GeNeViSTA

An approach to genetic disorders affecting the white matter

Vijayalakshmi SR and Prajnya Ranganath

Department of Medical Genetics, Nizam's Institute of Medical Sciences, Hyderabad, Telangana, India

Email: prajnyaranganath@gmail.com

Introduction

The white matter lies beneath the gray matter and consists of millions of nerve fibre bundles (axons) that serve as functional circuits linking different regions of the brain. White matter forms the bulk of the deep parts of the brain and the superficial parts of the spinal cord. Aggregates of gray matter are spread within the cerebral white matter. The gray matter is primarily associated with cognition and processing, while the white matter serves to conduct the action potentials and coordinate communication between different brain regions. Genetic disorders affecting the white matter of the brain are heterogeneous with variable and overlapping phenotypes. There is an ongoing process for classification of these disorders based on the genetic, histopathology and the neuroimaging pattern observed in these disorders. Few of the recent consensus definitions are as follows:

- Leukodystrophy: (Greek: leukos (white), dys – (disturbance), trophê (nutrient)-defective nutrition) refers to a group of genetic disorders primarily affecting the white matter with or without peripheral nervous system involvement. They are characterised by glial cell or myelin sheath abnormalities with magnetic resonance imaging (MRI) showing a hyperintense T2 signal in the affected white matter and a variable T1 signal (Vanderver A et al., 2015).

- Leukoencephalopathy: though often used interchangeably with leukodystrophy, actually refers to genetic or acquired disorders which have white matter changes comparable to that found in leukodystrophies, but primarily have either neuronal, vascular or systemic involvement with myelin involvement occurring as a secondary event (Vanderver A et al., 2015).

- Genetic leukoencephalopathies: have been defined as heritable white matter abnormalities which do not meet the criteria of being a leukodystrophy. Hence, all leukodystrophies are genetic encepahlopathies but not all genetic leukoencephalopathies are leukodystrophies.

Myelin and myelination

The myelin sheath, a modified plasma membrane extension of the oligodendroglial cells, spirals around the axons and encases it throughout its length except at the nodes of Ranvier. Myelin sheaths act as insulation sheaths and serve to transmit action potentials by saltatory conduction which is fast and energy efficient. Myelin also provides trophic support and protection for axons. Disturbances in myelin therefore result in motor, sensory and cognitive impairment.

Myelin is made up of an outer layer of glycolipid (galactocerebroside and sulfatide) and cholesterol, an inner phospholipid layer (phosphoinositol serine, phosphoinositol 4,5,diphosphate and ethanolamine plasmalogen) and an intervening area of hydrocarbon chains (long chain fatty acids). In addition, there are structural proteins namely the myelin basic protein (MBP) and the proteolipid protein (PLP) which maintain myelin structure and stability, the myelin-associated glycoprotein (MAG) which is essential for initiation of myelination by mediating axonal-glial contact, and myelin zero protein (MZP), myelin oligodendrocyte glycoprotein (MOP), oligodendrocyte myelin glycoprotein and 2,3-cyclic nucleotide 3-phosphodiesterase (van der Knaap, 2001).

Myelination begins as early as the 12th week of intrauterine life and occurs significantly from mid-gestation to the second year of postnatal life. Myelination is a high energy requiring process. Initiation of myelin and its maintenance is regulated by the availability of glycolytic and lipid substrates. Abnormalities of myelination can be in the form of failure of myelin formation (hypomyelination), for-

mation of abnormal myelin (dysmyelination) and loss of formed myelin (demyelination).

Classification of myelin disorders

There are various classifications of myelin disorders (based on pathological, biochemical, genetic and combined clinical/ histopathological/ biochemical criteria). As per the classification proposed by van der Knaap for myelin disorders, integrating the MRI pattern and pathophysiology (van der Knaap, 2001), all white matter disorders have been included under the umbrella term of leukoencephalopathies and these have been categorized as:

- Well defined leukoencephalopathies
- Undefined leukoencephalopathies

Under this classification, well defined leukoencephalopathies have been further subdivided into categories as listed in Table 1 (Di Rocco et al., 2004).

As per the recent GLIA (Global Leukodystrophy Initiative) Consortium consensus statement, more than 30 distinct leukodystrophy conditions have been characterized, which are listed below in the alphabetical order in Table 2 (Vanderver A et al., 2015).

Table 1 Types of well defined leukoencephalopathies.

