnostic Imaging, Oncological Radiotherapy, and Hematology, UOC Neuroradiology, Fondazione Policlinico Universitario Agostino Gemelli IRCCS and Università Cattolica del Sacro Cuore, 00168 Rome, Italy. 6. UOC Genetica Medica, Fondazione Policlinico Universitario "A. Gemelli" IRCCS, Rome, Italy.

Equal Author Contribution:

Contributions:
Salvatore Rossi: 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
Paola Concolino: Analysis or interpretation of data
Daniele Di Natale: Drafting/revision of the manuscript for content, including medical writing for content
Domizia Pasquetti: Drafting/revision of the manuscript for content, including medical writing for content
Giuseppe Maria Di Lella: Analysis or interpretation of data
Pietro Chiurazzi: Drafting/revision of the manuscript for content, including medical writing for content
Gabriella Silvestri: 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

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.
Abstract
Leukodystrophies are a group of rare, neurodegenerative disorders, usually presenting in infancy with a variable combination of cognitive, motor and coordination impairment. Adult-onset cases are even more rare, often representing a diagnostic challenge even for experienced neurologists. Here, we present a case of 44-year-old man with subacute and rapidly progressive spastic paraplegia, whose brain MRI revealed white matter abnormalities compatible with a diagnosis of leukodystrophy. We discuss how to apply a simplified diagnostic algorithm to distinguish acquired leukoencephalopathies from leukodystrophies, and how to delve in the maze of the genetic testing for white matter diseases. In our patient, we reached the diagnosis of a treatable disorder, whose early recognition is essential in order to prevent severe neurological deterioration.

Section 1
A 44-year-old male born to non-consanguineous parents presented with subacute onset and rapidly progressive walking difficulties requiring the need for one walking cane 4 months after onset, along with urinary incontinence and erectile dysfunction. He was affected by autosomal
dominant polycystic kidney disease associated with a mutation in *PKD1* inherited from his mother. His father died at the age of 62 of colorectal cancer. The proband required educational support at school, but was able to achieve a secondary school degree. He had a stable employment and participated in regular weightlifting exercise.

The first neurological evaluation at our center at 18 months from the onset of symptoms showed spastic paraparesis requiring canes to walk. Lower limb weakness was moderate (bilaterally grade 4 by Medical Research Council scale at iliopsoas and tibialis anterior muscles), and spasticity was marked (modified Ashworth scale=3 bilaterally). Spastic Paraplegia Rating Scale score was 26. No muscle atrophy or fasciculations were evident. Deep tendon limb reflexes were brisk (3+) in all extremities, and Hoffman and Babinski sign were present bilaterally. Upper limb, cranial nerve and sensory function were all normal.

Questions for considerations

1. Which is the most appropriate first-line investigation in this case?

Section 2

Firstly, as spastic paraplegia was accompanied by brisk reflexes also in upper limbs, a spinal cord MRI was performed to address possible cervical myelopathy or other structural lesions at that level, resulting normal (Figure). Next, brain MRI was done, showing extensive T2 hyperintensity involving deep, mainly posterior, white matter (WM), with corresponding T1 slightly hypointense signal and sparing of the subcortical U-fibers and corpus callosum (Figure). Mild cerebellar atrophy was also present. MR spectroscopy (MRS) did not show any abnormal peaks. Gadolinium contrast was not infused because of chronic kidney disease.

Electroneurography documented axonal sensory and demyelinating motor polyneuropathy. EEG showed generalized background theta slowing. Ophthalmologic examination was normal.

Questions for considerations

2. Is the brain MRI in this clinical picture suggestive of an acquired WM disorder or a genetic leukoencephalopathy?

Section 3

In our patient, the subacute and aggressive course of spastic paraplegia warranted exclusion of acquired causes of WM disease, namely of inflammatory, toxic/metabolic, and neoplastic...
Neurological manifestations did not appear to be related to the concomitant PKD1-disease, as even if kidney function was reduced, blood pressure was under good control.

Symmetry, confluence, and sparing of some structures (U-fibers, corpus callosum, spinal cord, juxtacortical WM), were inconsistent with a diagnosis of multiple sclerosis. JC virus-related progressive multifocal leukoencephalopathy was also unlikely, given that our patient has never been immunosuppressed.

