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Solving the hypomyelination conundrum - Imaging perspectives

Prateek Malik [a], Karthik Muthusamy [a], Kshitij Mankad [b], Manohar Shroff [c], Sniya Sudhakar [b, *]

[a] Christian Medical College, Vellore, India
[b] Great Ormond Street Hospital, London, UK
[c] Hospital for Sick Children, Toronto, Ontario

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ABSTRACT

Hypomyelinating Leukodystrophies (HLDs) are a genetically heterogeneous, clinically overlapping group of disorders with the unifying MR imaging appearance of myelin deficit in the brain. In fact, it is the MRI phenotype that typically raises the diagnostic suspicion in this single largest group of undiagnosed leukodystrophies and guides gene testing for confirmation. This article reviews the neurobiology of myelination, focussing on the complex interplay of molecular genetic pathways and presents a practical clinico-radiological diagnostic algorithm based on the neuroimaging patterns of the common hypomyelinating disorders. The authors also address the current controversies about the definition and use of the term 'hypomyelination'.

Contents

* Corresponding author. Department of Radiology, Great Ormond Street Hospital London, WC1N 3JH, UK.
E-mail address: sniya.sudhakar@gmail.com (S. Sudhakar).

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1. Introduction

The term 'hypomyelination' has been adopted to imply reduced myelin content due to abnormal development and structure of myelin, in contrast to other leukodystrophies wherein normally developed myelin is destroyed due to various mechanisms. This therefore translates into a characteristic MR appearance of *reduced T2 hypointensity (or relative T2 hyperintensity)* and *variable T1 signal (usually T1 hyper- or iso-, but can be mildly hypo-as well)* unlike other leukodystrophies displaying a marked T1 hypointensity and T2 hyperintensity as standard features. Since the first description of Pelizaeus-Merzbacher disease in 1885 [1], there has been an exponential increase in our understanding of normal and abnormal myelination as well as myelin repair (remyelination). Despite this, several questions about hypomyelination remain unanswered. Is hypomyelination a specific entity or only a radiological sign? Is it really best defined only as a permanent deficit in the myelin content of the brain, or does the scope of its definition need broadening to include aspects like the quality of myelin apart from its volume? Is it a fixed, transient or progressive imaging feature?

In spite of the decreasing cost and increasing availability and rapidity of genetic testing, technical and interpretational difficulties still exist. A neuroimaging based deep phenotyping along with clinical phenotyping remains paramount when understanding these disorders. In the day and age when therapeutic research is focussing on cell-based therapies for hypomyelinating leukodystrophies, the role of neuroimaging has become more pivotal not only in identifying and phenotyping these disorders to guide genetic confirmation, but also provide a surrogate biomarker for clinical endpoints in therapeutic trials [2].

2. Neurobiology of myelination

An understanding of the sequence of the synchronised events leading to myelination of axons provides a crucial insight into understanding the mechanisms behind HLDs. Oligodendrocytes (OLs), myelinating cells of the central nervous system, undergo a complex journey to eventually myelinate numerous segments of multiple axons through protoplasmic processes. Morphogens of the Sonic Hedgehog (SHH) pathway determine cell fates of most cell lines in CNS and play a pivotal role in ventral patterning [3]. Ventral plate neuroepithelial progenitor cells (neural stem cells/NSCs) located in the ventral sub-ventricular zone form the first sites of oligodendrocyte progenitor cell (OPC) formation in early embryogenesis. OPC generation occurs in multiple tightly controlled spatiotemporal waves. Under SHH and fibroblast growth factor (FGF) pathway signalling, Olig2+ and Nk 2 homeobox 2 (Nkx2.2) positive cells of the ventral neuroepithelium undergo a switch from motor neuron production to OPC generation [4]. Apart from OPC production and specification, co-expression of Olig1 and 2, Nkx2.2, along with Nkx6-2 and sex determining region Y-box 10 (Sox-10) play an additional role in OPC differentiation into OLs [4] (Fig. 1a).

After OPC generation, interplay of multiple internal (local) and external (neuronal and vascular factors) cues is essential for their migration (Fig. 1a). Local factors including SHH signalling, bone morphogenetic protein (BMP), wingless integrated/int-1 (WNT) signalling, multiple growth factors including platelet derived growth factor (PDGF) and vascular endothelial growth factor (VEGF), and extracellular matrix components stimulate migration of OPCs [5]. Neuronal activity also provides external cues to enable OPC migration. Neurotransmitter glutamate via α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and *N*-methyl-D-aspartate (NMDA) receptor mediated signalling plays a key role, along with synergistic effects from axonal guidance factors such as chemokine CXCL1 and neural cell adhesion molecules [5]. Finally, recent papers have shown the importance of vascular factors as OPCs migrate along developing blood vessels which provide them with chemotactic cues through WNT-mediated expression of chemokine receptor CXCR4 [6]. OPCs extend and retract cellular processes until axonal selection and glia-axonal contacts are established [7].

On arrival of OPCs at selective areas of intended myelination, there exists a close homeostatic balance to maintain a constant pool of OPCs at these sites. PDGF plays a crucial role as promoter of OPC proliferation, while WNT and Notch signalling and transcription factors such as Inhibitors of differentiation (Id2, Id 4) prevent OPC differentiation into OLs [5]. Downregulation of these inhibitors leads to differentiation of committed OPCs, which have already established glia-axonal contacts, into premyelinating OLs. These then undergo lateral and radial expansion (wrapping) along the axons under the influence of myelin regulatory factor (myrf) and simultaneously develop into mature myelinating OLs. Mature OLs express multiple myelin associated genes such as protein zero (P0), myelin basic protein (MBP) and periaxin (prx) in the peripheral nervous system and proteolipid protein 1 (PLP1), MBP, Cyclic nucleotide phosphodiesterase (Cnp), myelin oligodendrocyte glycoprotein (MOG), myelin associated glycoprotein (MAG) and Claudin 11 in CNS, each serving a specific function [8]. The myelin laid down thus undergoes a process of compaction heralded by formation of major dense lines (MDL) by MBP and intraperiod lines (IPL) by PLPs and galactolipids [7].

As can be noted, several genetic and molecular pathways can lead to a hypomyelinating leukodystrophy. These can include pathogenic variants in genes encoding structural proteins (PLP1, MBP, tubulin), transcription factors controlling expression of structural genes (SOX10 and NKX6-2) or pathogenic variants in other genes with cellular roles directly or indirectly linked with oligodendrocyte, axonal or astrocyte function (Fig. 1a and b). Interestingly, among newly identified genes, the pathogenic variants in housekeeping processes like mRNA translation far outnumber the structural protein defects [9].

3. Classification of hypomyelinating disorders

Based on the above pathway of myelinogenesis and close glial-axonal coupling tightly controlled by multiple extrinsic and intrinsic factors, it is clear that unlike our prior understanding of HLDs, defects in the oligodendrocyte lineage and subsequent myelin abnormalities are just one of the many ways in which they can occur. Based on these advances, the classification of leukodystrophies was recently updated to redefine these entities based on the primary cell lineage affected [10] which now includes primary myelin disorders, astrocytopathies, leuko-axonopathies, microgliopathies and leuko-vasculopathies [10]. Hypomyelinating disorders span many of these categories and are tabulated below based on existing understanding (Table 1).

While pathology may eloquently demonstrate the subcategory, these differences are not always obvious on imaging. The radiologist can however assist by first spotting that there is true hypomyelination, and second by looking for other specific imaging based clues to guide focussed testing. At times radiologists can even clinch the genetic diagnosis when characteristic patterns are present.

4. Identifying hypomyelination on imaging and using correct terminologies associated with hypomyelinating leukodystrophies

The current definition of the term 'leukodystrophies' encompasses all inherited disorders affecting CNS white matter

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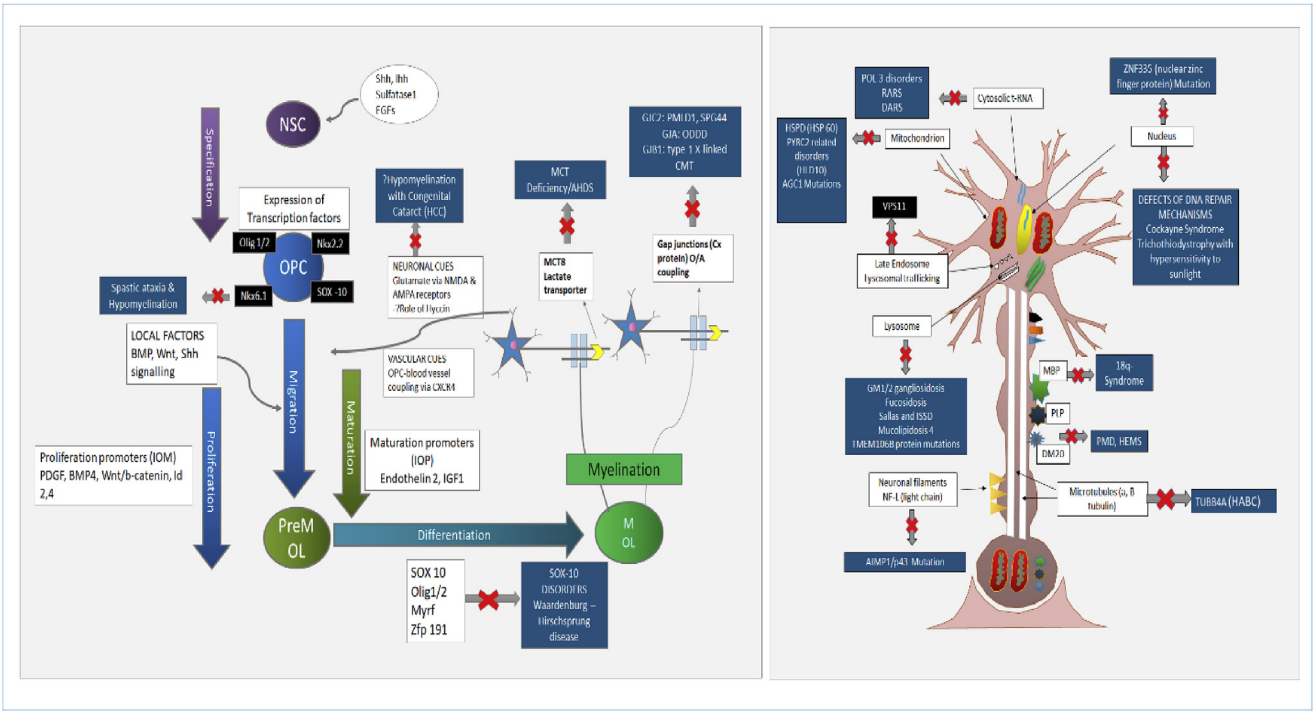