Type of well defined leukoencephalopathy	Underlying pathophysiology	Examples
Hypomyelinating disorders	Primary disturbance in the formation of myelin	• Pelizaeus- Merzbacher (PMD) and PMD-like diseases
	Secondary to neuron or astrocyte dysfunction (including abnormal interaction between oligodendrocytes and neurons)	• Cockayne syndrome • Tay syndrome • Salla disease • GM1 and GM2 gangliosidoses • Infantile neuronal ceroid lipofuscinosis • Hypomyelination with atrophy of the basal ganglia and cerebellum (HABC) syndrome
Dysmyelinating disorders (Delayed or disturbed myelination)	• Altered sequence of myelination • Irregular pattern of myelination • Additional component of hypomyelination observed	• 18q minus syndrome • Untreated aminoacidopathies • Organic acidurias
Demyelinating disorders (leukodystrophies)	• Abnormal myelin composition • Myelin instability and subsequent loss (demyelination)	• Metachromatic leukodystrophy (reduction of cerebroside and accumulation of sulphatides which is toxic to oligodendroctyes) • X-linked Adrenoleukodystrophy (ALD) (dysfunction of microglia-inflammatory response; incorporation of very long chain fatty acids in myelin leads to membrane instability) • Krabbe disease (accumulation of cerebroside and toxic metabolite psychosine leads to oligodendrocyte death) • Peroxisomal disorders such as Zellweger syndrome, neonatal ALD and Refsum disease. (decrease in myelin substrates)

Disorders related to myelin splitting (cystic degeneration of myelin)	With myelin loss	• Canavan disease (accumulation of N-acetyl aspartate and precursor N-acetylaspartlyglutamate leads to intramyelinic edema, vacuolization and oligodendrocyte failure) • Mitochondrial disorders • 1,2-hydroxyglutaric aciduria
	Without myelin loss	• Megalencephalic leukoencephalopathy with subcortical cysts
Disorders secondary to axonal damage		• Giant axonal neuropathy
Others		• Alexander disease (primary genetic disorder of astrocytes) • Childhood ataxia with central nervous system hypomyelination (CACH) • Sjogren-Larsson syndrome • Cerebrotendinous xanthomatosis • Leukodystrophy with polyol metabolism abnormality

Table 2 Different types of leukodystrophies with the causative genes and modes of inheritance.

Disorder	Gene(s)	Pattern of inheritance
Adrenoleukodystrophy X linked (X-ALD)	• *ABCD1*	XL
Adult onset leukodystrophy with neuroaxonal spheroids and pigmented glia (ALSP): • Hereditary diffuse leukoencephalopathy with spheroids (HDLS) • Pigmentary type of orthochromatic leukodystrophy with pigmented glia (POLD)	• *CSF1R*	AD
Aicardi– Goutières Syndrome (AGS)	• *ADAR1* • *RNASEH2A* • *RNASEH2B* • *RNASEH2C* • *SAMHD1* • *TREX1*	Usually AR but maybe AD
Alexander disease (AxD)	• *GFAB*	AD
Autosomal Dominant Leukodystrophy with Autonomic disease (ADLD)	• *LMNB1*	AD
Canavan disease	• *ASPA*	AR
Cerebrotendinous Xanthomatosis (CTX)	• *CYP27A1*	AR
Chloride Ion Channel 2 (ClC-2) related leukoencephalopathy with intramyelinic oedema (leukoencephalopathy with ataxia)	• *CLCN2*	AR

eIF2B-related disorders (Vanishing White Matter Disease (VWMD) or Childhood ataxia with central nervous system hypomyelination (CACH))	• *EIF2B1* • *EIF2B2* • *EIF2B3* • *EIF2B4* • *EIF2B5*	AR
Fucosidosis	• *FUCA1*	AR
Globoid cell Leukodystrophy (Krabbe)	• *GALC* • *PSAP*	AR
Hypomyelination with atrophy of the basal ganglia and cerebellum (H-ABC)	• *TUBB4A*	AD
Hypomyelination with brainstem and spinal cord involvement and leg spasticity (HBSL)	• *DARS*	AR
Hypomyelination with congenital cataract (HCC)	• *FAM126A*	AR
Leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation (LBSL)	• *DARS2*	AR
Leukoencephalopathy with thalamus and brainstem involvement and high lactate (LTBL)	• *EARS2*	AR
Megalencephalic Leukoencephalopathy with subcortical cysts (MLC)	• *MLC1* • *HEPACAM*	AR
Metachromatic leukodystrophy (MLD) and its biochemical variants	• *ARSA* • *PSAP*	AR
Oculodentodigital dysplasia (ODDD)	• *GJA1*	Usually AD maybe AR
Pelizaeus Merzbacher disease (PMD)	• *PLP1*	XL
Pelizaeus Merzbacher like-disease (PMLD)	• *GJC2*	AR
Peroxisomal Biogenesis disorders (including Zelleweger, neonatal Adrenoleukodystrophy and Infantile Refsum)	• *PEX* genes	AR
Pol-III related disorders (4H syndrome - hypomyelination, hypodontia and hypogonadotropic hypogonadism)	• *POLR3A* • *POLR3B*	AR
Polyglucosan Body Disease (PGBD)	• *GBE1*	AR
RNAse T2 deficient leukoencephalopathy	• *RNASET2*	AR
Sialic acid storage disorders (Salla disease, Infantile sialic acid storage disease and Intermediate form)	• *SLC17A5*	AR
Single enzyme deficiencies of peroxisomal fatty acid beta oxidation: • D-Bifunctional Protein Deficiency • Sterol Carrier Protein X (SCPx) deficiency • Peroxisomal acyl-CoA-Oxidase Deficiency	 • *HSD17B4* • *SCP2* • *ACOX1*	AR
Sjögren–Larsson syndrome	• *ALDH3A2*	AR
SOX10-associated PCWH - peripheral demyelinating neuropathy, central dysmyelinating leukodystrophy, Waardenburg syndrome and Hirschsprung disease	• *SOX10*	AD
18q minus syndrome	• Contiguous gene deletion involving the *MBP* gene	Majority are de novo; deletion can be inherited