Both drug abuse (heroin, methanol) and exposure to radio/chemotherapy (5-florouracil, methotrexate) may cause confluent, symmetrical WM abnormalities, however such etiologies were implausible in our patient.

Primary CNS lymphoma and gliomatosis cerebri may cause extensive WM brain abnormalities. In the former condition, brain MRI shows hypointense T1 signal, iso- to hypointense T2 signal and vivid contrast enhancement, often exhibiting crossing of the corpus callosum. In gliomatosis cerebri, a rare tumor involving at least three lobes, minimal mass effect and enhancement are found. The long medical history of our patient made unlikely both such hypotheses, even in the absence of contrast-enhanced images.

The initial diagnostic work-up of any subacute onset and progressive WM disorder should include serology for HIV, syphilis, hepatitis B/C, tuberculosis, JC virus, looking for autoimmune antibodies, blood lactate, folate and vitamin B12, and CSF examination looking for oligoclonal bands. All these test results were negative.

Also, one should consider cerebral small vessel disease, that can be acquired or inherited. Acquired form usually relates to exposure to long-standing cardiovascular risk factors; conversely, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL/NOTCH3), autosomal recessive cerebral arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL/HTRA1), collagen type IV/COL4A mutations, and Fabry disease/GLA represent etiologies of inherited forms. In cerebral small vessel disease, brain MRI initially shows multifocal, bilateral patchy WM abnormalities, merging to confluent WM lesions later in the disease course. However, basal ganglia, thalami, and brainstem are invariably affected, and microbleeds are commonly observed on Gradient Echo and Susceptibility-weighted scans. All these features were absent in our case.

Thus, confluent, bilateral, symmetric supratentorial WM abnormalities, suggested a genetic WM disorder, namely a leukodystrophy.
Questions for considerations

3. How do you approach genetic testing for leukodystrophies?

Section 4

Adult-onset leukodystrophies may have non-specific presentations, including variable combinations of cognitive decline, spasticity, and ataxia.\textsuperscript{6,7} Most leukodystrophies are slowly progressive, yet some forms may present abruptly, as cerebral adrenoleukodystrophy/\textit{ABCD1} and Vanishing White Matter/\textit{EIF2B} genes. The former was promptly excluded by normal levels of plasma Very Long Chain Fatty Acids, Adrenocorticotropic Hormone and cortisol, while the latter was considered unlikely, as in our patient neurological deterioration was not preceded by infections or head trauma, and brain MRI did not show cavitating leukencephalopathy.\textsuperscript{1,6}

Notwithstanding the advantage given by Next-generation sequencing (NGS) techniques, some discriminating clues are still fundamental in the diagnostic work-up of adult-onset leukodystrophies (Table), as some forms are associated to major genomic structural rearrangements not detectable by standard NGS. This is the case of an autosomal dominant adult-onset leukodystrophy characterized by early dysautonomia combined with spasticity and related to duplication of \textit{LMNB1}, detectable only by Multiplex ligation-dependent probe amplification. We specifically searched for it in our patient, with negative results.\textsuperscript{1}

Adult-onset leukencephalopathy with axonal spheroids and pigmented glia type 1 or 2, caused by autosomal dominant mutations in \textit{CSF1R} or \textit{AARS2} respectively, may be also rapidly progressive: both forms are characterized by extremely small, symmetric calcifications, better detected by brain CT, mainly located in the fronto-parietal subcortical WM, with basal ganglia sparing.\textsuperscript{8} Again, in our patient a normal brain CT made this condition unlikely.

