

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

Salvatore Rossi, MD, Paola Concolino, PhD, Daniele Di Natale, MD, Domizia Pasquetti, MD, Giuseppe Maria Di Lella, MD, PhD, Pietro Chiurazzi, MD, PhD, and Gabriella Silvestri, MD, PhD

Neurology[®] 2023;100:199-205. doi:10.1212/WNL.0000000000201516

Correspondence

Dr. Silvestri
gabriella.silvestri@unicatt.it

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 a 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 into the maze of genetic testing for white matter diseases. In our patient, we reached the diagnosis of a treatable disorder, whose early recognition is essential to prevent severe neurologic deterioration.

From the Dipartimento di Scienze dell'Invecchiamento (S.R., D.D.N., G.S.), Neurologiche, Ortopediche e della Testa-Collo, UOC Neurologia, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy; Dipartimento di Neuroscienze Università Cattolica del Sacro Cuore (S.R., D.D.N., G.S.), Facoltà di Medicina e Chirurgia, Rome, Italy; UOC Chimica (Paola Concolino), Biochimica e Biologia Molecolare Clinica - Area Diagnostica di Laboratorio, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy; Istituto di Medicina Genomica (D.P., Pietro Chiurazzi), Università Cattolica del Sacro Cuore, Rome, Italy; Department of Diagnostic Imaging (G.M.D.L.), Oncological Radiotherapy, and Hematology, UOC Neuroradiology, Fondazione Policlinico Universitario Agostino Gemelli IRCCS and Università Cattolica del Sacro Cuore, 00168 Rome, Italy; and UOC Genetica Medica (Pietro Chiurazzi), Fondazione Policlinico Universitario "A. Gemelli" IRCCS, Rome, Italy.

Go to [Neurology.org/N](https://www.neurology.org/N) for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Section 1

A 44-year-old man born to nonconsanguineous parents presented with subacute onset and rapidly progressive walking difficulties requiring the need for 1 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 pathogenic variant in *PKD1* inherited from his mother. His father died at the age of 62 years of colorectal cancer. The proband required educational support at school but was able to achieve a secondary school degree. He had stable employment and participated in regular weight-lifting exercise.

The first neurologic evaluation at our center 18 months from the onset of symptoms showed spastic paraparesis requiring canes to walk. Lower limb weakness was moderate (bilaterally grade 4 by the Medical Research Council scale at iliopsoas and tibialis anterior muscles), and spasticity was marked (modified Ashworth scale = 3 bilaterally). The 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 signs were present bilaterally. Upper limb, cranial nerve, and sensory function were all normal.

Question for Consideration:

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

GO TO SECTION 2

Section 2

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

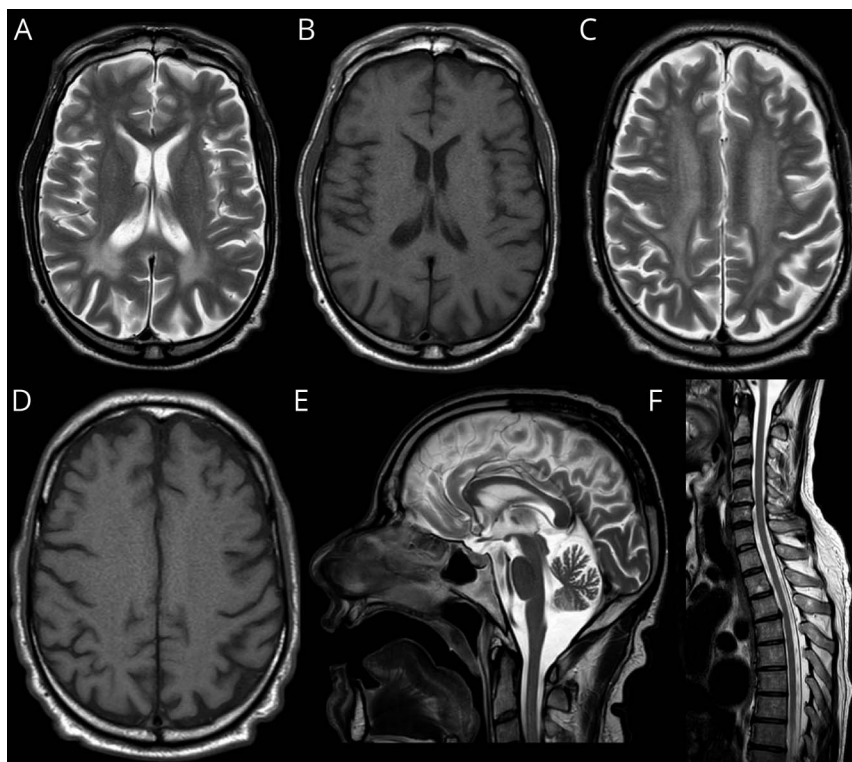
any abnormal peaks. Gadolinium contrast was not infused because of chronic kidney disease.

