

A stepwise approach to adult-onset leukodystrophy

^{1,2*}Vitalie Văcăraș, ^{1,3*}Zoltán Z. Major, ^{1,3}Emilia Mariș, ⁴Kinga Andrea Major, ¹Anca Dana Buzoianu

¹“Iuliu Hațieganu” University of Medicine and Pharmacy, Cluj-Napoca, Romania; ² Department of Neurology, Cluj County Emergency Hospital, Cluj-Napoca, Romania; ³ Department of Neurology, Municipal Clinical Hospital Cluj-Napoca, Cluj-Napoca, Romania; ⁴ Cluj County Emergency Hospital, ICU, Cluj-Napoca, Romania.

* Pointed authors had equal contribution

Abstract. Leukodystrophies are a heterogeneous group of disorders characterized by a vast array of neuropsychiatric symptoms. Adult-onset disease presentation is often mistaken for multiple sclerosis, which delays positive diagnosis. Our goal was to present some diagnostic features of frequently seen adult-onset leukodystrophies on the margin of a clinical case.

Key Words: leukodystrophy, adult-onset, case report

Copyright: This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Corresponding Authors: Z. Z. Major, email: zoltan.major@eeg-emg.ro

Introduction

Leukodystrophies are a group of neurological diseases constituting a challenging diagnostic task, thus frequently misdiagnosed (Coffeen et al 2000). These conditions are characterized by degeneration of white matter, caused by inherited (autosomal dominant, recessive, X-linked or mitochondrial) defects, usually affecting components of myelin, or involving metabolites having toxic, deleterious effects on oligodendrocytes and consecutive destruction of myelin or severe reduction of its production (Maria et al 2003).

Leukodystrophies are overall rare conditions, which might manifest themselves already in early childhood; still, almost each entity has adult-onset form also. The heraldic disease of the group is X-linked adrenoleukodystrophy. As its name suggests, the inheritance pattern is X-linked, the gene is the ATP-binding cassette, subfamily D, member 1 (ABCD1) on Xq28 (Schiffmann et al 2001).

Another condition is metachromatic leukodystrophy – a lysosomal disease with sphingolipid storage caused by arylsulphatase A deficiency (Gieselmann & Krägeloh-Mann 2010).

Adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (Marotti et al 2004), including hereditary diffuse leukoencephalopathy with neuroaxonal spheroids and pigmentary orthochromatic leukodystrophy (Wider et al 2009) are rarely occurring conditions; the inheritance is autosomal dominant, mutated colony stimulating factor 1 receptor gene (CSF1R) on chromosome 5q32 (Sundal et al 2012), having insufficient data to this point how the mutation determines the leukoencephalopathic pattern (Van Gerpen et al 2008).

Rare forms are represented by adult polyglucosan body disease, cerebrotendinous xanthomatosis, Krabbe disease, Alexander disease (Tian et al 2010; Farina et al 2008) vanishing white

matter disease, adult onset autosomal dominant leukodystrophy, Pelizaeus-Merzbacher disease etc.

Some classifications are including among leukodystrophies cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL) and various mitochondrial diseases (Kearns-Sayre syndrome, mitochondrial encephalopathy lactic acidosis and stroke-like episodes (MELAS), Leigh disease, Leber's hereditary optic neuropathy etc.), although their pathophysiology differs significantly (Suzuki et al 2001).

Leukodystrophy-like conditions might develop as a secondary state also, at least from the point of view of imagery and clinical features, but history and disease characteristics are easily orienting the diagnostic process.

Clinical presentation usually involves gait disturbances, behavioral changes, cognitive decline, spasticity, seizures, incontinence or neurogenic bladder and progression towards severe dementia, vegetative state and death, although the disease course requires a longer time period as the childhood-onset forms.

Pathogenetic treatment options are subject of intensive, ongoing research, and are covering fields of exogeneous enzyme replacement, bone marrow and stem cell transplantation and gene therapy, each still in study, applied only sporadically (Solders et al 1998). Current clinical approach is mainly restricted to symptomatic treatment, and the goal is essentially palliative.