CNS hypomyelination is suggested if the T2/FLAIR WM hyperintensity is diffuse, and the corresponding signal in T1 images is isointense, mildly hypointense or hyperintense, in contrast to demyelinating disorders where the WM displays invariably hypointense T1 signal.\textsuperscript{9} The most common form of hypomyelinating leukodystrophy, Pelizaeus-Merzbacher disease due to duplication of \textit{PLP1}, was not investigated, as it is a an extremely severe, usually very early-onset form of X-linked leukodystrophy, with a characteristic tigroid pattern at the brain MRI and peculiar torsional nystagmus.\textsuperscript{10} Similarly, normal MRS made leukencephalopathy with brainstem and spinal cord involvement with elevated lactate (due to \textit{DARS2} variants) unlikely.\textsuperscript{9}

Besides plasma levels of Very Long Chain Fatty Acids, other metabolic tests easily performed on peripheral blood or urines may help in the differential diagnosis of adult-onset leukodystrophies manifesting with spastic paraparesis associated with peripheral neuropathy,
including: galactocerebrosidase, glycogen-branching enzyme, and arylsulfatase activity in leukocytes (reduced in Krabbe disease, Adult Polyglucosan Body Disease, and Metachromatic Leukodystrophy, due to variants in \textit{GALC}, \textit{GBE1} and \textit{ARSA}/\textit{PSAP}, respectively); serum cholestanol (raised in cerebrotendineous xanthomatosis, due to \textit{CYP27A1} variants); gonadotropins and free testosterone (both reduced in Gordon Holmes syndrome, due to \textit{POLR3} variants); homocysteine (raised in Methylentetrahydrofolate Reductase deficiency, due to \textit{MTHFR} variants).\textsuperscript{1,6-7,11} All these tests were normal in our case.

An initial diagnostic NGS approach by targeted resequencing panel tailored for leukodystrophies gave negative results. Therefore, clinical exome was performed, leading to the identification of two pathogenic variants in \textit{PAH}: c.842C>T p.(Pro281Leu), inherited from his mother, and c.143T>C p.(Leu48Ser), presumably inherited from the deceased father. A molecular diagnosis of Phenylketonuria (PKU) was made, and confirmed by plasmatic hyperphenylalaninemia (1592 μmol/L).\textsuperscript{12} After an unsuccessful 1-month trial of tetrahydrobiopterin (BH\textsubscript{4}), a low phenylalanine diet was started, with stabilization of the patient’s motor performances at the 3-month follow-up visit.\textsuperscript{13}

**Discussion**

PKU, also known as phenylalanine hydroxylase (PAH) deficiency (OMIM #261600), is a rare, autosomal recessive inborn error of phenylalanine metabolism.\textsuperscript{12} PAH is responsible for the conversion of phenylalanine to tyrosine. Infants with PKU are normal at birth, but if untreated invariably develop intellectual disability, epilepsy, aberrant behaviour and psychiatric symptoms.\textsuperscript{12} PKU mainly affects brain WM, as related hyperphenylalaninemia alters the synthesis of brain lipids that form myelin. In Italy, a mandatory, nationwide, population-based newborn blood screening for PKU in 1992, 15 years after the birth of our patient.\textsuperscript{13}

Most PKU patients are compound heterozygotes for different PAH pathogenic variants, mainly missense changes expected to impair PAH enzymatic activity.\textsuperscript{13} Genetic heterogeneity and compound heterozygosis lead to a wide phenotypic spectrum in PAH deficiency, in which mild PKU patients can be responsive to tetrahydrobiopterin (BH\textsubscript{4}).\textsuperscript{12} Thus, PAH genotyping and genotype-phenotype studies may help to predict responsiveness to BH\textsubscript{4}, which can substitute low-phenylalanine diet.\textsuperscript{12} In our case, both variants have been associated with both classic (55%) and mild (45%) PKU forms;\textsuperscript{14} nevertheless, the mild, late-onset clinical presentation and the predicted BH\textsubscript{4}-sensitivity of the c.143T>C variant, supported to test BH\textsubscript{4} as the first therapeutic option, whose lack of response shifted treatment toward low-phenylalanine diet.\textsuperscript{15}
Regarding PKU, the availability of a specific treatment may improve symptoms and/or prevent further disease progression\textsuperscript{12,13}, so neurologists should be aware that undiagnosed adult-onset PKU can still occur in developed countries among individuals born before the establishment of PKU screening program and among migrants from developing countries. In conclusion, plasma aminoacidogram should be part of the diagnostic panel of progressive leukoencephalopathies.

References

Legend to figure

Figure. Brain and spine MRI of the proband.