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

Question for Consideration:

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

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) and sparing of the subcortical U-fibers and corpus callosum, is depicted. (E) T2-weighted sagittal brain MRI scans showing mild vermian cerebellar atrophy. (F) T2-weighted sagittal MRI scans of the spinal cord.

GO TO SECTION 3

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 etiologies.¹ Neurologic 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, and juxtacortical WM) were inconsistent with a diagnosis of multiple sclerosis.² JC virus–related progressive multifocal leukoencephalopathy was also unlikely, given that our patient has never been immunosuppressed.³

Both drug abuse (heroin and methanol) and exposure to radiotherapy/chemotherapy (5-fluorouracil and methotrexate) may cause confluent, symmetrical WM abnormalities¹; however, such etiologies were implausible in our patient.

Primary CNS lymphoma and gliomatosis cerebri may cause extensive WM brain abnormalities.⁴ In the former condition, brain MRI shows hypointense T1 signal, isointense to hypointense T2 signal, and vivid contrast enhancement, often exhibiting crossing of the corpus callosum.⁴ In gliomatosis cerebri, a rare tumor involving at least 3 lobes, minimal mass effect and enhancement are found. The long medical history of our patient made both hypotheses unlikely, even in the absence of contrast-enhanced images.

The initial diagnostic workup 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.¹ All these test results were negative.

Also, one should consider cerebral small vessel disease that can be acquired or inherited. The 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* variants, and Fabry disease/*GLA* represent etiologies of inherited forms.⁵ 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.⁵ All these features were absent in our case.

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

Question for Consideration:

1. How do you approach genetic testing for leukodystrophies?

GO TO SECTION 4

Section 4

Adult-onset leukodystrophies may have nonspecific presentations, including variable combinations of cognitive decline, spasticity, and ataxia.^{6,7} Most leukodystrophies are slowly progressive, yet some forms may present abruptly, as cerebral adrenoleukodystrophy/*ABCD1* and vanishing white matter/*EIF2B*. Cerebral adrenoleukodystrophy was promptly excluded by normal levels of plasma very long chain fatty acids, adrenocorticotropic hormone, and cortisol, whereas vanishing white matter disease was considered unlikely, as in our patient neurologic deterioration was not preceded by infections or head trauma, and brain MRI did not show cavitating leukoencephalopathy.^{1,6}

Notwithstanding the advantage given by next-generation sequencing (NGS) techniques, some discriminating clues are still fundamental in the diagnostic workup of adult-onset leukodystrophies (Table) because some forms are associated with 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 *LMNB1*, detectable only by multiplex ligation-dependent probe amplification. We specifically searched for it in our patient, with negative results.¹

Adult-onset leukoencephalopathy with axonal spheroids and pigmented glia type 1 or 2, caused by autosomal dominant variants in *CSF1R* or *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 frontoparietal subcortical WM, with basal ganglia sparing.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 in which the WM displays invariably hypointense T1 signal.⁹ The most common form of hypomyelinating leukodystrophy, Pelizaeus-Merzbacher disease due to duplication of *PLP1*, was not investigated because it is an extremely severe, usually very early-onset form of X-linked

