



**European
Reference
Network**

for rare or low prevalence
complex diseases



Network

Neurological Diseases
(ERN-RND)

Diagnostic flowcharts for Leukodystrophies

Introduction to the European Reference Network for Rare Neurological Diseases (ERN-RND):

ERN-RND is a European Reference Network established and approved by the European Union. ERN-RND is a healthcare infrastructure which focuses on rare neurological diseases (RND). The three main pillars of ERN-RND are (i) network of experts and expertise centres, (ii) generation, pooling and dissemination of RND knowledge, and (iii) implementation of e-health to allow the expertise to travel instead of patients and families.

ERN-RND unites 32 of Europe's leading expert centres in 13 Member States and includes highly active patient organizations. Centres are located in Belgium, Bulgaria, Czech Republic, France, Germany, Hungary, Italy, Lithuania, Netherlands, Poland, Slovenia, Spain and the UK.

The following disease groups are covered by ERN-RND:

- Ataxias and Hereditary Spastic Paraplegias
- Atypical Parkinsonism and genetic Parkinsons' Disease
- Dystonia, Paroxysmal Disorder and Neurodegeneration with Brain Ion Accumulation
- Frontotemporal Dementia
- Huntingtons' Disease and other Chorea
- Leukodystrophies

Specific information about the network, the expert centres and the diseases covered can be found at the networks web site www.ern-rnd.eu.

Recommendation for clinical use:

The European Reference Network for Rare Neurological Diseases developed the Diagnostic Flowcharts for Leukodystrophies to help guide the diagnosis of Leukodystrophy patients. The Reference Network recommends the use of these Diagnostic Flowcharts.



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METHODOLOGY

The development of the Diagnostic Flowcharts for Dystonia was done by the Disease group for Leukodystrophies of ERN-RND.

Disease group for Leukodystrophies:

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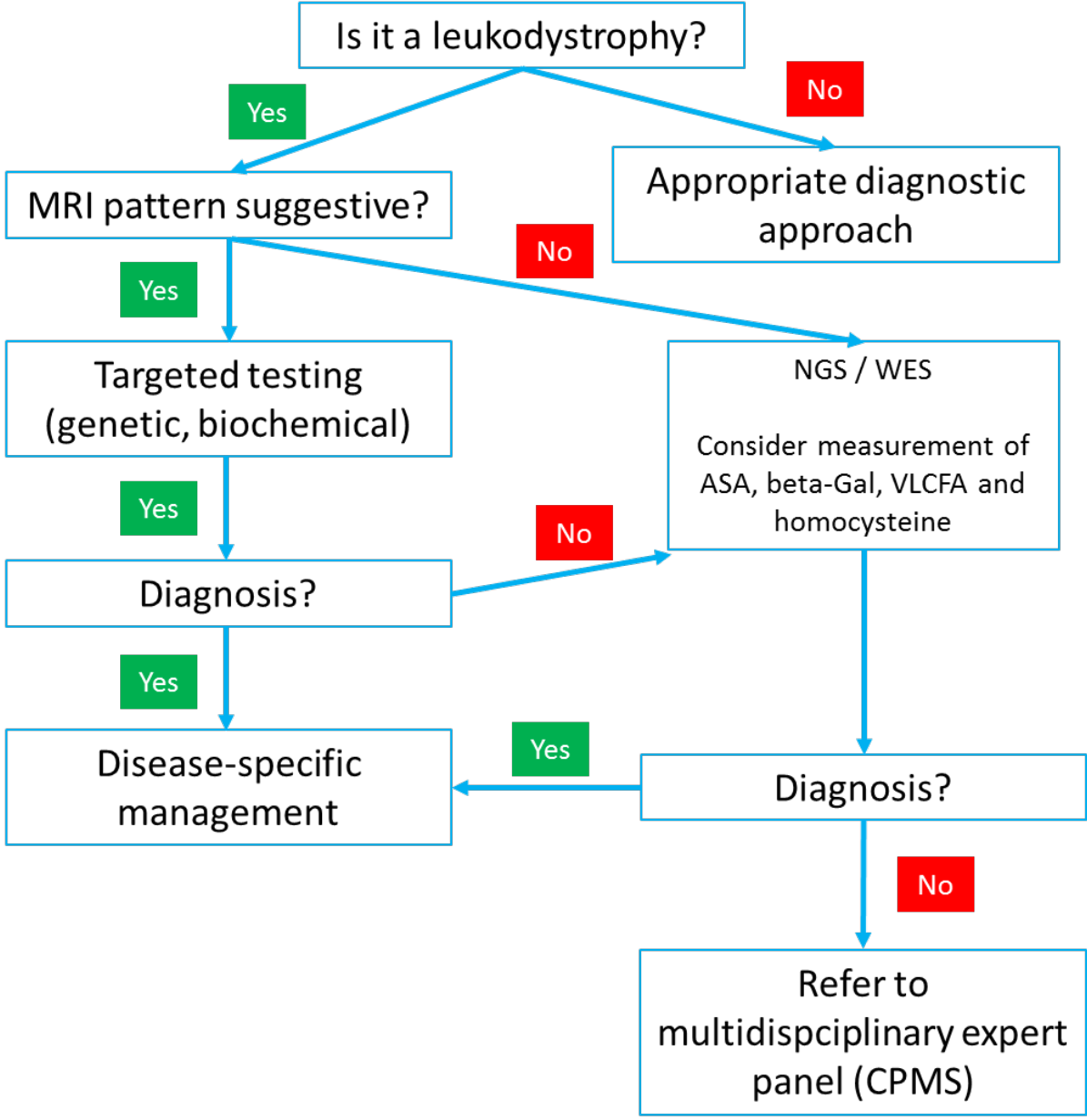
Groningen, Netherlands; ⁵ AOU Siena, Italy; ⁶ Semmelweis University, Hungary; ⁷ Klinikum der Universität München, Germany; ⁸ Foundation IRCCS neurological institute Carlo Besta – Milan, Italy; ⁹ VU University Medical Center Amsterdam, Netherlands.