Fig. 1. Fig. 1a. Summary of the important signalling pathways, transcription factors, internal and external cues governing the tightly controlled machinery of myelination from OPC specification, migration and proliferation, and differentiation into myelin forming OLs. Fig. 1b. Details of various cell functions directly or indirectly supporting the myelination machinery. Red crossed arrows indicate the associated specific disorders (Abbreviations: Fig. 1a. NSC: neural stem cells, OPC: Oligodendrocyte Progenitor Cell, BMP: Bone morphogenetic protein, Wnt: Wingless integrated/int-1, Shh: Sonic hedgehog Ihh: Indian Hedgehog Nkx: Nk 2 homeobox,SOX: Sex determining region Y-box, HCC: Hypomyelination with congenital cataracts, MCT: AHDS: Allan–Herndon–Dudley syndrome, IGF: Insulin-like growth factor 1, Id: Inhibitors of differentiation, FGF: fibroblast growth factor, PDGF: platelet derived growth factor, IOM: Inhibitors of maturation, IOP: Inhibitors of proliferation, Myrf: myelin regulatory factors, Zfp: zinc finger protein. Fig. 1b. PYRC: pyrroline-5-carboxylate reductase, HABC: Hypomyelination with atrophy of the basal ganglia and cerebellum, SPG44: hereditary spastic paraparesis 44, ODDD: Oculodentodigital dysplasia, CMT: Charcot-Marie-Tooth, PMLD: Pelizaeus–Merzbacher like Disease, RARS: arginyl-tRNA synthetase, DARS: aspartyl-tRNA synthetase, HSP: Heat shock protein, HEMS: Hypomyelination of early myelinating structures, MBP: myelin basic protein, PLP: proteolipid protein, VPS11: vacuolar protein sorting11, TUBB4A: tubulin β-4A, AIMP1: aminoacyl-tRNA synthetase complex interacting multifunctional protein 1). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Table 1
Pathology based classification of Hypomyelinating Leukodystrophies (HLDs).

Primary myelin Disorders	Leuko-axonopathies	Astrocytopathy
• Pelizaeus–Merzbacher • Pelizaeus–Merzbacher like Dz (PMLD): GJC2 (previously GJA12) mutations/Connexin 47 (Cx47) disorder • HEMS	• Pol III related leukodystrophies • HCC • HABC Early-onset neuronal degenerative disorders • Gangliosidosis GM1 and GM2 • Infantile neuronal ceroid lipofuscinosis • *AGC1*-related disease • *AIMP1*-related diseases • *HSPD1*-related disease	• Oculodentodigital dysplasia

irrespective of involvement of the structural (oligodendrocytes, astrocytes, non-neuronal cells and axons) or molecular component, and/or disease evolution [10]. Imaging appearances are pivotal in differentiating leukodystrophies and the first step as previously alluded to is to determine the presence of hypomyelination. On MRI, hypomyelination is characterised by less myelin than expected for age identified as mild T2 hyperintensity with variable preservation of the T1 signal of myelin which can be hyper-, iso- or minimally hypo-intense compared to cortical grey matter (Fig. 2) [2].

Primary hypomyelination is characterised by permanently deficient myelin due to abnormal myelin formation, and on MRI is seen as an unchanged pattern of deficient myelination on two MRI scans performed at least 6 months apart in a child older than 1 year [11]. *Delayed* myelination on the contrary, implies a lagging pattern of myelination than expected for age that may improve or "catch up" on subsequent imaging. Delayed myelination in itself is a non-specific finding that can be seen with several systemic disorders [12], however, in the appropriate setting and with other clinical and radiological findings can imply specific neurological disorders like Allan–Herndon–Dudley syndrome (SLC16A2 related X linked disorder), a defect in the monocarboxylate transporter 8 (MCT8). Secondary myelin loss may be associated with early onset primary neuronal disorders, which are classified under leuko-axonopathies and can mimic hypomyelination [10]. Axonal insult and cortical atrophy in these

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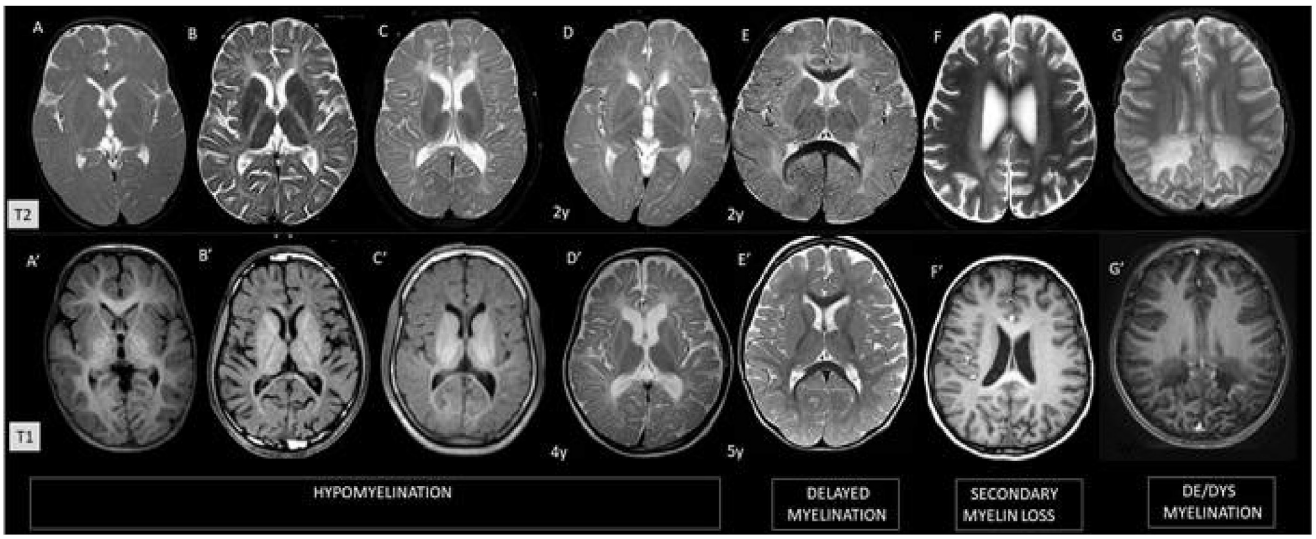

Fig. 2. MRI appearance of Hypomyelination, delayed myelination, secondary myelin loss and demyelination. A-A' to C–C′ shows hypomyelination on T1 and T2 weighted images with varying degrees of T2 hyperintensity and loss of T1hyperintensity (hyper, iso and hypo to cortex respectively) D-D′ is hypomyelination on serial imaging at 2 and 4 years of age showing no progression of myelination. Contrast this to Delayed Myelination(E-E′) where the subsequent MRI shows significant increase in myelination. F–F′ portrays white matter hyperintensity associated with axonal loss in Neuronal Ceroid Lipofuscinosis. G-G′ shows the pronounced T2 hyperintensity and corresponding T1 hypo intensity of demyelinating areas in XALD.

disorders leads to a hypomyelinating pattern of white matter involvement. Further, the term 'dysmyelination' has been used to imply structurally or biochemically abnormal myelin, but of all the currently used terminologies, this perhaps is the most esoteric and has been rather vaguely and variably used. Fig. 2 summarises the typical appearances of these terminologies.

T1 and T2 are the key sequences for the assessment of myelin maturation. T1-weighted sequences show a completion of the myelination process by the end of first year, while this occurs by the end of the second year on T2-weighted sequences. Relative preservation of T1 hyper-intense signal (as opposed to the hypointensity seen in other leukodystrophies), a diffuse involvement of white matter and absence of myelination in the later myelinating structures (suggesting an absence or arrest at an early stage rather than involvement of already formed myelin) are the typical findings suggestive of HLDs. While these indicators work most of the time, there are exceptions. Many disorders display relative preservation or involvement of selected white matter structures. Another caveat is the coexisting dysmyelination causing more T1 hypointensity especially in more advanced stages of the disease. Fig. 3 summarises the MRI signal characteristics and potential imaging caveats and pitfalls in diagnosing HLDs.

5. Neuroimaging patterns in hypomyelination

From the classification above, it is clear that HLDs are a heterogeneous group of disorders with a common underlying imaging pattern of hypomyelination on MRI. Based on imaging patterns and selective involvement of other structures, HLDs can further be grouped under clusters that allow further differentiation between them. The neuroimaging patterns in HLDs in this review will be discussed under the clusters detailed in Table 2. While there may be overlaps, the grouping is based on the most useful distinguishing feature.

5.1. Diffuse hypomyelination

This is the most recognised and typical pattern of hypomyelination wherein most of the white matter structures show homogeneous mild T2 hyperintensity with variably preserved T1 signal and there is absence of other specific imaging features.