Table Differential Diagnosis of Main Adult-Onset Leukodystrophies

Disease (<i>gene</i>)	Distinguishing features (brain MRI pattern)	Look for
Adrenoleukodystrophy (<i>ABCD1</i>)	Possible rapid deterioration, possible Addisonian crisis, and polyneuropathy (parieto-occipital, contrast enhancement)	Serum very long chain fatty acids (↑)
Vanishing white matter (<i>EIF2B</i>)	Possible optic nerve atrophy (diffuse brain involvement, cavitating leukoencephalopathy, and corpus callosum thinning)	
Autosomal dominant adult-onset demyelinating leukodystrophy (duplication of <i>LMNB1</i>)	Autonomic dysfunction (frontal predominance)	Single-gene testing by MLPA (not detected by NGS)
Adult-onset leukoencephalopathy with axonal spheroids and pigmented glia type 1 and 2 (<i>CSF1R</i> or <i>AARS2</i>)	Early-onset dementia and polyneuropathy (bifrontal/bifrontoparietal involvement, calcifications, asymmetric lesions, and corpus callosum thinning)	
Pelizaeus-Merzbacher disease (duplication of <i>PLP1</i>)	Torsional nystagmus and polyneuropathy (hypomyelination and tigroid pattern)	Single-gene testing by MLPA (not detected by NGS)
Leukoencephalopathy with brainstem and spinal cord involvement with elevated lactate (<i>DARS2</i>)	Long-tract involvement and lactate peak at brain MRI spectroscopy	
Alexander disease (<i>GFAP</i>)	Early bulbar symptoms (cerebellar involvement, frontal predominance, and possible contrast enhancement)	GFAP in CSF (↑)
Cerebrotendinous xanthomatosis (<i>CYP27A1</i>)	Spastic ataxia, cataracts, chronic diarrhea, xanthomas, and polyneuropathy (dentate nuclei hyperintensities)	Serum cholestanol (↑)
Krabbe disease (<i>GALC</i>)	Possible optic nerve atrophy (periventricular and parieto-occipital predominance)	Leukocytes galactocerebrosidase activity (↓)
Adult polyglucosan body disease (<i>GBE1</i>)	Upper and lower motor neuron impairment (periventricular and asymmetric predominance)	Leukocytes glycogen-branching enzyme activity (↓)
Metachromatic leukodystrophy (<i>ARSA/PSAP</i>)	Early-onset dementia, possible rapid deterioration, possible optic nerve atrophy, polyneuropathy, and gallbladder dysfunction (periventricular and frontal predominance)	Leukocytes arylsulfatase A activity (↓), urinary sulfatides (↑)
Gordon Holmes syndrome (<i>POL3</i>)	Hypodontia and delayed or absent puberty (hypomyelination)	Hypogonadotropic hypogonadism
Methylenetetrahydrofolate reductase deficiency (<i>MTHFR</i>)	Bilateral posterior prevalence	Serum homocysteine (↑)

leukodystrophy, with a characteristic tigroid pattern on the brain MRI and peculiar torsional nystagmus.¹⁰ Similarly, normal MRS made leukoencephalopathy with brainstem and spinal cord involvement with elevated lactate (due to *DARS2* variants) unlikely.⁹

Besides plasma levels of very long chain fatty acids, other metabolic tests easily performed on peripheral blood or urine 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 *GALC*, *GBE1*, and *ARSA/PSAP*, respectively); serum cholestanol (raised in cerebrotendinous xanthomatosis, due to *CYP27A1* variants); gonadotropins and free testosterone (both reduced in Gordon Holmes syndrome, due to *POLR3* variants); and homocysteine (raised in methylenetetrahydrofolate reductase deficiency, due to *MTHFR* variants).^{1,6,7,11} All these tests were normal in our case.

An initial diagnostic NGS approach by a targeted resequencing panel tailored for leukodystrophies gave negative results. Therefore, clinical exome was performed, leading to the identification of 2 pathogenic variants in *PAH*: c.842C>T p.(Pro281-Leu), 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 (1,592 $\mu\text{mol/L}$).¹² After an unsuccessful 1-month trial of tetrahydrobiopterin (BH_4), a low phenylalanine diet was started, with stabilization of the patient's motor performances at the 3-month follow-up visit.¹³

Discussion

PKU, also known as phenylalanine hydroxylase (*PAH*) deficiency (OMIM #261600), is a rare autosomal recessive in-born error of phenylalanine metabolism.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 behavior, and psychiatric symptoms.¹² PKU mainly affects brain WM because related hyperphenylalaninemia alters the synthesis of brain lipids that form myelin. In Italy, a mandatory, nationwide, population-based newborn blood screening for PKU was introduced in 1992, 15 years after the birth of our patient.¹³