Flowchart development process:

- Development of flowcharts – June 2017– June 2018
- Discussion/Revision in ERN-RND disease group during ERN-RND annual meeting 2018 – 08/06/2018
- Consent on document by whole disease group – 02/10/2018



Diagnostic flowchart for Leukodystrophies



A guide to pattern recognition in leukodystrophies

(adapted from Schiffmann and van der Knaap 2009)

Prominent T₂-hyperintensity and prominent T₁-hypointensity relative to gray matter structures -
pathologies other than hypomyelination (demyelination and others)

May be CONFLUENT

Diffuse Cerebral	Periventricular Predominance	Subcortical Predominance	Large Asymmetric Lesions	Cerebellum + Middle Cerebellar Peduncles Predominance or Prominence	Brain stem Predominance or Prominence	Frontal Predominance	Parieto-occipital Predominance	Temporal Predominance
<p>MLC eIF-2B-related disorder</p> <p>Laminin alpha-2 deficiency</p> <p>Some mitochondrial defects</p> <p>Inborn errors of metabolism including:</p> <p>Molybdenum cofactor deficiency, Glutaric aciduria II, Dihydropterine reductase deficiency, Disorders of branched chain amino acids, Homocystinuria</p> <p>Early-onset peroxisomal disorders</p> <p>End stage of all progressive white matter disease</p>	<p>Metachromatic leukodystrophy*</p> <p>Krabbe disease*</p> <p>LBSL*</p> <p>*spares arcuate fibers</p> <p>Sjogren Larsson syndrome</p> <p>APBD</p> <p>ODDD</p> <p>Inborn errors of metabolism including:</p> <p>Phenylketonuria, FA2H-related disorders, Adenylosuccinate lyase deficiency, Glutaric aciduria type II, Mucopolysaccharidosis</p> <p>Later-onset neurodegenerative disorders, including:</p> <p>Neuronal ceroid-lipofuscinosis, Niemann Pick C (NB: often early cerebral atrophy)</p> <p>Acquired disorders, including:</p> <p>Periventricular leukomalacia, HIV related encephalopathy</p>	<p>L2-hydroxyglutaric aciduria</p> <p>Canavan disease</p> <p>Kearns-Sayre syndrome</p> <p>Propionic acidemia</p> <p>Urea cycle defects</p> <p>Ribose-5-phosphate isomerase deficiency</p> <p>LTBL</p>	<p>HDLS</p> <p>L2-hydroxyglutaric aciduria</p> <p>CRMCC</p> <p>Mitochondrial diseases</p> <p>Most infectious and inflammatory disorders</p> <p>Inborn errors of metabolism (e.g., urea cycle disorders)</p>	<p>CTX</p> <p>Peroxisomal disorders</p> <p>Alexander disease</p> <p>LBSL</p> <p>ADLD</p> <p>Histiocytosis</p> <p>Early-onset maple syrup urine disease</p> <p>Premutation fragile X syndrome</p> <p>Heroin and cocaine toxicity</p> <p>FA2H-related disorders (atrophy)</p> <p>Mitochondrial leukoencephalopathies</p>	<p>LBSL</p> <p>LTBL</p> <p>HBSL</p> <p>ADLD</p> <p>Peroxisomal disorders</p> <p>APBD</p> <p>Wilson disease</p> <p>Alexander disease</p> <p>Leigh syndrome</p> <p>DRPLA</p> <p>Mitochondrial leukoencephalopathies</p>	<p>Alexander disease</p> <p>Metachromatic leukodystrophy</p> <p>Frontal variant of X-ALD</p> <p>HDLS</p> <p>Aicardi-Goutières syndrome</p> <p>Laminin alpha-2 deficiency</p>	<p>Krabbe disease</p> <p>X-ALD</p> <p>Early-onset peroxisomal disorders</p> <p>Neonatal hypoglycemia</p> <p>APBD</p>	<p>Menkes disease</p> <p>Herpes simplex encephalitis</p> <p>Aicardi-Goutières syndrome</p> <p>Congenital CMV</p> <p>RNAse T2 deficiency</p>