Pelizaeus–Merzbacher Disease (PMD): PMD as the prototype for diffuse hypomyelinating leukodystrophy is an X-linked recessive disorder caused by pathogenic variants of the proteolipid protein 1 (*PLP1*). PMD displays a broad continuum of disease phenotypes ranging from a severe connatal form (neonatal), classical PMD (infantile) and transitional forms. The major disease forms show a strong genotype-phenotype correlation, although some pathogenic variant groups, especially missense pathogenic variants, tend to be heterogeneous as portrayed in Table 3. Connatal form often shows complete absence of myelin with diffuse white matter changes involving also the posterior limbs of the internal capsules (PLICs) and cerebellar white matter, while sparing the pons and diencephalic structures including globus pallidus and thalami (Fig. 4) [13]. Classic forms may show preservation of myelin in early myelinating structures like PLIC. While corticospinal tract involvement can be seen in the brainstem, diffuse brainstem changes are typically absent. Cerebral and cerebellar atrophy may be seen late in the disease course.

Pelizaeus–Merzbacher like Disease (PMLD): These are a continuously expanding broad category of disorders that present clinically as a mild *PLP1*/PMD phenotype. They are most commonly caused by autosomal recessive *GJC2* pathogenic variants, even though this particular mutation constitutes only 8% of the PMLD patients [14]. While a diffuse hypomyelination is seen in both PMD and PMLD, the latter has additional brainstem, especially pontine, and dentate hilar involvement (Fig. 5). *PMLD1/GJC2* pathogenic variant disorder comes under a broad category of disorders called Gap-junction/connexin protein disorders. Gap junctions are small intercellular channels that traverse lipid bilayers of adjacent cells and play a role in transport of multiple metabolites, brain development and glia-axonal coupling. Each gap junction consists of two hemichannels or connexons which are in turn formed by 6 transmembrane proteins called connexins [15]. While astrocytes in central nervous system express connexins Cx43 and Cx30, oligodendrocytes express Cx29, Cx32 and Cx47 [15]. Oligodendrocyte and astrocyte coupling occur by heterotypic Cx47/43 and Cx32/30 O/A gap junctions and is essential for proper maintenance of

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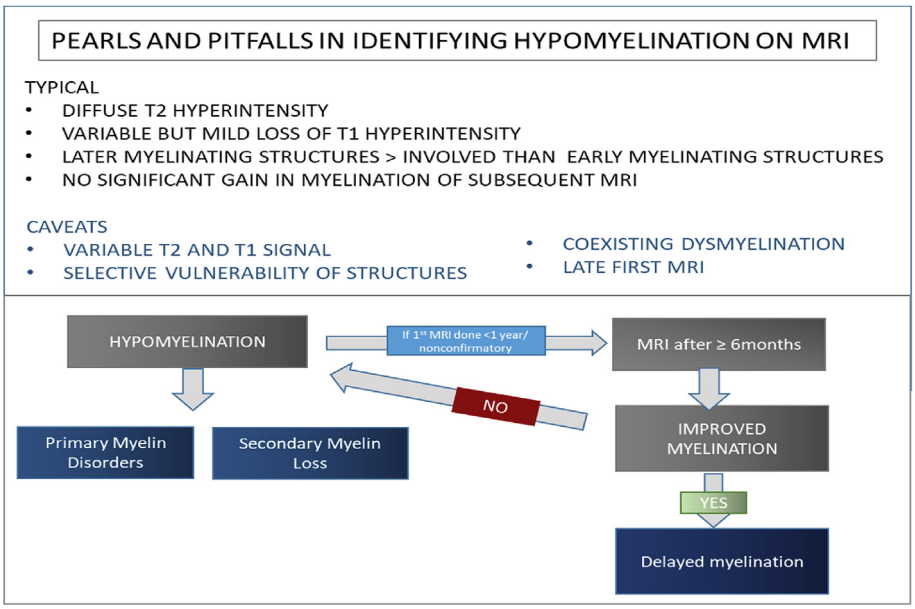

Fig. 3. Typical features and Confounding factors in identifying Hypomyelination on MRI and differentiating from common mimics.

Table 2
Neuroimaging patterns in Hypomyelinating leukodystrophies.

Imaging Feature	Disorders covered
Diffuse hypomyelination	• PMD • PMLD • SOX10mutation
Selective sparing/involvement of white matter structures/Focal white matter lesions	• HEMS • HCC • HBSL
Basal ganglia changes	• Salla disease • T2 Hypo-Fucosidosis • T2 Hyper- GM1,GM2
Cerebellar Atrophy	• Small - HABC • 4H • 18Q-
Cerebral Atrophy, Calcification	• ODDD • Trichothiodystrophy • AGS • Cockayne

myelin. Pathogenic variants in with Cx47, Cx43 and Cx32 are therefore responsible for CNS dysfunction.

SOX 10 associated PCWH (Peripheral neuropathy, central dysmyelination, Waardenburg syndrome, and Hirschsprung disease Syndrome): Central nervous system findings in SOX10 associated PCWH include diffuse hypomyelination with or without cerebral, cerebellar and brainstem atrophy along with cochlear hypoplasia, vestibular and semicircular canal dysplasia and cochlear nerve hypoplasia (Fig. 6) [16–18].

5.2. Selective white matter sparing/involvement

Some HLDs show selective involvement of certain white matter structures or are associated with more T2 hyperintense focal lesions superimposed on background hypomyelination. It is important to be aware of this pattern and identify the hypomyelination present in the background.

Hypomyelination of early myelinating structures (HEMS): HEMS is a recently described entity related to distinct pathogenic variants of *PLP1* specific region in exon 3b and intron 3 [19]. On imaging, mild T2 hyperintensity is seen in the dentate hilus and peridentate white matter, periventricular white matter including the optic radiations, and within the pons. Other than the peculiar distribution of hypomyelination involving early myelinating structures, these cases also show other distinguishing findings-the trilaminar posterior limb of internal capsule (PLIC) (alternate hyperintense and hypointense signal), and mild T2 hypointensity of the anterolateral thalamus (Fig. 7) [20]. Although the number of reported cases have been few, on follow up, the subcortical white matter tends to show a slow progression of myelination appearing nearly mature in adolescence, while the rest of the involved structures show a static appearance [20].

Hypomyelination with brain stem and spinal cord involvement and leg spasticity (HBSL): HBSL falls under the broad category of Aminoacyl-tRNA synthetase (*ARS*) pathogenic variant disorders which are housekeeping genes (including 9 ARSs and 3 auxiliary proteins: AIMP 1,2,3) that are involved in various signalling pathways and protein synthesis [21]. Pathogenic variants in cytoplasmic aspartyl-tRNA synthetase (DARS) demonstrate a characteristic MRI pattern with diffuse confluent periventricular and deep white matter hyperintensity along with involvement of the superior and inferior cerebellar peduncles, the medial lemniscus and pyramidal

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Table 3
Disease types with genotype-phenotype correlation in PMD. Adapted from ([11]).

PLP1 DUPLICATIONS

Most Common Phenotype: Classic PMD Mechanism: Tandem Repeat at Xq22.2 Other sites of duplication: Xq26, Xp, 19pter, and Y Overexpression of PLP1/DM20 Accumulation golgi bodies/ER/Lysosomes	Pathology: - Less severe OL apoptosis, patchy decreased myelin - Preserved myelin islets - Tigroid pattern on pathology - Relatively well preserved axons Clinical Presentation: - By 1st year of life, almost exclusively boys - Early: Developmental delay, axial hypotonia, nystagmus - Late: Spasticity, Seizures, extrapyramidal movement disorder, optic atrophy

PLP1 MISSENSE MUTATIONS

Most common Phenotype: PLP1 + DM20 = Severe connatal type PLP1 only = Milder phenotypes Mechanism: - Unfolded abnormal PLP1 and DM20 proteins - Activation of Unfolded protein response - Extensive OL apoptosis	Pathology: - Severe OL apoptosis - Axonal loss +/- Clinical Presentation: - At birth or neonatal, female patients can be seen - Stridor, seizures common - Rapid progression, fatal in the first decade

PLP 1 related disorders

PLP1 NULL DISEASE

Most common Phenotype: Milder forms of disease - Pure Spastic Paraplegia (SPG) Type 2 - Complicated Spastic paraplegia/PLP null syndrome Mechanism: - Loose myelin wraps from defective intraperiod lines (IPL) and poor compaction and stabilisation - Subsequent axonal injury and peripheral neuropathy (complicated form)	Pathology: - Pure type: Limited literature, Minimal OL Loss - Myelin deficiency in spinal cord, mild deficit in the brain - Complicated type: Wallerian degeneration, length dependent axonal injury, - Demyelinating peripheral neuropathy Clinical Presentation: Pure form: Slowly progressive spasticity, near normal life span and cognition Complicated: Spasticity + nystagmus, optic atrophy, cerebellar ataxia, cognitive deficits

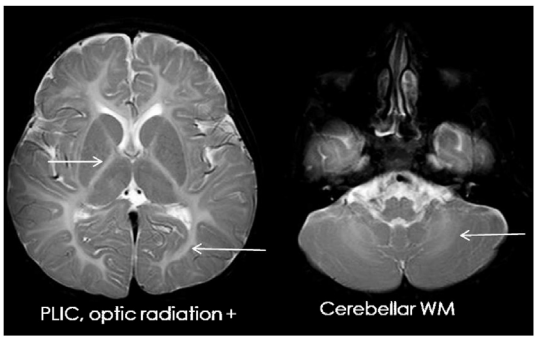

Fig. 4. ***Pelizaeus–Merzbacher Disease:*** T2 axial (A, B) shows diffuse hypomyelination of supra and infratentorial white matter with sparing of brainstem. T1 signal is nearly isointense in deep and subcortical regions with preserved hyperintensity of Internal capsule.