AD = autosomal dominant; AR = autosomal recessive; XL = X-linked

Leukoencephalopathies include inherited vasculopathies (eg. Cerebral Autosomal-Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL) and *COLA1* & *COLA2*-related disorders), inborn errors of metabolism (e.g. organic acidemias and disorders of aminoacid metabolism), disorders affecting the neurons of the cerebral cortex or other gray matter structures (e.g. infantile variants of GM1 and GM2 gangliosidosis and neuronal ceroid lipofuscinosis), those with both white and gray matter involvement (e.g. mitochondriopathies such as Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) and Myoclonic Epilepsy with Ragged-Red Fibers (MERRF) syndromes, POLG-related disorders and familial hemophagocytic lymphohistiocytosis) and acquired myelin disorders (eg. multiple sclerosis) which may be of infectious or post infectious etiology or due to toxic, hypoxic or non-genetic vascular insults.

Prevalence

There is limited data on the overall prevalence of leukodystrophies and the relative frequencies of different leukodystrophies. Metachromatic leukodystrophy is reported to occur in 1 in 40,000 to 170,000 individuals world-wide (von Figura et al., 2001). Ethnic preponderance has been reported in some leukodystrophies. Canavan disease is relatively common with a high carrier frequency in the Ashkenazi Jewish population. Two common mutations (E285A and Y231X) accounting for 98% of the disease-causing alleles of the *ASPA* gene (Sistermans et al., 2001). Megalencephalic leukodystrophy with subcortical cysts (MLC) is a common leukodystrophy described in the Agarwal community in India and in a study by Gorospe et al (2004) all 31 cases tested were found to result from a common mutation (320insC) in the MLC1 gene, suggesting a founder effect in this population (Gorospe et al. 2004).

Evaluation of leukodystrophies and genetic leukoencephalopathies

The clinical diagnosis of leukodystrophies and genetic leukoencephalopathies is often challenging due to considerable overlap in the clinical features. Though the advances in recognition of the neuroimaging patterns of these disorders has improved the diagnostic yield, more than half of these disorders still remain undiagnosed.

Clinical features

The clinical features are predominantly neurologic and almost invariably affect the motor system and are progressive in nature. Extra neurologic features provide vital clues to arrive at a specific diagnosis.

Age of onset

The onset of the symptoms is variable ranging from connatal (at birth) to adulthood (Table 3) and most of these disorders present with variable severity across all age groups.

Neurologic manifestations

- Motor impairment: Motor symptoms are the predominant presenting feature in majority of the white matter disorders, while cognitive decline (personality changes and dementia) and seizures are the initial manifestations in neuronal (gray matter) disorders. These caveats may not be applicable in all cases as many disorders with primary gray matter involvement may also affect the white matter due the underlying pathology, leading to a clinical dilemma.

A variable period of normal development followed by regression is the most common presentation. The pattern of motor regression may vary in each condition (Table 4). They may also present with delayed or stagnated development in some cases.

Hypomyelinating conditions usually present as developmental delay, while genetic leukoencephalopathies are characterised by a period of normal development followed by stagnation i.e. no further acquisition of skills. Older children and adults may report frequent falls, altered gait or difficulty in sporting activities.

Spasticity and hypereflexia are characteristic signs in majority of the white matter disorders. There may be an initial hypotonia which invariably progresses to spasticity. Severe hypotonia with head lag is a feature of Canavan disease. A hypotonic infant with facial dysmorphism, seizures, dolichocephaly and a wide open anterior fontanelle may suggest Zellweger syndrome. Spasticity with diminished deep tendon reflexes occurs when the peripheral nervous system is involved as in Metachromatic leukodystrophy(MLD), Krabbe and other hypomeylinating conditions such as with *PLP*-null mutations.

Table 3 Age of onset of common leukodystrophies.

Disorder	Infantile (first year)	Late infantile (1-5yrs)	Juvenile (5-12yrs)	Adolescent and adulthood
Metachromatic leukodystrophy (MLD)		√ (most common type of MLD)	√	√
Pelizaeus Merzbacher Disease	√	√ (classic form)		
Krabbe disease	√ (classic form)	√	√	√
Alexander disease	√ (most common variant)	√	√	√
Canavan disease	√			
X-linked adrenoleukodystrophy			√	√
Childhood ataxia with central nervous system hypomyelination (CACH)	√	√	√	√
Megalencephalic Leukoencephalopathy with subcortical cysts (MLC)	√	√	√	√
Aicardi–Goutières Syndrome (AGS)	√			
Giant axonal neuropathy type I		√		
Hypomyelination with atrophy of the basal ganglia and cerebellum (H-ABC)	√	√		
Leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation (LBSL)		√	√	√

Table 4 Pattern of motor regression.