Or may be MULTIFOCAL

Progressive (may evolve to confluency)	Static	Prominent Perivascular Spaces
<p>HDLS</p> <p>APBD</p> <p>L2-hydroxyglutaric aciduria</p> <p>LBSL, HBSL</p> <p>Urea cycle disorders</p> <p>HMG-CoA lyase deficiency</p> <p>Histiocytosis</p> <p>Incontinentia pigmenti</p> <p>Vasculopathies (CADASIL, CARASIL, Fabry, Susac syndrome, arteriolosclerosis, vasculitis)</p> <p>Multiple sclerosis</p> <p>Neuromyelitis optica</p> <p>Acute disseminated encephalomyelitis</p> <p>Progressive multifocal leukoencephalopathy</p> <p>Mitochondrial diseases</p> <p>Subacute sclerosing panencephalitis</p>	<p>18q minus syndrome</p> <p>Sjogren Larsson syndrome</p> <p>RNAse T2-deficient leukoencephalopathy</p> <p>Congenital CMV</p>	<p>Mucopolysaccharidoses</p> <p>Chromosomal abnormalities or genetic mosaicism</p> <p>Lowe syndrome</p> <p>PTEN-associated disorders</p> <p>Histiocytosis</p> <p>Disorders of branched chain amino acids</p>

Legend

APBD: Adult polyglucosan body disease
 ADLD: Autosomal dominant leukodystrophy with autonomic symptoms
 CRMCC: Cerebroretinal microangiopathy with calcifications and cysts
 CTX: Cerebrotendinous Xanthomatosis
 DRPLA: Dentatorubro-pallidolysian atrophy
 EIF2B-related disorder: Vanishing white matter disease or CACH
 HDLS: Hereditary diffuse leukoencephalopathy with spheroids/ Neuroaxonal leukodystrophy with spheroids
 HBSL: Hypomyelination with brain stem and spinal cord and leg involvement
 LTBL: Leukoencephalopathy with thalamic and brain stem involvement and high lactate
 LBSL: Leukoencephalopathy with brain stem and spinal cord involvement and lactate elevation
 MLC: Megalencephalic leukodystrophy with subcortical cysts
 ODDD: Oculodentodigital dysplasia
 X-ALD: X-linked adrenoleukodystrophy

Prominent T₂-hyperintensity and prominent T₁-hypointensity relative to gray matter structures -
pathologies other than hypomyelination (demyelination and others)

May be CONFLUENT

Diffuse Cerebral	Periventricular Predominance	Subcortical Predominance	Large Asymmetric Lesions	Cerebellum + Middle Cerebellar Peduncles Predominance or Prominence	Brain stem Predominance or Prominence	Frontal Predominance	Parieto-occipital Predominance	Temporal Predominance





References:

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