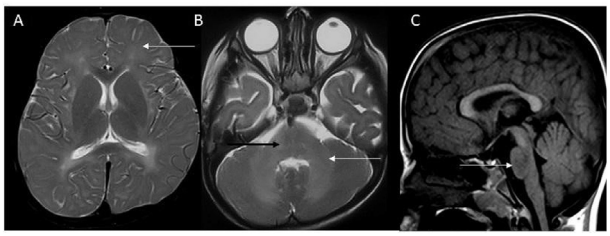

Fig. 5. Pelizaeus Merzbacher like disease: T2 axial (A, B) images show diffuse hypomyelination of supra and infratentorial white matter. Note that there is diffuse pontine hyperintense signal changes as well (black arrow). T1 sagittal image (C) shows corresponding pontine hypo intensity.

tracts in the brain stem and the dorsal columns, and the lateral corticospinal tracts in the spinal cord (Fig. 8). LBSL (leukoencephalopathy with brain stem and spinal cord involvement and elevated lactate) caused by *DARS* 2 pathogenic variants shares a similar imaging picture except for absent/milder supratentorial white matter changes [22]. Diffuse hypomyelination has also been described with arginyl-tRNA synthetase (*RARS*) pathogenic variant, another component of the multisynthetase complex [23].

Hypomyelination with congenital cataracts (HCC): This disorder is caused by deficiency of a membrane protein hyccin, and has autosomal recessive inheritance. The most common pattern on MRI is of superimposed T2 hyperintense and T1 hypointense lesions in the periventricular and deep locations against a background of diffuse hypomyelination [24]. There is relative subcortical sparing as well making this pattern quite distinct from other HLDs (Fig. 9).

There are a few differentials for the imaging pattern of focal T2 hyperintense lesions on a background of hypomyelination including *18 q*-syndrome, d-2 hydroxy glutaric aciduria and dystroglycanopathies [25].

Salla disease: One of the milder variants of lysosomal free sialic acid storage disorders caused by a defect in the lysosomal membrane transporter sialin, leading to intralysosomal accumulation of monosaccharide sialic acid. As a group, these show a variable degree of myelin deficiency on MRI with cortical and white matter atrophy and thinning of the corpus callosum [26]. More severe forms tend to show a marked T2 periventricular hyperintensity. However, in general, imaging features are very nonspecific and can show an overlap with other lysosomal storage and metabolic disorders [24].

5.3. Hypomyelination with cerebellar atrophy

Pol R3 related leukodystrophies: These represent a group of disorders related to the RNA polymerase complex deficiency from pathogenic variants in *POLR3A, POLR3B*, or *POLR1C* genes. The clinical spectrum is extremely heterogeneous and is characterised by different combinations of neurological dysfunction, abnormal dentition, endocrine abnormalities and myopia. ***4H syndrome*** for

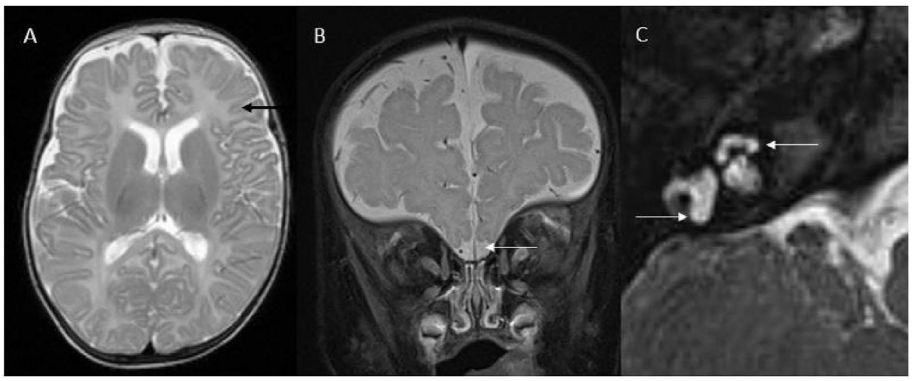

Fig. 6. SOX 10 related leukodystrophy. T2 axial at 15 months show significantly reduced myelin for age. T2 coronal image (B) shows absent olfactory bulbs. DRIVE axial image of inner ear (C) shows cochlear hypoplasia and dysplastic semicircular canals. Hypoplastic cochlear nerve is partly imaged.

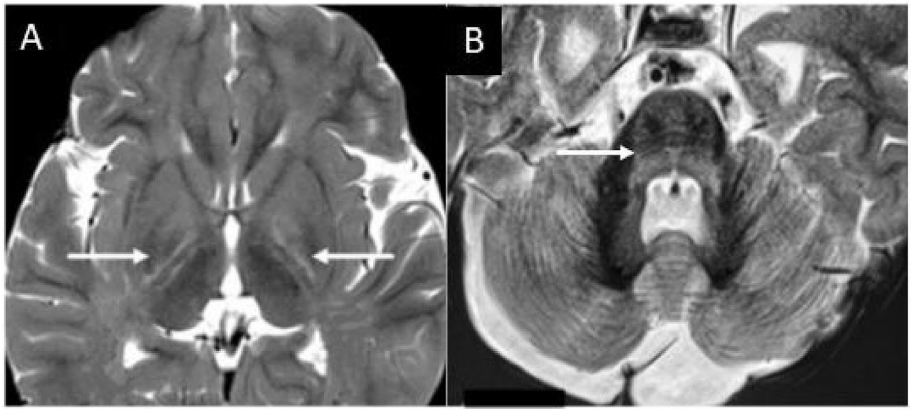

Fig. 7. Hypomyelination of early myelinating structures HEMS: T2 axial images show altered signal intensity with trilaminar pattern of PLIC (white arrows in A).Also note the heterogenous pontine hyperintensity with dorsal predominance(White arrow in B).

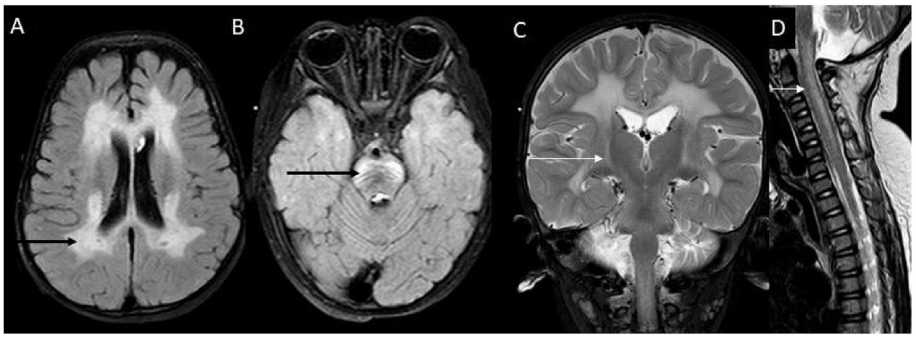

Fig. 8. ***Hypomyelination with brain stem and spinal cord involvement and leg spasticity (HBSL)*** Axial FLAIR images show diffuse confluent periventricular and deep white matter hyperintensity (black arrow in A) and symmetric hyperintensities of the pontine corticospinal tracts (black arrow in B). T2 coronal images also show hyperintensities of the corticospinal tracts in the region of PLIC (white arrow in C) as well as along the spinal cord(white arrow in T2 sagittal-D).

instance encompasses non-neurological symptoms of hypodontia, hypogonadotropic hypogonadism along with diffuse hypomyelination, although any of these features can be absent or mild. ***Tremor-ataxia with central hypomyelination (TACH), Hypomyelination with cerebellar atrophy and hypoplasia of the corpus callosum (HCAHC)*** and ***Ataxia, delayed dentition, and hypomyelination (ADDH)*** also come under the POLR3 spectrum.

On imaging, the extent of hypomyelination can be extremely variable. Typically, there is diffuse hypomyelination with T2 hypointensity of the optic radiations, ventrolateral thalami, globi pallidi and cerebellar atrophy, and as a constellation these features have a high sensitivity and specificity (Fig. 10) [24,27]. Callosal thinning is variably present in children and more frequent in *POLR3A*. [27] *POLR3B* has a milder clinical course with an earlier onset and better myelination of the PLIC on imaging, even though it tends to show more cerebellar volume loss compared to *POLR3A*. Atypical findings of isolated corticospinal involvement, cerebellar atrophy without hypomyelination, striatal and red nucleus involvement and splenial cysts have also been described within this spectrum [28].

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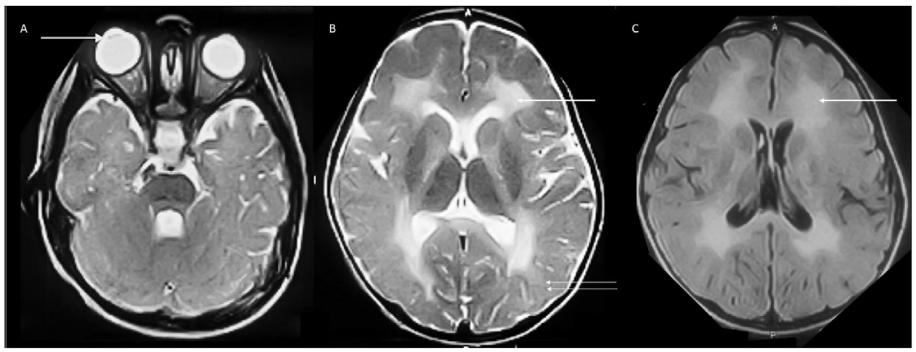

Fig. 9. ***Hypomyelination with congenital cataracts (HCC)***: Axial T2 image (A) shows bilateral cataracts and mild diffuse infratentorial and temporal hypomyelination. Image (B) shows confluent more T2 hyperintense white matter changes in periventricular and deep distribution against a background of diffuse hypomyelination. FLAIR axial (C) better delineates the differential involvement of white matter (white arrow).