Gradual progressive decline	• Majority of leukodystrophies • Megalencephalic leukoencephalopathy with subcortical cysts (MLC)
Rapid decline	• Infantile Krabbe
Episodic decline (triggers may be an event of minor head trauma or febrile illness)	• Childhood ataxia with central nervous system hypomyelination (CACH)/Vanishing white matter disease • Inborn errors of metabolism • Mitochondrial disorders • Pol III related disorders • X-linked adrenoleukodystrophy

• Ataxia: Ataxia, a feature of cerebellar involvement, may occur as an isolated finding, as a predominant finding e.g. Childhood ataxia with central nervous system hypomyelination (CACH) and 4H syndrome (hypomyelination, hypodontia and hypogonadotropic hypogonadism) or in association with predominant spasticity. Sensory ataxia may be present due to impaired proprioception in

peripheral sensory system involvement.

- Extrapyramidal symptoms: Extrapyramidal symptoms appear with involvement of the deep gray nuclei and are seen in 1,2 hydroxyglutaric aciduria. Choreoathetosis is a feature of the classic form of Pelizaeus-Merzbacher disease. Dystonia, when it occurs, is usually generalised and appears as repetitive movements, torsion or abnormal posturing, which may be exacerbated by voluntary movements, emotions and physical discomfort.

- Cognitive impairment: Cognitive decline inevitably appears in the course of the disease, although the nature and severity varies. It presents as intellectual disability in childhood, or as dementia and psychiatric features in adult onset leukodystrophies. Cognitive decline can be rapid in X-ALD and lysosomal storage leukodystrophies. Relative sparing of the mental abilities is seen in MLC and CACH. Irritability is a feature of Krabbe, Canavan and Aicardi–Goutières syndromes.

- Seizures: Seizures usually occur in the more advanced stage of the disease, but may be the presenting feature of Alexander disease or may occur early in the course in Canavan, Krabbe, Cerebrotendinous Xanthomatosis (CTX), Leukoencephalopathy with thalamus and brainstem involvement and high lactate (LTBL), Metachromatic leukodystrophy (MLD), Oculodentodigital dysplasia (ODDD), Megalencephalic leukoencephalopathy with subcortical cysts (MLC), peroxisomal disorders, sialic acid storage disorders and Sjogren Larsson syndrome. An acute onset with focal seizures may be seen in childhood onset X-ALD. Impact seizures (following minor head trauma) are seen in MLC.

- Autonomic dysfunction: Autonomic dysfunction causes bladder (retention, incontinence), bowel (constipation/ incontinence), cardiac (arrhythmias), vascular (postural hypotension) and thermoregulatory (decreased sweating) symptoms. It is a prominent feature of adult onset or adolescent phenotypes of Alexander disease, Autosomal dominant leukodystrophy with autonomic disease (ADLD) and MLD, and can affect younger patients late in the disease.

- Others: Progressive loss may appear in speech, ability to eat (swallowing, chewing), vision and hearing as the disease advances. Deafness can occur early in mitochondrial disorders and 18q deletion syndrome. Bulbar dysfunction (palatal myoclonus and dysphonia) is unique to Alexander disease. Macro or microcephaly may be a feature of the different leukodystrophy conditions, as listed below in Table 5.

Extraneurologic manifestations

Associated extraneurologic features provide additional clues to the diagnosis. They are summarised in the following table (Table 6).

Table 5 Diagnostic clues from head circumference.

Macrocephaly
• Alexander disease- head circumference exceeds 98th centile at 6 to 18 months; obstructive hydrocephalus may be present
• Canavan disease- occurs by the first year of life; normal head size is described in some variants
• Childhood ataxia with central nervous system hypomyelination (CACH) -megalencephaly
• Megalencephalic leukoencephalopathy with subcortical cysts - megalencephaly
• 1,2-hydroxy glutaric aciduria - relative macrocephaly which is usually an inconsistent feature
• GM2 gangliosidosis - infantile Tay-Sachs and Sandhoff
Microcephaly
• Krabbe syndrome
• Cockayne syndrome
• Tay (Trichothiodystrophy) syndrome

Table 6 Extraneurologic manifestations of leukodystrophies and genetic leukoencephalopathies.