In the followings we present a possible clinical case of leukodystrophy with its characteristics, then, in the discussion section we face the features with the frequently seen adult-onset forms, which raised questions of differential diagnosis for the presented patient.

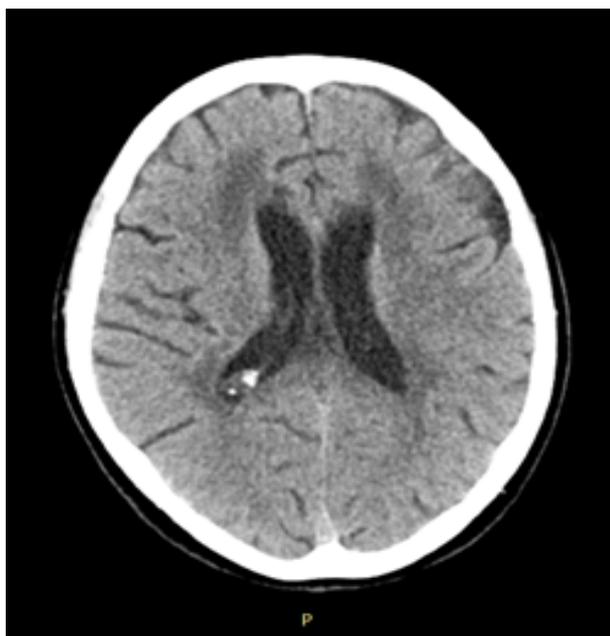


Figure 1. A CT scan revealed periventricular leukoaraiosis, the image showing discrepancies with the more severe clinical feature

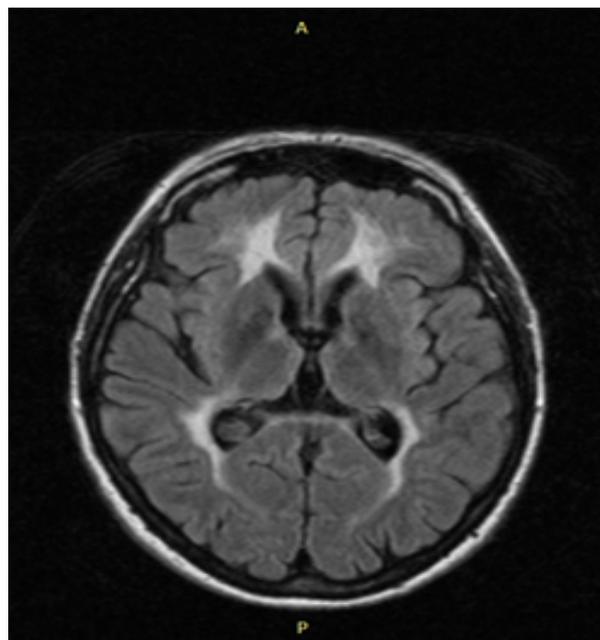


Figure 2a.

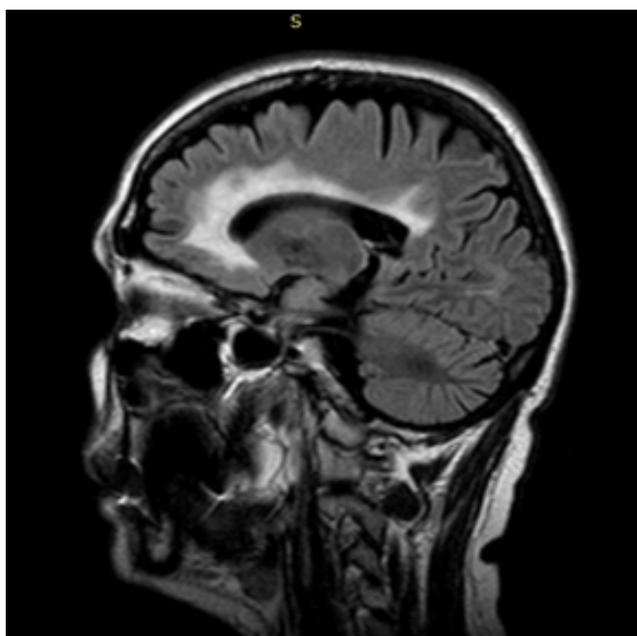


Figure 2b.