Most patients with PKU are compound heterozygotes for different *PAH* pathogenic variants, mainly missense changes expected to impair *PAH* enzymatic activity.¹³ Genetic heterogeneity and compound heterozygosity lead to a wide phenotypic spectrum in *PAH* deficiency, in which patients with mild PKU can be responsive to BH_4 .¹² Thus, *PAH* genotyping and genotype-phenotype studies may help to predict responsiveness to BH_4 , which can substitute low phenylalanine diet.¹² In our case, both variants have been associated with both classic (55%) and mild (45%) PKU forms¹⁴; nevertheless, the

mild, late-onset clinical presentation and the predicted BH_4 sensitivity of the c.143T>C variant supported the choice of BH_4 as the first therapeutic option, whose lack of response shifted treatment toward low phenylalanine diet.¹⁵

Regarding PKU, the availability of a specific treatment may improve symptoms and/or prevent further disease progression,^{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 programs and among migrants from developing countries. In conclusion, plasma aminoacidogram should be part of the diagnostic panel of progressive leukoencephalopathies.

Acknowledgment

The authors thank Prof. Glen W. McWilliams and Dr. Stephanie Efthymiou for revising the English form of the manuscript.

Study Funding

The authors report no targeted funding.

Disclosure

The authors report no disclosures relevant to the manuscript. Go to [Neurology.org/N](https://www.neurology.org/N) for full disclosures.

Publication History

Received by *Neurology* April 5, 2022. Accepted in final form September 20, 2022. Submitted and externally peer reviewed. The handling editor was Whitley Aamodt, MD, MPH.

Appendix Authors

Name	Location	Contribution
Salvatore Rossi, MD	Dipartimento di Scienze dell'Invecchiamento, Neurologiche, Ortopediche e della Testa-Collo, UOC Neurologia, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy; Dipartimento di Neuroscienze Università Cattolica del Sacro Cuore, Facoltà di Medicina e Chirurgia, Rome, Italy	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data
Paola Concolino, PhD	UOC Chimica, Biochimica e Biologia Molecolare Clinica - Area Diagnostica di Laboratorio, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy	Analysis or interpretation of data
Daniele Di Natale, MD	Dipartimento di Scienze dell'Invecchiamento, Neurologiche, Ortopediche e della Testa-Collo, UOC Neurologia, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy; Dipartimento di Neuroscienze Università Cattolica del Sacro Cuore, Facoltà di Medicina e Chirurgia, Rome, Italy	Drafting/revision of the manuscript for content, including medical writing for content

Appendix (continued)

Name	Location	Contribution
Domizia Pasquetti, MD	Istituto di Medicina Genomica, Università Cattolica del Sacro Cuore, Rome, Italy	Drafting/revision of the manuscript for content, including medical writing for content
Giuseppe Maria Di Lella, MD, PhD	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	Analysis or interpretation of data
Pietro Chiurazzi, MD, PhD	Istituto di Medicina Genomica, Università Cattolica del Sacro Cuore, Rome, Italy; UOC Genetica Medica, Fondazione Policlinico Universitario "A. Gemelli" IRCCS, Rome, Italy	Drafting/revision of the manuscript for content, including medical writing for content
Gabriella Silvestri, MD, PhD	Dipartimento di Scienze dell'Invecchiamento, Neurologiche, Ortopediche e della Testa-Collo, UOC Neurologia, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy; Dipartimento di Neuroscienze Università Cattolica del Sacro Cuore, Facoltà di Medicina e Chirurgia, Rome, Italy	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data