Clinical feature		Disorder
Facies		
Dysmorphism		18q microdeletion Peroxisomal disorders Cohen syndrome Costello syndrome
Coarse facies		Sialic acid storage disease, Fucosidosis, Multiple sulfatase deficiency, Mucopolysaccharidosis
Progeroid appearance		Cockayne syndrome
Dental anomalies		
Dental anomalies		Oculodentodigital dysplasia (enamel hypoplasia)
		POL III related disorders (not universal and highly variable-oligodontia, hypodontia, delayed eruption, altered sequence of eruption, abnormal colour /shape)
		Cockayne syndrome (propensity for cavities (most common), abnormal shape, hypodontia, oligodontia and enamel hypoplasia)
		Peroxisomal disorders (enamel defects of secondary teeth)
Eyes		
Cataracts	At birth	Hypomyelination with congenital cataract (HCC), Childhood ataxia with central nervous system hypomyelination (CACH) (only connatal cases), peroxisomal disorders
	Childhood onset	Cerebrotendinous Xanthomatosis
Cherry red spot		Sialidosis GM1 gangliosidosis GM2 gangliosidosis (helps differentiate from other disorders with infantile onset macrocephaly) Metachromatic leukodystrophy (some cases)
Glaucoma		Aicardi–Goutières Syndrome, Oculodentodigital dysplasia
Optic atrophy		Metachromatic leukodystrophy Canavan, Childhood ataxia with central nervous system hypomyelination (CACH), Cerebrotendinous xanthomatosis, peroxisomal disorders (+/-), Pol III related (+/-) Hypomyelinating and mitochondrial disorders
Retinitis pigmentosa (night blindness)		Refsum disease (adolescent and adults) Peroxisomal disorders
Vascular retinal defects		Cerebroretinal microangiopathy with calcifications and cysts (Coats plus syndrome)
Glistening white dots in the retina (perifoveal)		Sjogren Larsson syndrome (pathognomonic in a patient with ichthyosis)
Nystagmus	Early onset/ congenital	PMD & PMLD (prominent feature) SOX10 related disease
	Later age	Oculodentodigital dysplasia, Pol III related 4H syndrome - hypomyelination, hypodontia and hypogonadotropic hypogonadism),18q del, Alexander, Canavan

Skin manifestations		
Angiokeratoma corporis diffusum		Fucosidosis
Icthyosis	Congenital	Sjogren Larsson syndrome
	Childhood	Multiple sulfatase deficiency Sialic acid storage disorder
	Adulthood	Refsum disease
Hyperpigmentation		X-ALD/AMN [Figure 1]
Xanthomas		Cerebrotendinous xanthomatosis
Photosensitivity		Cockayne, Tay syndrome
Chilblains		Aicardi– Goutières Syndrome
Endocrinologic manifestations		
Adrenal insufficiency		X-ALD, peroxisome biogenesis disorders
Hypothyroidism		4H syndrome - hypomyelination, hypodontia and hypogonadotropic hypogonadism), Aicardi– Goutières Syndrome
Hypogonadotropic hypogonadism		4H syndrome - hypomyelination, hypodontia and hypogonadotropic hypogonadism)
Ovarian dysgenesis (Premature ovarian failure)		Ovarioleukodystrophy (CACH), *AARS2* mutation-related
Hepatobiliary manifestations		
Hepatosplenomegaly		Lysosomal storage disorders's, (multiple sulfatase deficiency, galactosialidosis, sialic acid disorders)
Hepatic dysfunction		Peroxisomal disorders (isolated hepatomegaly +/- hepatic dysfunction) Aicardi– Goutières Syndrome (congenital period, rarely in infancy) Mitochondriopathies
Gall bladder dysfunction		MLD (causes gall bladder papillomatosis) Cerbrotendinous xanthomatosis (can present as neonatal jaundice)
Skeletal system		
Chondrodysplasia punctata		Peroxisomal disorders
Dysostosis multiplex		Multiple sulfatase deficiency, sialidosis
Short stature		Cockayne syndrome, 4H leukodystrophy
Hearing deficit		
Hearing impairment (Commonly central origin-sensorineural)		Peroxisomal biogenesis disorders (early onset) SOX 10 associated LD (early onset) RNAseT2 deficiency Refsum disease (adult onset)

Diagnostic workup

• Neuroimaging: MRI pattern recognition is an important step in the further workup towards a specific diagnosis of white matter disorders. Myelin assessment by MRI with associated features can provide clues to a differential diagnosis. In general, myelinated white matter is hyperintense to the cortex on T1-weighted images and hypointense to the cortex on T2-weighted images. This pattern is

reversed in demeylination with the white matter demonstrating T1 hypointensity and T2 hyperintensity relative to the cortex. While T1 weighted images are most useful for assessing myelination until the first year of life, T2-weighted images are most useful in later stages of myelination. A high signal on T2-weighted images is abnormal for cerebral white matter after 1.5 years. Furthermore, knowledge of the sequential pattern of myelination is essential for distingushing abnormal and normal patterns of myelination.

The minimum sequences recommended are (Parikh et al., 2015):

- Sagittal T1
- Axial T1
- T2 weighted
- Fluid attenuated inversion recovery (FLAIR) (Cystic lesions are best detected using FLAIR studies)

Figure 1 Generalised skin hyperpigmentation in a patient with juvenile onset X -linked adrenoleukodystrophy (confirmed by plasma VLCFA analysis).

Table 7 Hypomyelination on MRI.