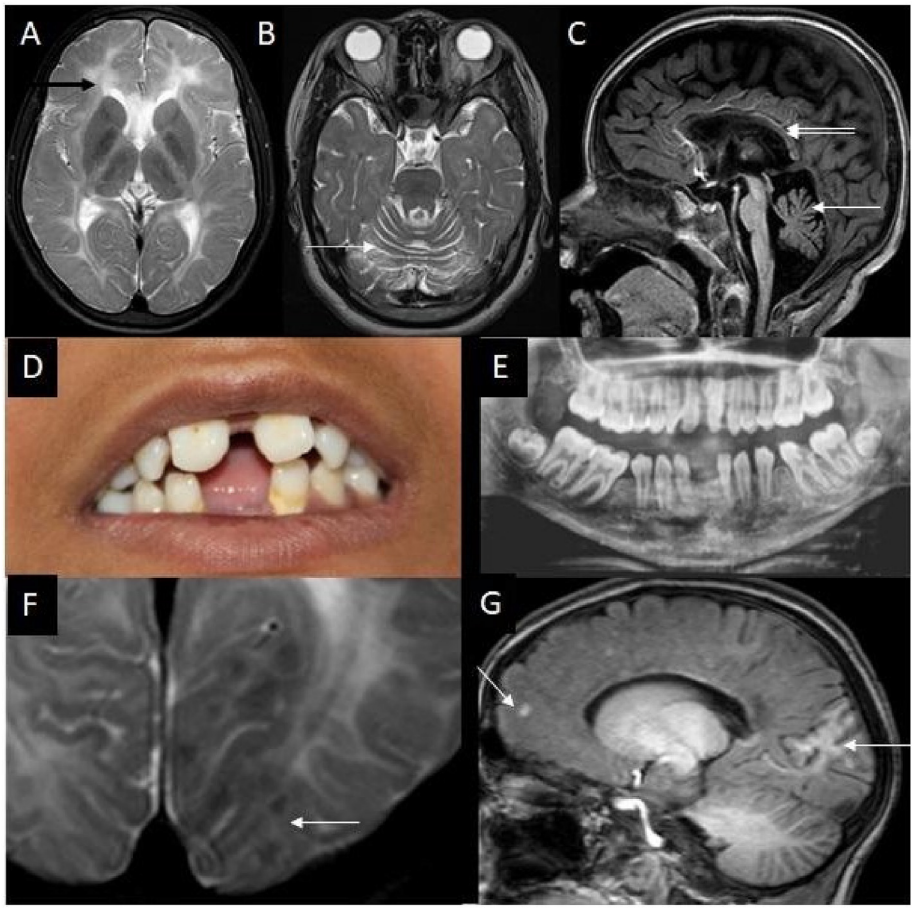

Fig. 10. POL 3 related leukodystrophy: Axial T2 demonstrates the diffuse white matter involvement with mild hypo intensity of globus pallidus and ventrolateral thalamus. Pronounced cerebellar volume loss is seen (white arrow in B). T1 sagittal image (C) shows vermian atrophy (arrow)and marked callosal thinning is seen (double arrows). Clinical (D) and OPG(E) images show hypodontia in this 8-year-old boy. T2 axial(F) and T1 sagittal(G) images show islands of normal myelin in occipital and frontal lobes as well as relative sparing of optic radiations.

18q-syndrome: Characteristic dysmorphic facies, cardiac anomalies and sensorineural hearing loss are seen in the context of mild diffuse hypomyelination with cerebellar atrophy with 18q-syndrome. The white matter signal abnormality can however be quite patchy [13,29,30]

Oculodentodigital Dysplasia (ODDD): Autosomal dominant, most commonly missense *GJA 1/Cx43* pathogenic variants, lead to a characteristic disorder with facial (hypoplastic ala nasi, inverted nares with thin nostrils), ocular (microopthalmia, microcornea), dental (enamel hypoplasia, microdontia) and digital (syndactyly of 3rd and 4th fingers) abnormalities [31]. On MRI, diffuse hyperintensity of the periventricular white mater, PLICs, pons and brainstem is noted. Globus Pallidus (GP) hypointensity and cerebellar atrophy is variably present. Subclinical phenotypes also exist with MRI findings out of proportion to the clinical picture. Hallermann-Streiff syndrome deserves mention here as it is an

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autosomal recessive or sporadic syndrome that may or may not have *GJA* pathogenic variants, with clinical and radiological findings overlapping with ODDD [15].

5.4. Hypomyelination with basal ganglia abnormalities

Hypomyelination with atrophy of the basal ganglia and cerebellum (HABC). [32–34]

Hypomyelination with atrophy of the basal ganglia and cerebellum (H-ABC) occurs due to microtubule dysfunction caused by dominant pathogenic variants in *TUBB4A* which codes for tubulin β-4A. *TUBB4A* pathogenic variants form a disease continuum including dystonia (DYT4-Dystonia type 4), isolated hypomyelination and HABC. Our understanding of the pathobiology of HABC is still speculative. Microtubule instability can cause impaired development and maintenance of myelin through axonal dysfunction causing oligodendrocyte loss through its effect on PLP and MBP transport. Axonal dysfunction may also underlie the neuronal apoptosis seen in the striatum and cerebellum. The selective vulnerability of these structures probably reflects higher expression and function of TUBB4A. Unlike pathogenic variants in other tubulin genes which are malformative, HABC is a degenerative disease associated with hypomyelination.

Disease has an early onset characterised by hypotonia, developmental delay, nystagmus, extrapyramidal symptoms, bulbar dysfunction and at times epilepsy with progressive deterioration of motor functions and a fatal outcome. MRI is diagnostic, characterised by the triad of extensive and severe hypomyelination, volume loss of the neostriatum without signal changes (putamen > caudate) and cerebellum (vermis > hemispheres) (Fig. 11). The globi pallidi can show significant T2 hypointensity, mimicking neurodegeneration with brain iron accumulation. Serial imaging can specifically reveal progressive putaminal volume loss and eventual disappearance with progressive white matter atrophy. The combination of hypomyelination and extrapyramidal symptoms is unique and should prompt *TUBB4A* testing.

Pathogenic variants in *UFM1* (ubiquitin-fold modifier 1) have been described in a cohort of patients who fulfill the MRI criteria for HABC but have no identifiable variants in *TUBB4A* on genetic testing. MRI in *UFM1* pathogenic variants show an additional feature of lateral caudate head hyperintensity. They are also characterised by early infantile onset, severe encephalopathy and early death [35].

Fucosidosis: A lysosomal storage disorder caused by deficiency of α-L-fucosidase that shows a characteristic MRI pattern of diffuse hypomyelination and T2 and SWI hypointensity involving the globi pallidi (Fig. 12). This is possibly related to high iron or calcium content. Related T1 hyperintensity is also seen. Substantia nigra, thalamus and lateral geniculate body also often show marked T2 hypointense signal than expected for age, again mimicking neurodegeneration with brain iron accumulation. Thalamic and globus pallidus 'laminar' hyperintensity can also be seen as on Fig. 12 Pronounced cerebral and cerebellar atrophy may be seen particularly in older patients [24,35]. Like in other lysosomal storage disorders, skeletal survey reveals dysostosis.

GM1and GM2 Gangliosidosis: These lysosomal storage disorders are indistinguishable on MRI and show diffuse hypomyelination with hyperintense signal changes of the caudate and putamen. The corpus callosum is often spared [24]. On follow-up imaging changes related to coexisting demyelination and gliosis may be seen. Thalami are small, show T2 hypointensity or heterogeneity and are hyperdense on CT (Fig. 13). Later onset forms lack white matter changes and may only reveal globus pallidus T2 hypointensity, best on susceptibility weighted imaging [36].

5.5. Hypomyelination with cerebral calcification

Hypomyelination with cerebral calcification is characteristic of DNA repair disorders like Cockayne Syndrome and Trichothiosdystrophy. It is important to remember that MRI is less sensitive than CT in demonstrating often-subtle calcifications and judicious use of CT should be considered in the work up of unresolved leukodystrophies.

Cockayne Syndrome: Bilateral homogeneous pattern of calcifications can be seen involving the globus pallidus, dentate nuclei, caudate and putamen in the order of frequency of involvement. White matter and cortical calcifications can be seen in both cerebrum and cerebellum and are often asymmetric [13]. White matter signal changes can have variable patterns and severity. Based on the disease severity and clinical course, two distinct subtypes are observed: classic Type I and severe Type II. Remarkable cerebral and cerebellar atrophy is seen in both subtypes.

Fig. 14 Myelin deficiency and cortical calcifications are more pronounced in Type II and often associated with hypoplasia of the cerebellum and brainstem [13,37].

Trichothiodystrophy with photosensitivity (TTD): This condition is related to pathogenic variants in DNA repair genes *ECCR2, ECCR3*. Like Cockayne, diffuse hypomyelination which is often mild along with cerebral and cerebellar atrophy is noted. When calcification is absent, TTD resembles other HLDs on imaging, but coarse hair showing tiger tail pattern under polarised microscopy is a helpful bedside clue (Fig. 15).

The combination of white matter changes and calcifications can also be seen in ***Aicardi Goutières Syndrome (AGS)***, a genetically heterogeneous autoimmune mediated encephalopathy with microangiopathy related calcifications in the basal ganglia, thalamus, dentate, cerebral (periventricular predominance) and cerebellar white matter (Fig. 16). The pattern of calcification is however

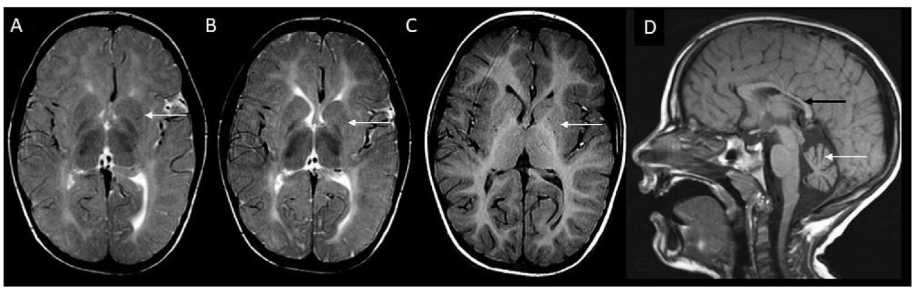

Fig. 11. Hypomyelination with atrophy of the basal ganglia and cerebellum (HABC): Axial T2 images show diffuse hypomyelination along with small volume putamen. Subsequent MRI after one year shows no improvement in myelination but interval progressive volume loss of putamen. This is also evident on T1 axial image. T1 sagittal image (D) shows significant vermian atrophy as well as callosal thinning.