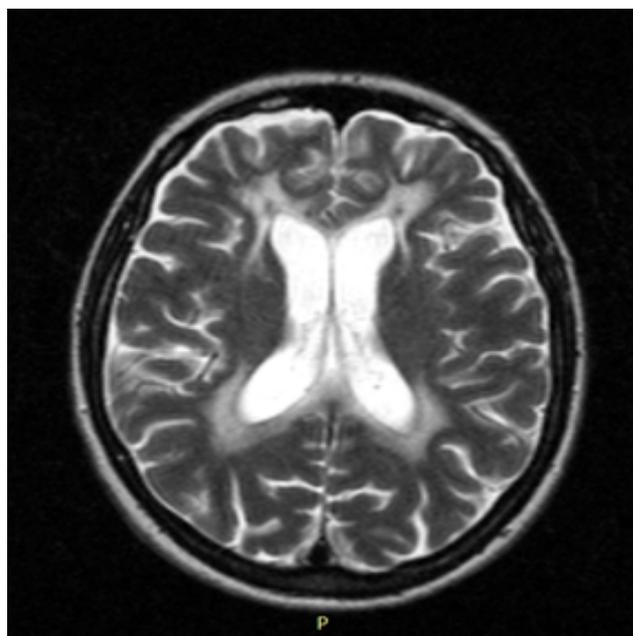


Figure 2c.

Figure 2. (2a, 2b, 2c) The MRI shows confluent periventricular intensity changes usually seen in leukodystrophies

Case presentation

Clinical features

General data

N.E. a fifty year old woman presented to our department having already an almost five year history of attention deficit, memory loss, abulia. She is 165 cm tall, 60 kg, normal BMI person, without any other known chronic disease.

Neurological examination reveals reduction of tendon reflexes, mainly in the lower limbs, without significant, quantifiable functional effect.

The evolution was tracked in different institutions for over five years already, without a definite diagnosis. Among possibilities leukodystrophies were suggested.

Psychological evaluation

The last Mini Mental State Evaluation score was 9, the patient showing a considerable decline in the last 3 years, from a score of 20.

Biological parameters

Our patient presented normal hematological, physiological liver and kidney parameters. In case of inflammation ESR, CRP, rheumatoid factor, complement (C_{3c} , C_4) were in normal range. During the evaluation process there were two elevated values for circulating immune complexes (CIC) (160×10^3 U, 190×10^3 U, normal <150). Lupus-anticoagulant, IgG for beta2 glycoprotein, anti-phospholipid IgG and anti pANCA antibodies were negative.