Panel showing T2-weighted (A, C) and T1-weighted (B, D) axial brain MRI scans at the basal ganglia (A, B) and centrum semiovale (C, D) level. An extensive and symmetric T2 hyperintensity (A, C) involving mainly occipital and parietal white matter, with corresponding T1 slightly hypointense signal (B), sparing subcortical U-fibers and corpus callosum, is depicted. (E) T2-weighted sagittal brain MRI scans showing mild vermian cerebellar atrophy. (F) Sagittal T2-weighted MRI scans of the spinal cord.
Table. Differential diagnosis of main adult-onset leukodystrophies.

<table>
<thead>
<tr>
<th>Disease (gene)</th>
<th>Distinguishing features (brain MRI pattern)</th>
<th>Look for</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenoleukodystrophy (ABCD1)</td>
<td>Possible rapid deterioration, possible addisonian crisis, polyneuropathy (parieto-occipital, contrast enhancement)</td>
<td>Serum Very Long Chain Fatty Acids (↑)</td>
</tr>
<tr>
<td>Vanishing White Matter (EIF2B)</td>
<td>Possible optic nerve atrophy (diffuse brain involvement, cavitating leukoencephalopathy, corpus callosum thinning)</td>
<td></td>
</tr>
<tr>
<td>Autosomal dominant adult-onset demyelinating leukodystrophy (duplication of LMNB1)</td>
<td>Autonomic dysfunction (frontal predominance)</td>
<td>Single-gene testing by MLPA (not detected by NGS)</td>
</tr>
<tr>
<td>Adult-onset leukoencephalopathy with axonal spheroids and pigmented glia type 1 and 2 (CSF1R or AARS2)</td>
<td>Early-onset dementia, polyneuropathy (bifrontal/bifrontoparietal involvement, calcifications, asymmetric lesions, corpus callosum thinning)</td>
<td></td>
</tr>
<tr>
<td>Pelizaeus-Merzbacher disease (duplication of PLP1)</td>
<td>Torsional nystagmus, polyneuropathy (hypomyelination, tigroid pattern)</td>
<td>Single-gene testing by MLPA (not detected by NGS)</td>
</tr>
<tr>
<td>Leukoencephalopathy with brainstem and spinal cord involvement with elevated lactate (DARS2)</td>
<td>(long-tract involvement, lactate peak at brain MRI spectroscopy)</td>
<td></td>
</tr>
<tr>
<td>Alexander disease (GFAP)</td>
<td>Early bulbar symptoms (cerebellar involvement, frontal predominance, possible contrast enhancement)</td>
<td>GFAP in CSF (↑)</td>
</tr>
<tr>
<td>Cerebrotendineous xanthomatosis (CYP27A1)</td>
<td>Spastic ataxia, cataracts, chronic diarrhoea, xanthomas, polyneuropathy (dentate nucleus hyperintensities)</td>
<td>serum cholestanol (↑)</td>
</tr>
<tr>
<td>Krabbe disease (GALC)</td>
<td>Possible optic nerve atrophy (periventricular, parieto-occipital predominance)</td>
<td>leukocytes galactocerebroside activity (↓)</td>
</tr>
<tr>
<td>Adult Polyglucosan Body Disease (GBE1)</td>
<td>Upper and lower motor neuron impairment (periventricular, asymmetric predominance)</td>
<td>leukocytes glycogen-branching enzyme activity (↓)</td>
</tr>
<tr>
<td>Metachromatic Leukodystrophy (ARSA/PSAP)</td>
<td>Early-onset dementia, possible rapid deterioration, possible optic nerve atrophy, polyneuropathy, gallbladder dysfunction (periventricular, frontal predominance)</td>
<td>leukocytes arylsulfatase A activity (↓), urinary sulfatides (↑)</td>
</tr>
<tr>
<td>Gordon Holmes syndrome (POL3)</td>
<td>Hypodontia and delayed or absent puberty (hypomyelination)</td>
<td>Hypogonadotropic hypogonadism</td>
</tr>
<tr>
<td>Methyltetrahydrofolate Reductase deficiency (MTHFR)</td>
<td>(bilateral posterior prevalence)</td>
<td>serum homocysteine (↑)</td>
</tr>
</tbody>
</table>