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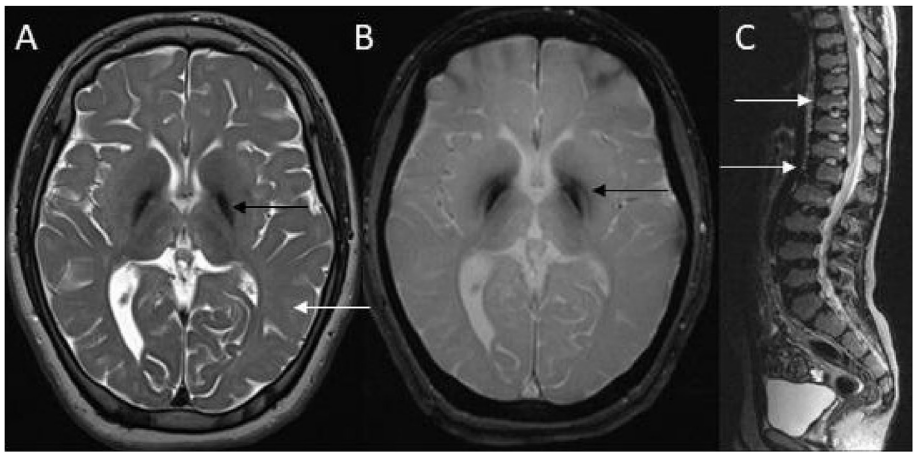

Fig. 12. Fucosidosis: T2 axial image shows diffuse T2 hyperintensity related to hypomyelination. (white arrow in A). There is T2 and SWI hypo intensity of globus pallidus (black arrows). T2 sagittal spine(C) shows features of dysostosis with platyspondyly, anterior beaking and hypoplasia of L1.

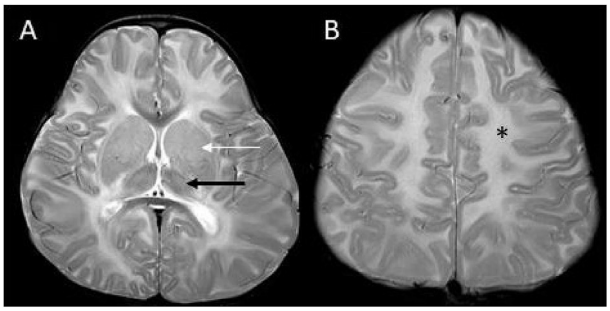

Fig. 13. GM1 Gangliosidosis. T2 axial images show Diffuse white matter hyperintensity with sparing of corpus callosum. There is mild hyperintensity and prominence of the caudate and putamen (white arrow). Thalami appear dark and small (black arrow). Supraventricular level shows mild gyral broadening (asterix in B).

different compared to DNA repair disorders being typically punctate and discrete or coalescing into larger areas. White matter signal changes are also of variable severity, typically showing an anterior to posterior gradient with demyelination and astrogliosis seen as pathological correlates [13]. Intracranial vasculopathy with stenosis and aneurysms are described in the subtype with *SAMHD* pathogenic variants [38,39]. Temporal cysts have been described as well similar to Cytomegalovirus (CMV) and *RNAase* T2 deficiency.

6. Delayed myelination

HLDs show no significant progression of myelination on follow up imaging. There are some diseases which show significantly reduced myelin than expected for age on initial imaging but may demonstrate improved myelination on serial imaging. Initial imaging can mimic other HLDs, hence these should be considered in the diagnosis and included in hypomyelination panels.

Allan–Herndon–Dudley syndrome (SLC16A2 related X linked disorder) is the prototype disorder which shows catch up myelination on follow up imaging and is due to defect in the monocarboxylate transporter 8 (*MCT8*) which is involved in Thyroxine T3 transport across blood brain barrier and its neuronal uptake. This plays a pivotal role in myelination along with dendritic out growth and synaptic formation [40]. Elevated T3, reduced T4 and a normal or slightly elevated TSH is characteristic. MRI shows features of diffuse myelin reduction for age with slowly progressing myelination (Fig. 17) [41]. No basal ganglia abnormalities other than myelin delay is demonstrated although extrapyramidal symptoms dominate the clinical picture [42]. Small pituitary gland has also been described [43].

As discussed earlier, many other genetic, metabolic and acquired conditions are associated with delayed myelination including Cerebral Folate deficiency (Fig. 18), Creatine deficiency, Downs's syndrome, Biotinidase deficiency, hypoxic ischemic injury, hypothyroidism, malnutrition and congenital Infections.

7. Specific clinical clues

The radiological picture should always be considered in conjunction with the clinical profile of the patient. Common clinical correlations are tabulated in Table 4. Specific features on neurological examination also point towards probable distinct diagnoses. Given below are some commonly seen features which may suggest a diagnosis clinically (Table 5, Table 6).

8. Semantic confusions and incertitudes

Many different terms have been used in relation to abnormalities of myelin: hypomyelination (deficient deposition), dysmyelination (deposition of abnormal myelin), demyelination (damage to normally laid myelin), or even false hypomyelination (myelin loss secondary to axonal loss). The recently described 'transient myelin deficiency' caused by *TMEM63A* pathogenic variants (similar to PMD with no detectable myelin and normalisation on later MRIs after 4 years of age) further illustrate the complexity of the terminologies [44]. The confusion exists because semantic updates do not catch up with the expanding knowledge on the pathological bases of diseases.

Recent research has clearly shown a shift of focus from myelin and oligodendrocytes as the only key players in white matter function, integrity and disease. In light of these developments, it is best to use "hypomyelination" strictly as a neuroimaging sign without dogmatic underpinnings on any clearly definable pathogenesis. It is also important to understand that a single disease entity can have different underlying pathobiologic mechanisms and different molecular pathways can give similar radiological appearances.

9. Future perspectives

HLDs have overlapping clinical and radiological features. Molecular diagnosis is the only way to get a confirmatory diagnosis.

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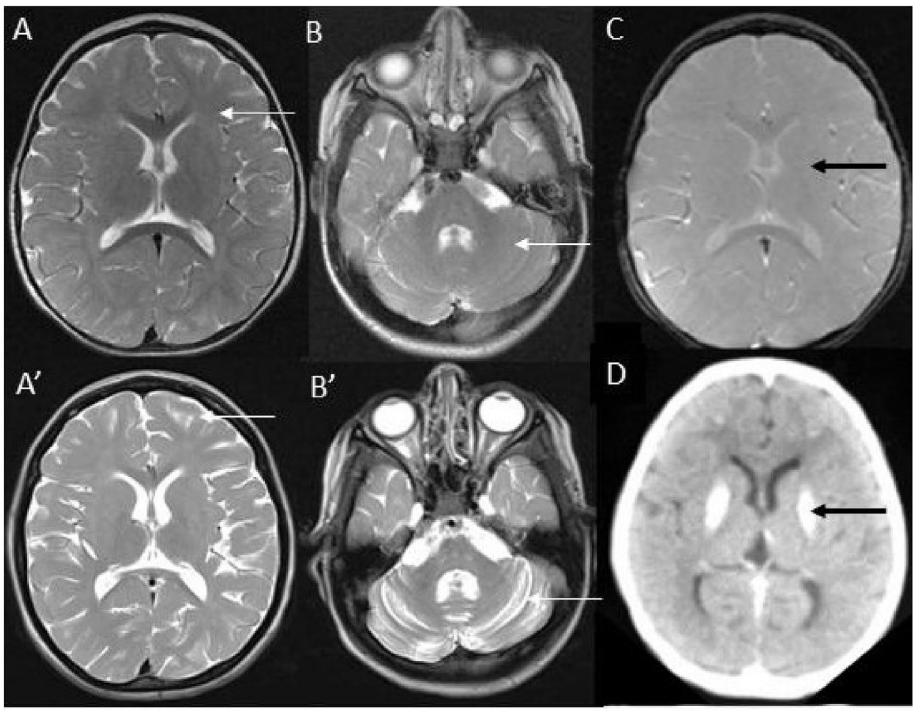

Fig. 14. Cockayne Syndrome: T2 axial images at 2 years and 5 years show diffuse hypomyelination (white arrows A -A′) with progressive diffuse cerebral and cerebellar (arrows B−B′) volume loss. Note homogenous calcifications in putamen bilaterally on CT (Black arrow in D). Note that this is not apparent on gradient MRI sequence (C).