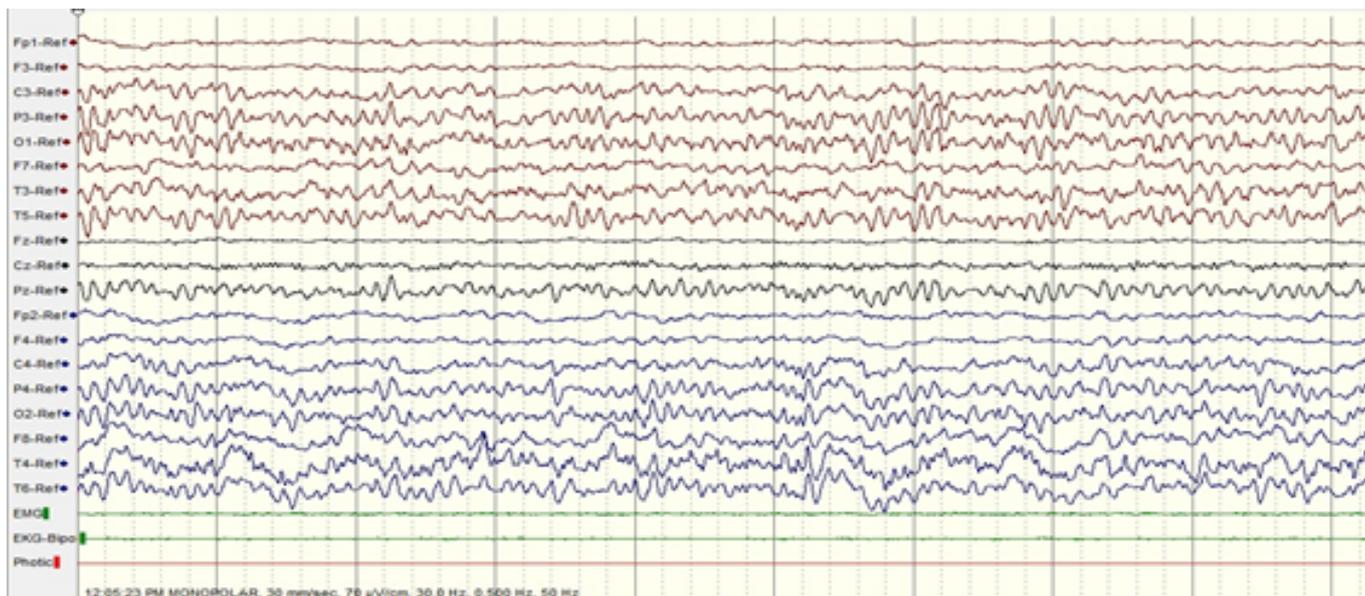


Figure 3. The EEG has a dominant, symmetric, insufficiently modulated low alpha frequency. On this base rhythm one might observe more slower discharges, 5-6 Hz, more frequently occurring apparently on the right side.

During the investigation for leukodystrophies A arylsulphatase was 4.4 nmol/h/ml (normal values 3,6-9,4). Very long chain fatty acids (VLCFA) were also in normal range.

Thyroid function, FT₄ and TSH, were also in physiological range. From the point of view of infections anti HIV 1+2 antibodies, anti Toxoplasma gondii antibodies and VDRL were all negative. In opposition, Borrelia IgG were positive >200 (>25 U/ml positive), IgM negative.

The patient was negative for oligoclonal bands.

Electrophysiology

Evoked potentials

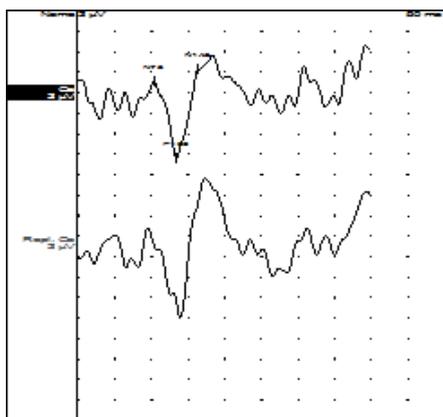


Figure 4. Visual Evoked Potentials, Side: Right – significantly prolonged latency values (the annexed table shows the parameter values).

Name	Lat. [ms]	Lat. [ms]	Lat. [ms]	N75-P100 [µV]	N145-P100 [µV]
Oz	103.28	134.22	163.82	7.54	8.7

Somatosensory evoked potentials were performed, without quantifiable potentials.

Electroneurography

All measured velocities were altered, regardless the investigated nerve, the mean being around 30 m/s. Below are presented motor and sensory nerve parameters from both lower and upper limbs.