With cerebellar involvement (inconstant)	**Normal corpus callosum** • Hypomyelination with atrophy of the basal ganglia and cerebellum (H-ABC) • Oculodentodigital dysplasia **Thin corpus callosum** • 4H syndrome - hypomyelination, hypodontia and hypogonadotropic hypogonadism) • Salla disease • Fucosidosis • Cockayne • PMD
With basal ganglia involvement	• Hypomyelination with atrophy of the basal ganglia and cerebellum (H-ABC) (atrophy especially putamen) • Oculodentodigital dysplasia • Fucosidosis (globus pallidus) • Mucolipidosis type IV
With absence of cerebral atrophy (or atrophy in late stages) with normal basal ganglia	• 18q del (cerebellar hypoplasia) • Hypomyelination with congenital cataract (HCC) • HEMS (hypomyelination of early myelinating structure) • PMD • PMLD (hypomyelination of brainstem especially pons) • Salla disease • SOX 10 associated disorders
With global atrophy	• Infantile sialic acid storage disorders • Aicardi– Goutières Syndrome (calcifications present)

Other specific sequences include:

- Contrast administration- for disorders with an inflammatory component eg. cerebral X-ALD
- Susceptibility weighted- for disorders with calcifications eg. Aicardi– Goutières Syndrome, Cockayne syndrome (basal ganglia calcifications), Krabbe (calcifications of thalami, basal ganglia and putamen)
- MR spectroscopy (MRS)- lactate peak is seen in mitochondrial disorders and Leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation (LBSL), while a markedly increased N-acetyl aspartate (NAA) peak is typical of Canavan disease.
- Diffusion weighted- for AARS2-related leukoencephalopathy

Serial imaging with an interval of atleast 6-12 months is pertinent to distinguish between permanent hypomyelination and delayed myelination especially in children less than 2 years of age. CT scan is useful for detecting calcifications.

A stepwise approach to recognising the MRI pattern helps in differentiating various white matter disorders (Schiffmann & van der Knaap, 2009). This involves first recognising whether it is hypomyelination or delayed myelination or demyelination.

- Hypomyelination: Hypomyelination on MRI is characterised by mild T2 hyperintensity in combination with T1 hyperintensity (=normal signal), T1-isointensity or mild T1-hypointensity relative to gray matter structures. Table 7 lists the conditions with hypomyelination and additional findings which provide a possible clue to diagnosis.

- Demyelination: Demyelination on MRI is characterised by prominent T2 hyperintensity with prominent T1 hyporintensity relative to gray matter structures. These can be further analysed as to whether they are confluent or isolated and multifocal and further on the area of predominance of the lesion. Confluent and bilateral symmetric lesions are characteristic of genetic white matter disorders while isolated and multifocal are suggestive of acquired causes such as infections and vasculopathies and is also seen in structural chromosomal disorders. Table 8 lists the conditions with confluent lesions and their area of predominance.

- Delayed myelination: Improvement of myelination on serial MRI is suggestive of delayed myelination and can occur in SOX 10 related, MCT8 related and other neuronal disorders.

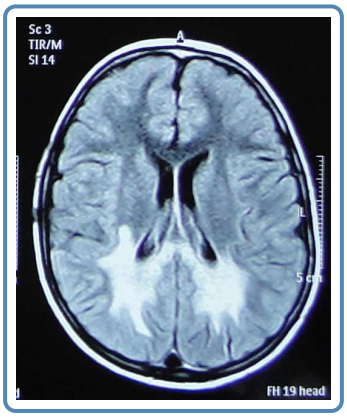

Figure 2 Brain MRI (axial FLAIR image) showing bilateral deep white matter involvement with posterior predominance and sparing of the subcortical U fibers in X-linked adrenoleukodystrophy. (Courtesy: Dr Shubha R Phadke, SGPGIMS, Lucknow)

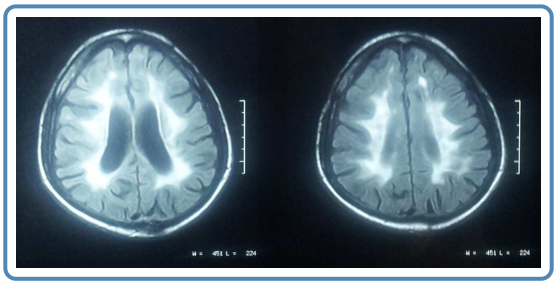

Figure 3 MRI brain (axial FLAIR image) showing periventricular hyperintensities in the frontal and parieto occipital region in metachromatic leukodystrophy.

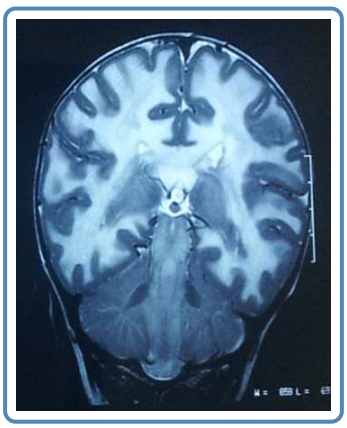

Figure 4 MRI brain (coronal FLAIR image) showing diffuse extensive white matter involvement in Canavan disease.