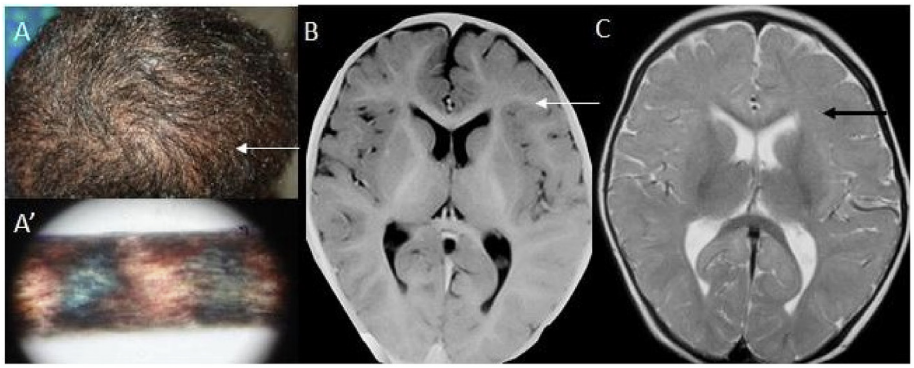

Fig. 15. Trichothiodystrophy. Clinical (A) and light microscopy photographs (A′) show coarse brittle hair and tiger tail pattern respectively. T1(B-white arrow) and T2(C-black arrow) images show diffuse hypomyelination in this 4-year-old boy. Hypomyelination is mild with relative preservation of internal capsule and callosum.

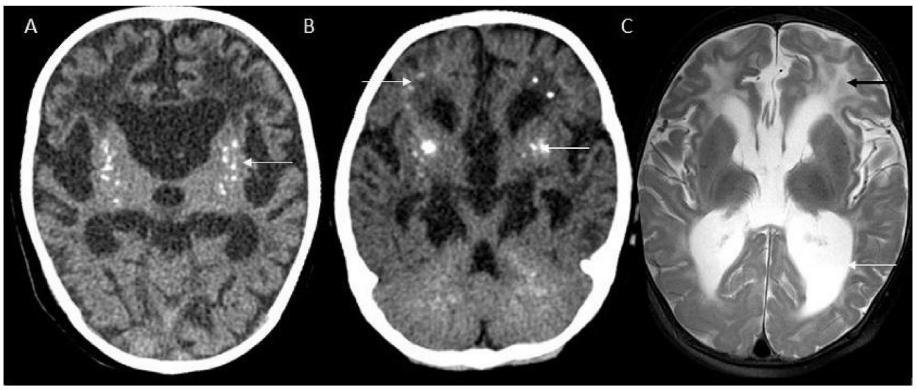

Fig. 16. Aicardi Goutières Syndrome: Axial CT (A, B) shows discrete punctate pattern of calcification in the putamen and periventricular white matter. Coalescent punctate calcification of the cerebellar white matter is also seen. T2 axial image(C) shows diffuse white matter hyperintensity with volume loss and associated lateral ventricular enlargement.

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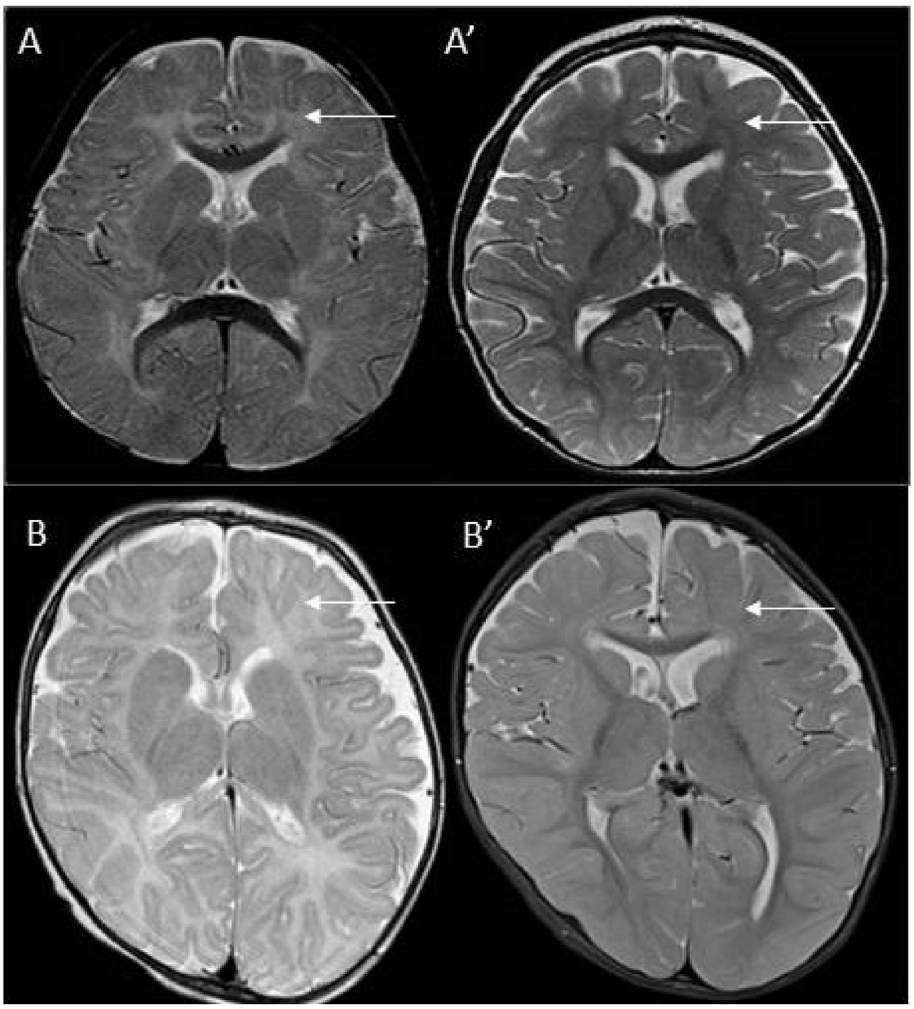

Fig. 17. SLC16A2 related *Allan–Herndon–Dudley syndrome* in two children: A-A′ at 2 and 5 years and B–B′ at one and 4 years show significantly reduced myelin in initial scans with significant progression in subsequent scans suggestive of delayed myelination. Note that myelination is still less than expected for age in the later scans.

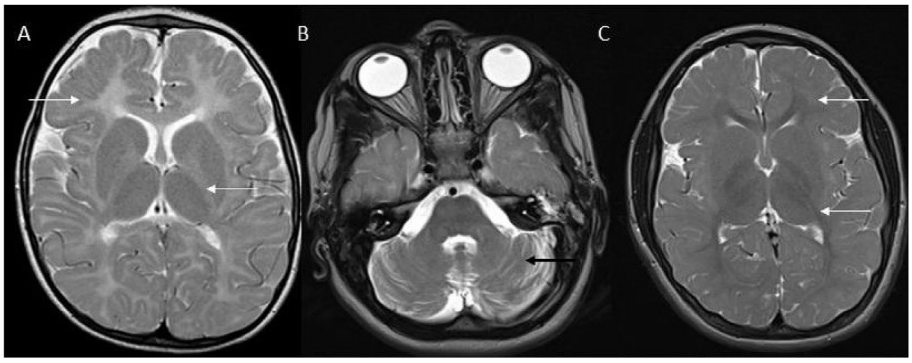

Fig. 18. Cerebral Folate deficiency: T2 axial images at 18 months showing marked reduction in myelin for age along with cerebellar atrophy (black arrow in B). Post folinic acid treatment MRI at 5 years shows significant improvement in myelination although still less than expected for age.

However, in a large majority of cases, genetic testing returns negative/non-confirmatory results. A comprehensive clinicoradiological phenotyping remains the cornerstone of diagnostic workup. It is also notable that clustering of highly distinct clinical and imaging phenotypes often leads to description of new nosologic entities (HABC and HEMS are good examples).

Advanced MRI techniques are available to better assess the presence of myelin and quantify it [45]. Multiple component relaxation analysis-based technique using Myelin Water Fraction (MWF) assessment for instance strongly correlates with the histological assessment of myelin content. Magnetisation Transfer Imaging is another robust technique which uses magnetisation exchange between immobile macromolecules like myelin and free water. Magnetisation transfer ratios are significantly reduced in

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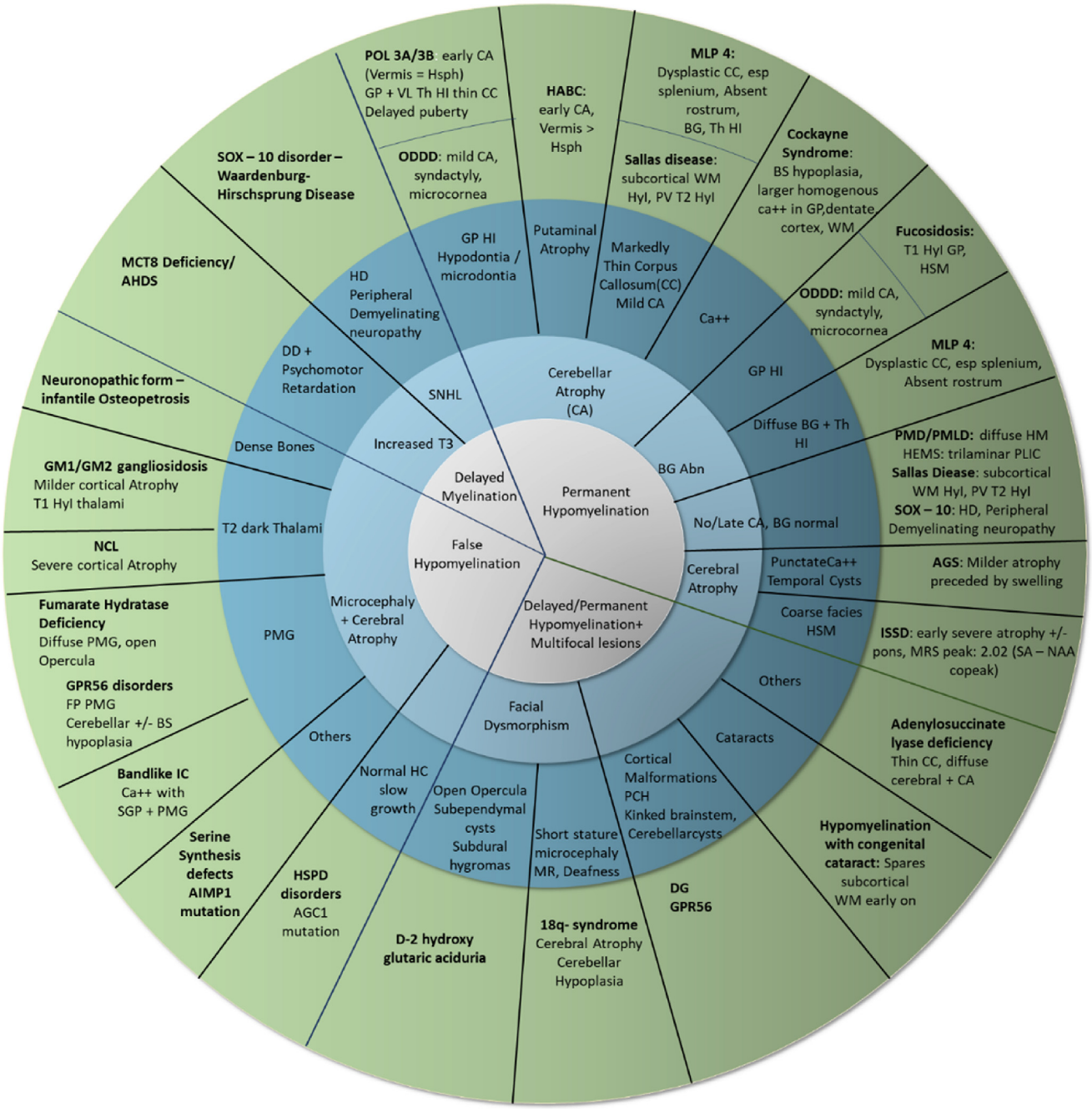