Motor Nerve Conduction

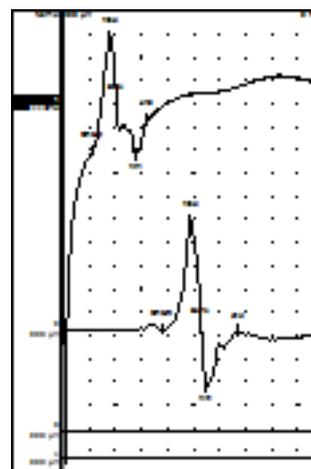


Figure 5. N. peroneus profundus right – reduced velocity and slightly diminished amplitude (the annexed tables contain the measured parameters)

Name	Distance [mm]	Lat. diff [ms]	CV no corr. [m/s]
1-2	385	13.42	28.697

Name	Latency [ms]	Duration [ms]	Amplitude [mV]	Stim. level [mA]
1	5.6	10.58	1.03	64
2	19.02	14.53	1.44	55

Motor Nerve Conduction

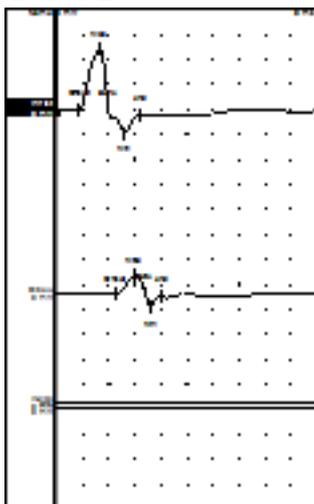


Figure 6. N. medianus right – reduced velocity and normal amplitude (the annexed tables contain the measured parameters)

Name	Distance [mm]	Lat. diff [ms]	CV no corr. [m/s]
Rec - Wrist	70	4.4	
Wrist - Elbow	212	7.05	30.071

Name	Latency [ms]	Duration [ms]	Amplitude [mV]	Stim. level [mA]
Wrist	4.4	11.78	6.68	46
Elbow	11.45	8.82	2.52	45

Sensory Nerve Conduction

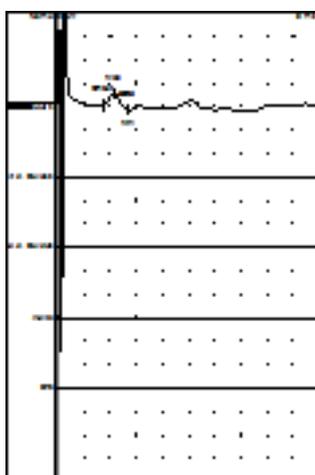


Figure 7. N. ulnaris left – reduced velocity and amplitude (the annexed tables contain the measured parameters)

Name	Distance [mm]	Lat. diff [ms]	CV no corr. [m/s]
Stim - Wrist	112	3.42	32.787

Name	Latency [ms]	Duration [ms]	Amplitude [μV]	Area [mVms]
Wrist	3.42	1.949	3.575	0.003

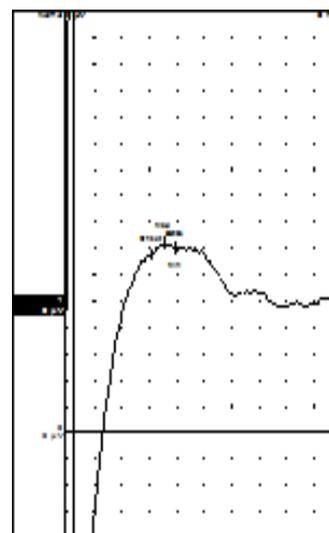


Figure 8. N. peroneus superficialis left – reduced velocity and amplitude (the annexed tables contain the measured parameters)

Name	Distance [mm]	Lat. diff [ms]	CV no corr. [m/s]
Rec - 1	135	6.22	21.72

Name	Latency [ms]	Duration [ms]	Amplitude [μV]	Stim. level [mA]
1	6.22	1.7	0.52	30

Discussion

The above presented case raised quite a diagnostic controversy. The presence of a progressive decline affecting mainly cognitive functions might represent the feature of several diseases. When one discovers demyelination, the first possible diagnostic guess is searched among MS spectrum diseases. This was the case here also, given the fact that the subject was female, and relatively young at disease debut. Lack of typical neurological deficit, typical demyelinations, and negative lumbar puncture for oligoclonal bands makes the diagnosis unlikely.