References

1. Lynch DS, Wade C, Paiva ARB, et al. Practical approach to the diagnosis of adult-onset leukodystrophies: an updated guide in the genomic era. *J Neurol Neurosurg Psychiatry*. 2019;90(5):543-554. doi:10.1136/jnnp-2018-319481
2. Etemadifar M, Ashourizadeh H, Nouri H, et al. MRI signs of CNS demyelinating diseases. *Mult Scler Relat Disord*. 2021;47:102665. doi:10.1016/j.msard.2020.102665
3. Berger JR, Aksamit AJ, Clifford DB, et al. PML diagnostic criteria: consensus statement from the AAN Neuroinfectious Disease Section. *Neurology*. 2013;80(15):1430-1438. doi:10.1212/WNL.0b013e31828c2fa1
4. Butowski NA. Epidemiology and diagnosis of brain tumors. *Continuum*. 2015;21(2 Neuro-oncology):301-313. doi:10.1212/01.CON.0000464171.50638.f8
5. Cannistraro RJ, Badi M, Eidelman BH, et al. CNS small vessel disease: a clinical review. *Neurology*. 2019;92(24):1146-1156. doi:10.1212/WNL.0000000000007654
6. Köhler W, Curiel J, Vanderver A. Adulthood leukodystrophies. *Nat Rev Neurol*. 2018;14(2):94-105. doi:10.1038/nrneuro.2017.175
7. van der Knaap MS, Schiffmann R, Mochel F, Wolf NI. Diagnosis, prognosis, and treatment of leukodystrophies. *Lancet Neurol*. 2019;18(10):962-972. doi:10.1016/S1474-4422(19)30143-7
8. Aygnac X, Nicolas G, Carra-Dallièrè C, et al. Brain calcifications in adult-onset genetic leukoencephalopathies: a review. *JAMA Neurol*. 2017;74(8):1000-1008. doi:10.1001/jamaneuro.2017.1062
9. Resende LL, de Paiva ARB, Kok F, et al. Adult leukodystrophies: a step-by-step diagnostic approach. *Radiographics*. 2019;39(1):153-168. doi:10.1148/rf.2019180081
10. Manara R, Burlina AP, Citton V, et al. Brain MRI diffusion-weighted imaging in patients with classical phenylketonuria. *Neuroradiology*. 2009;51(12):803-812. doi:10.1007/s00234-009-0574-z
11. Perna A, Masciullo M, Modoni A, et al. Severe S,10-methylenetetrahydrofolate reductase deficiency: a rare, treatable cause of complicated hereditary spastic paraplegia. *Eur J Neurol*. 2018;25(3):602-605. doi:10.1111/ene.13557
12. van Spronsen FJ, Blau N, Harding C, et al. *Phenylketonuria Nat Rev Dis Primers*. 2021;7(1):36. doi:10.1038/s41572-021-00267-0
13. van Wegberg AMJ, MacDonald A, Ahring K, et al. The complete European guidelines on phenylketonuria: diagnosis and treatment. *Orphanet J Rare Dis*. 2017;12(1):162. doi:10.1186/s13023-017-0685-2
14. Liu X, Guo H, Dahal M, et al. Unusual presentation of two Chinese phenylketonuria sisters who were misdiagnosed for years. *BMJ Case Rep*. 2013;2013:bcr2013010270. doi:10.1136/bcr-2013-010270
15. Santos LL, Fonseca CG, Starling AL, et al. Variations in genotype-phenotype correlations in phenylketonuria patients. *Genet Mol Res*. 2010;9(1):1-8.

Subspecialty Alerts by E-mail!

Customize your online journal experience by signing up for e-mail alerts related to your subspecialty or area of interest. Access this free service by clicking on the “My Alerts” link on the home page. An extensive list of subspecialties, methods, and study design choices will be available for you to choose from—allowing you priority alerts to cutting-edge research in your field!

Did You Know...

...you can browse by subspecialty topics on Neurology.org?

Go to: Neurology.org and click on “Collections” in the top navigation bar, then choose “Topics A-Z” from the drop down menu.

Neurology®

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

Salvatore Rossi, Paola Concolino, Daniele Di Natale, et al.

Neurology 2023;100;199-205 Published Online before print October 27, 2022

DOI 10.1212/WNL.0000000000201516

This information is current as of October 27, 2022

Updated Information & Services	including high resolution figures, can be found at: http://n.neurology.org/content/100/4/199.full
References	This article cites 15 articles, 4 of which you can access for free at: http://n.neurology.org/content/100/4/199.full#ref-list-1
Subspecialty Collections	This article, along with others on similar topics, appears in the following collection(s): Leukodystrophies http://n.neurology.org/cgi/collection/leukodystrophies Metabolic disease (inherited) http://n.neurology.org/cgi/collection/metabolic_disease_inherited Spastic paraplegia http://n.neurology.org/cgi/collection/spastic_paraplegia
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://www.neurology.org/about/about_the_journal#permissions
Reprints	Information about ordering reprints can be found online: http://n.neurology.org/subscribers/advertise

Neurology® is the official journal of the American Academy of Neurology. Published continuously since 1951, it is now a weekly with 48 issues per year. Copyright © 2022 American Academy of Neurology. All rights reserved. Print ISSN: 0028-3878. Online ISSN: 1526-632X.