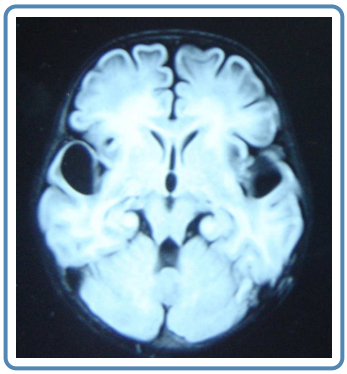

Figure 5 MRI brain (axial FLAIR image) showing diffuse white matter involvement with temporal subcortical cysts in a case of megalencephalic leukoencephalopathy with subcortical cysts (van der Knaap disease).

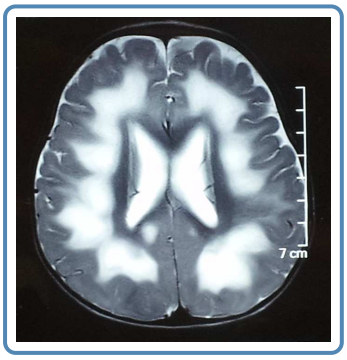

Figure 6 MRI brain (axial T2 image) showing periventricular deep white matter as well as subcortical white matter involvement in a case of Leigh disease.

Table 8 Disorders with MRI features of demyelination and confluent lesions and their area of predominance.

Confluent lesions	
Predominant localization	**Disorder**
Frontal	• Alexander disease • Metachromatic leukodystrophy • Aicardi– Goutières Syndrome • X-ALD (frontal variant) • Hereditary diffuse leukoencephalopathy with spheroids (HDLS)
Pareito-occipital	• X-ALD (involvement of splenium of corpus callosum and sparing of the occipital arcuate fibers) [Figure 2] • Krabbe • Adult Polyglucosan Body Disease (PGBD) • Early onset peroxisomal disorders • Neonatal hypoglycemia
Periventricular	• MLD (sparing of the arcuate fibers) [Figure 3] • Krabbe (sparing of the arcuate fibers) • Leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation (LBSL) (sparing of the arcuate fibers) • Sjogren Larsson syndrome • Adult Polyglucosan Body Disease (PGBD) • Oculodentodigital dysplasia • Inborn errors of metabolism • Periventricular leukomalacia • HIV related encephalopathy
Subcortical	• Canavan [Figure 4] • L2 glutaric aciduria • Propionic acidemia • Urea cycle defects • Ribose 5 phosphate isomerase deficiency

	• Kearns Sayre syndrome • Leukoencephalopathy with thalamus and brainstem involvement and high lactate (LTBL)
Diffuse cerebral	• Childhood ataxia with central nervous system hypomyelination (CACH) / vanishing white matter disease (cystic degeneration of white matter) • Megalencephalic leukoencephalopathy with subcortical cysts (subcortical sycts in the anterior-temporal regions with sparing of central white matter) [Figure 5] • Inborn errors of metabolism • Early onset peroxisomal disorders • Laminin alpha 2 deficiency • Mitochondrial defects [Figure 6] • End stage of progressive white matter disorders
Posterior fossa	Cerebellum + middle cerebellar peduncles + Brainstem predominance • Peroxisomal disorders • Alexander disease • Autosomal Dominant Leukodystrophy with Autonomic disease (ADLD) • Leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation (LBSL) • Mitochondriopathies
	Cerebellum and cerebellar peduncles predominance • Histiocytosis • Early onset Mple syrup urine disease • Cerebrotendinous xanthomatosis • FMR1 premutation • FA2Hrelated disorders • Heroin and cocaine toxicity
	Brainstem predominance • Leukoencephalopathy with thalamus and brainstem involvement and high lactate (LTBL) • Adult Polyglucosan Body Disease (PGBD) • Wilson disease • Leigh syndrome • Dentatorubral-pallidoluysian atrophy (DRPLA)
Temporal	• Menkes disease • Herpes simplex encephalitis • Aicardi– Goutières Syndrome (AGS) • Congenital Cytomegalovirus infection • RNASET2 deficiency

Metabolic testing

Serial biochemical testing can be done to look for the disease etiology. The type of testing, either biochemical testing or direct single gene testing, may be dictated by the clinical and neuroimaging findings. If a specific etiology cannot be conclusively established by clinical evaluation and imaging features then an approach of ruling out the rapidly diagnosable and those with treatment options may be undertaken. Table 9 lists the biochemical screening tests and the specific target disorders. It is also important to rule out nutritional deficiencies which can cause white matter changes such as vitamin B12 deficiency which can be treated. Some laboratory tests useful in diagnosing genetic white matter disorders are listed below in Table 9.

Table 9 Some laboratory tests useful in diagnosing genetic white matter disorders.