Another possibility was represented by neuroborreliosis, the diagnosis being confirmed during the evolution, and the patient was treated accordingly. Joint pain was interpreted as part of this pathology, and not as a rheumatic feature, given their disappearance after the antimicrobial treatment. From the point of view of the peripheral neuropathy, this pathology might have a contribution to the altered parameters, although their progressive, ongoing nature is not characteristic for borreliosis.

Circulating immune complexes were raised two times during the disease course, still, there was no other modified diagnostic test – including the vessels harvested during the nerve biopsy. Rheumatological evaluation excludes systemic rheumatic disease. CADASIL/CARASIL and Binswanger disease were not sustainable diagnoses: there was no positive familial history for suggestive cardio-vascular diseases, and no significant personal disease history like hypertension, dyslipidemia, atherosclerosis, etc. Creutzfeldt-Jakob disease was not yet entirely ruled out, still, it seems unlikely: repeated EEGs failed to reveal the characteristic periodic sharp-wave pattern; the patient never had seizures;

the MRI is non-characteristic, (caudate- and putamen hyperintensity is not the main feature). Peripheral neuropathy, electroneurography and histologically confirmed demyelination, is also not a part of the clinical picture in CJD.

The row might continue, but the characteristics of the case oriented us towards the leukodystrophies. If we consider the more frequently occurring representatives of the spectrum, then adrenoleukodystrophy, metachromatic leukodystrophy and adult-onset leukoencephalopathy with axonal spheroids and pigmented glia, including hereditary diffuse leukoencephalopathy with neuroaxonal spheroids and pigmentary orthochromatic leukodystrophy are the most likely diseases. The last disease is autosomal dominant, but there is no suggestive feature in the family history. Arylsulphatase A was negative, this excludes metachromatic leukodystrophy.

VLCFAs were also negative, but this might be so in carriers. Carrier women also might show the adrenomyeloneuropathic phenotype, this being the case with our patient also. We also have no suggestive history regarding the family history, one generation of relatives being represented exclusively by women. Our quest towards a definite diagnosis is on halt for the moment, the price for genetic testing being prohibitive for the family. The same is true for the possible treatment: if considered adrenomyeloneuropathy, then there's no available treatment besides the well-known Lorenzo's oil (a 4:1 mixture of oleic acid and erucic acid), with questionable efficiency and impressive price, around 400 euros monthly, also prohibitive for the family, and not supported by the insurance.

Conclusion

Even if our patient was initially thought as a case of demyelinating disease, adrenomyeloneuropathy represents a rare, but sometimes feasible diagnosis; if clinical and laboratory features suggest the diagnosis, this should be considered as likely, even if the patient is only a carrier.

Acknowledgements

We would like to thank Stan Oana for her kind contribution. This paper was published under the frame of European Social Fund, Human Resources Development Operational Programme 2007-2013, project no. POSDRU/159/1.5/138776.

References

- Barker PB, Horská A. Neuroimaging in leukodystrophies. *J Child Neurol* 2004;19(8):559–570.
- Coffeen CM, McKenna CE, Koeppen AH, et al. Genetic localization of an autosomal dominant leukodystrophy mimicking chronic progressive multiple sclerosis to chromosome 5q31. *Hum Mol Genet* 2000;9:787–793.
- Farina L, Pareyson D, Minati L, et al. Can MR imaging diagnose adult-onset Alexander disease? *AJNR Am J Neuroradiol*. 2008;29:1190–6.
- Gieselmann V, Krägeloh-Mann I. Metachromatic Leukodystrophy – An Update. *Neuropediatrics* 2010;41(1):1-6.
- Maria BL, Deidrick KM, Moser H, et al. Leukodystrophies: pathogenesis, diagnosis, strategies, therapies, and future research directions. *J Child Neurol* 2003;18:578–590.