Fig. 19. Clinico-radiological algorithm for approaching hypomyelination Abbreviations: NCL: neuronal ceroid Lipofuscinosis, MCT8: monocarboxylate transporter 8, AHDS: Allan- Herndon- Dudley syndrome, DD: developmental delay, HD: Hirschsprung Disease, Hsph: hemsipheres, GP: Globus Pallidus, HI: hypointensity, Hyl: Hypertintensity, PV: periventricular, WM: white matter, SNL: sensorineural, CA: cerebellar atrophy, CC: corpus callosum, HABC: hypomyelination with atrophy of basal ganglia and cerebellum, MLP4: Mucolipidosis 4, BG: basal ganglia, Th: Thalamic, BS: brainstem, Ca++: calcification, PLIC: posterior limb of internal capsule, AGS: Aicardi-Goutieres Syndrome, ISSD: infantile sialic acid storage disorder, PCH: pontocerebellar hypoplasia, MR: mental retardation, IC: intracranial, SGP: simplified gyral pattern, PMG: polymicrogyria.

Table 4
When to suspect hypomyelination clinically.

Common clinical presentations suggesting a hypomyelinating leukodystrophy:
• Onset of symptoms usually from early infancy to childhood
• Initial motor predominant developmental delay followed by periods of stagnation of developmental milestones and then varying rates of neurological deterioration in a child with no adverse perinatal events
• Prominent nystagmus since early infancy
• Relatively preserved cognition
• Unexplained acute/subacute neurological deterioration in a child with developmental delay, precipitated by an inter-current illnesses, which might improve to baseline neurological functions gradually, though majority of times recruitment of progressive deficits eventually occurs

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Table 5
Neurological clues to diagnosis of HLDs.

Clinical Clue	Disease
Infantile onset neurological deterioration	Pelizaeus Merzbacher disease, Pelizaeus Merzbacher like disease, Hypomyelination with atrophy of basal ganglia and cerebellum, Hypomyelination with brainstem and spinal cord involvement and leg spasticity, GM1 gangliosidosis, GM2 gangliosidosis, Peripheral neuropathy central hypomyelination Waardenburg- Hirschsprung disease, Allen Herndon Dudley syndrome, serine synthesis defects
Late childhood onset neurological deterioration	Pol III related leukodystrophies, Hypomyelination with congenital cataract, sialidosis, 18q- syndrome, cockayne syndrome, Hypomyelination of early myelinated structures, fucosidosis
Early onset nystagmus	Pelizaeus Merzbacher disease, Pelizaeus Merzbacher like disease, Peripheral neuropathy central hypomyelination Waardenburg-Hirschsprung disease (PCWH)
Late onset nystagmus	Pol III-related leukodystrophies, 18q- syndrome, Oculodentodigital dysplasia
Early extrapyramidal features	Hypomyelination with atrophy of basal ganglia and cerebellum
Optic atrophy	GM1 and GM2 gangliosidosis, Pelizaeus Merzbacher like disease, Pol III-related leukodystrophies, serine synthesis defects, Oculodentodigital dysplasia
Seizures	Serine synthesis defects, GM1 and GM2 gangliosidosis, Oculodentodigital dysplasia, hypomyelination with congenital cataract, Salla disease, Hypomyelination with atrophy of basal ganglia and cerebellum (HABC), 18q- syndrome
Exaggerated startle	GM2 gangliosidosis
Neuropathy	Hypomyelination with congenital cataract, Peripheral neuropathy central hypomyelination Waardenburg-Hirschsprung disease (PCWH)
Muscle hypoplasia	Allen Herndon Dudley syndrome

Table 6
Non-neurological clues to diagnosis of HLDs.

Abnormal facies	
Dysmorphic facies	18q- syndrome, Oculodentodigital dysplasia
Coarse facies	Salla disease, Fucosidosis, GM1 gangliosidosis
Progeroid facies	Cockayne syndrome
Limb anomalies	18q- syndrome, Oculodentodigital dysplasia
Cardiac abnormalities	
Structural heart defect	18q- syndrome
Cardiomegaly	Fucosidosis
Skin	
Icthyosis	Trichothiodystrophy
Photosensitivity	Cockayne syndrome, Trichothiodystrophy
Angiokeratoma	Fucosidosis
Depigmentation	Peripheral neuropathy central hypomyelination Waardenburg-Hirschsprung disease (PCWH)
Persistent mongoloid spots	GM1 gangliosidosis
Hair	
Brittle hair with tiger tail banding pattern under polarised microscopy	Trichothiodystrophy
Endocrine abnormalities	
Hypogonadotropic hypogonadism, growth hormone deficiency, hypothyroidism	Pol 3 related leukodystrophies
Eye	
Microphthalmia, microcornea, glaucoma	Oculodentodigital dysplasia
Cherry red spot	GM1 and GM2 gangliosidosis
Cataract	Hypomyelination with congenital cataract, Pol III related leukodystrophies, galactosemia, oculodentodigital dysplasia,
Pigmentary retinopathy	Cockayne syndrome
Myopia	Pol III related leukodystrophies
Heterochromia iridis	Peripheral neuropathy central hypomyelination Waardenburg-Hirschsprung disease (PCWH)
Hearing loss	Peripheral neuropathy central hypomyelination Waardenburg-Hirschsprung disease (PCWH), GM1, GM2 gangliosidosis, 18q- syndrome, Pelizaeus Merzbacher like disease
Dysostosis multiplex	Fucosidosis, GM1 gangliosidosis, Salla disease, HSMD (AIFM1 related hypomyelination with spondylometaphyseal dysplasia)
Dental abnormalities	
Hypo/oligodontia	Pol 3 related leukodystrophies
Enamel hypoplasia, multiple caries tooth	Oculodentodigital dysplasia, Cockayne syndrome
Hepatosplenomegaly	GM1 gangliosidosis, Fucosidosis, Salla disease
Hypoglycemia, jaundice, bleeding manifestations, sepsis	Galactosemia
Genitourinary abnormalities	18q- syndrome
Hirschsprung disease and autonomic dysfunction	Peripheral neuropathy central hypomyelination Waardenburg-Hirschsprung disease (PCWH)
Recurrent infections	Trichothiodystrophy

hypomyelination.

In Diffusion Tensor Imaging, the Eigen value perpendicular to the axons (Radial Diffusivity) is an indicator of myelin density and increased values has been found to be most sensitive in detecting hypomyelination [2,29].

These techniques may not contribute much to the initial diagnosis but have potential as biomarkers of surrogate endpoints of clinical efficacy. This is especially true since it is difficult to define clinical endpoints for these rare disorders [2]. With increasing use of cell-based therapies in research and clinical trials, MRI will be a non-invasive tool to assess functional myelin engraftment and remyelination. In particular, MWF with its robust myelin quantification capabilities might be most useful in this respect.

MR Spectroscopy is limited as it cannot be used for myelin

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quantification but may be used to demonstrate some specific patterns like elevated NAA in classic PMD and reduced NAA in null disease [2]. Systematic analysis of spectroscopy data in these rare diseases needs further exploration for an enhanced role in distinguishing pathological subtypes.

10. Conclusion

Hypomyelination is associated with a large spectrum of pathologies that directly or indirectly affect myelin development and repair. The last few years have witnessed an exponential increase in the number of distinct genetically defined leukodystrophies, enhanced understanding of white matter pathobiology and evolving definitions and classifications. This has significantly impacted the landscape of therapeutic research. As the focus shifts from evaluation to management of these rare disorders, multidisciplinary approach and international collaborations are extremely essential to achieve the much-awaited goals of stopping the disease process or limiting disability. Clinicians, Radiologists, geneticists and researchers should each appreciate and incorporate the various methodologies in their repertoire towards this.

Funding

No funding was received for this study.

Ethical approval

All procedures performed in the studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

A clinico-radiological algorithmic approach based on clinical and MRI features is presented in Fig. 19. A comprehensive summary of HLDs is also presented as table in Supplementary data. The list of diseases presented is not all inclusive and will continue to expand as new genomic findings emerge.

Informed consent

Informed consent was obtained from all individual participants included in the study.

Declaration of competing interest

The authors declare that they have no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejpn.2020.04.007.

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