Screening test		Disorder
Enzyme assays		Krabbe (galactosyl cerebrosidase) MLD (arylsulphatse A) Multiple sulfatase deficiency (arylsulphatase A,B,C,D) GM1 gangliosidosis (beta galactosidase) GM2 gangliosidosis (hexosaminidase A & B) Sialidosis (neuraminidase) Galactosialidosis (neuraminidase + beta galactosidase)
Urinary Analysis	Sulfatides	MLD
	Glysoaminoglycans	Multiple sulfatase deficiency
	Organic acids	L2 glutaric aciduria (↑ concentration of L-2-hydroxyglutaric acid and lysine) Canavan disease (↑ N-acetylaspartic acid) Mitochondrial disorders (Krebs cycle intermediates)
	Aminoacids	Aminoacidopathies
Plasma Very long chain fatty acids		ALD (C26:0, ↑ ratio of C24:0 to C22:0, ↑ ratio of C26:0 to C22:0) Peroxisomal biogenesis disorders Peroxisomal beta oxidation defects
Plasma cholestanol		CTX
Mitochondrial disorders Blood lactate, pyruvate, aminoacids		

Other tests

Additional specific testing can be done at the discretion of the physician and as required, to detect abnormalities which may either provide additional diagnostic clues or may help in the overall patient management such as ophthalmologic evaluation (including slit lamp examination and fundoscopy), hearing evaluation, endocrinologic workup and neurophysiologic studies such as BAER, EMG/NCV,VEP, SSEP) to characterise the involvement of cranial and peripheral nerves (AMN, MLD, Krabbe), optic tracts and spinal tracts.

Molecular genetic testing

Molecular diagnostic confirmation can be done by sequence analysis of the relevant gene, based on the recognition of a definitive pattern in MRI or based on the metabolic testing results. However, for many of the leukoencephalopathies, especially the rarer types, there is often a significant overlap in the clinical and neuroimaging features and reliable metabolic testing may not be available; therefore, broad spectrum testing in the form of next generation sequencing-based multigene panel testing for leukodystrophy and genetic leukoencephalopathy genes or whole exome sequencing can be applied to come to a conclusive diagnosis.

Management

Treatment options in general at present are largely symptomatic and supportive, while curative therapies are limited and inadequate. Supportive therapy is aimed at improving the quality of life and involves various strategies, common as well as tailored to individual needs. These include management of spasticity (medications, physiotherapy, orthotics), seizure control and prevention (anticonvulsants), surgical release of contractures and scoliosis correction, gastrostomy for severe dysphagia, proper wheelchair seating, special education, assistive communication devices, and nutritional support.

Genetic counseling is an important component of management of these conditions and the affected families can be offered appropriate counseling about the recurrence risks and about prenatal diagnostic testing options to prevent re-

currence.

Specific therapies are available for certain disorders. Early hematopoietic stem cell transplantation (HSCT), though not curative, attenuates the clinical course and prolongs survival of infantile Krabbe disease and X-ALD. Dietary therapy with oral chenodeoxycholic acid (750 mg/day) corrects the biochemical abnormalities and reverses symptoms in Cerebrotendinous xanthomatosis. Hormone therapy can be life saving by preventing Addisonian crisis in susceptible individuals with X-ALD. Early institution (prior to occurrence of MRI abnormalities) of oral Lorenzo's oil (erucic acid and oleic acid combination) lowers plasma levels of very long chain fatty acids (VLCFA) in patients with X-ALD. Early recognition can be beneficial in those conditions with definite treatment options, and on the whole, preventive, symptomatic and supportive care with multidisciplinary involvement, are of prime importance in the management of patients with genetic white matter disorders.

References

1. Di Rocco M, et al. Genetic disorders affecting white matter in the pediatric age. Am J Med Genet B Neuropsychiatr Genet. 2004; 129B: 85-93.
2. Gorospe JR, et al. Indian Agarwal megalencephalic leukodystrophy with cysts is caused by a common *MLC1* mutation. Neurology 2004; 62: 878-82.
3. Parikh S, et al, A clinical approach to the diagnosis of patients with leukodystrophies and genetic leukoencephalopathies. Mol Genet Metab 2015; 114: 501-515.
4. Schiffmann R, van der Knaap MS. Invited article: an MRI-based approach to the diagnosis of white matter disorders. Neurology 2009; 72:750-759.
5. Sistermans EA, et al. Mutation detection in the aspartoacylase gene in 17 patients with Canavan disease: four new mutations in the non-Jewish population. Europ J Hum Genet 2000; 8: 557-560.
6. van der Knaap MS. Magnetic resonance in childhood white matter disorders. Dev Med Child Neurol 2001; 43:705-712.
7. Vanderver A, et al. Case definition and classification of leukodystrophies and leukoencephalopathies. Mol Genet Metab 2015; 114: 494-550.
8. von Figura K, Gieselmann V, Jaeken J. Metachromatic leukodystrophy. In: Scriver CR, Beaudet AL, Sly WS, Valle D, editors. The Metabolic and Molecular Bases of Inherited Disease. New York: McGraw-Hill; 2001: 3695-3724.