Marotti JD, Tobias S, Fratkin JD, et al. Adult onset leukodystrophy with neuroaxonal spheroids and pigmented glia: report of a family, historical perspective, and review of the literature. *Acta Neuropathol (Berl)* 2004;107:481–488.

Schiffmann R, Boespflug-Tanguy O. An update on the leukodystrophies. *Curr Opin Neurol* 2001;14:789–794.

Schiffmann R, van der Knaap MS. Invited article: an MRI-based approach to the diagnosis of white matter disorders. *Neurology* 2009;72(8):750–759.

Solders G, Celsing G, Hagenfeldt L, et al. Improved peripheral nerve conduction, EEG and verbal IQ after bone marrow transplantation for adult metachromatic leukodystrophy. *Bone Marrow Transplant* 1998;22:1119–1122.

Steenweg ME, Vanderver A, Blaser S, et al. Magnetic resonance imaging pattern recognition in hypomyelinating disorders. *Brain* 2010;133(10):2971–2982.

Sundal C, Van Gerpen JA, Nicholson AM, Wider C, Shuster EA, Aasly J, Spina S et al. MRI characteristics and scoring in HDLS due to CSF1R gene mutations. *Neurology* 2012c;79:566–74.

Suzuki K, Armao D, Stone JA, et al. Demyelinating diseases, leukodystrophies, and other myelin disorders. *Neuroimaging Clin N Am* 2001;11:15–35.

Tian R, Wu X, Hagemann TL, et al. Alexander disease mutant glial fibrillary acidic protein compromises glutamate transport in astrocytes. *J Neuropathol Exp Neurol* 2010;69:335–45.

Van Gerpen JA, Wider C, Broderick DF, et al. Insights into the dynamics of hereditary diffuse leukoencephalopathy with axonal spheroids. *Neurology* 2008;71:925–9.

Wider C, Van Gerpen JA, Dearmond S, et al. Leukoencephalopathy with spheroids (HDLS) and pigmentary leukodystrophy (POLD): a single entity? *Neurology* 2009;72:1953–9.

Authors

- Vitalie Văcăraș, Department of Neurosciences, “Iuliu Hațieganu” University of Medicine and Pharmacy, 43 Victor Babes Street, 400012, Cluj-Napoca, Cluj, Romania, EU, email: vvacaras@umfcluj.ro
- Zoltán Z. Major, Department of Functional Sciences, “Iuliu Hațieganu” University of Medicine and Pharmacy, 23 Gheorghe Marinescu Street, 400337, Cluj-Napoca, Cluj, Romania, EU, email: zoltan.major@eeg-emg.ro
- Emilia Mariș, Department of Neurosciences, “Iuliu Hațieganu” University of Medicine and Pharmacy, 43 Victor Babes Street, 400012, Cluj-Napoca, Cluj, Romania, EU, email: maris_emilia@yahoo.com
- Kinga A. Major, Cluj County Emergency Hospital, ICU, 3-5 Clinicilor Street, 400006, Cluj-Napoca, Cluj, Romania, EU, email: majorkinga@yahoo.com
- Buzoianu Anca Dana – Department of Functional Sciences, Iuliu Hațieganu” University of Medicine and Pharmacy, 23 Gheorghe Marinescu Street, 400337, Cluj-Napoca, Cluj, Romania, EU, email: abuzoianu@umfcluj.ro

Citation Văcăraş V, Major ZZ, Mariş E, Major KA, Buzoianu AD. A stepwise approach to adult-onset leukodystrophy. *HVM Bioflux* 2015;7(3):191-196.

Editor Stefan C. Vesa

Received 10 May 2015

Accepted 23 May 2015

Published Online 12 July 2015

Funding This paper was published under the frame of European Social Fund, Human Resources Development Operational Programme 2007-2013, project no. POSDRU/159/1.5/138776.

**Conflicts/
Competing
Interests** None reported