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## Leucodystrophies at children

### Wiktoria Sielwanowska

ORCID: 0000-0002-4660-5027; e-mail: wiktoria.sielwanowska@gmail.com

Affiliation: Department of Child Neurology, Medical University of Lublin, Poland

### Bartłomiej Syzdol

ORCID: 0000-0001-5940-7399; e-mail: bartlomiej.syzdol@gmail.com

Affiliation: Department of Child Neurology, Medical University of Lublin, Poland

### Anna Rzewuska

ORCID: 0000-0003-4553-0825; e-mail: aniarzewuska@wp.pl

Affiliation: Department of Child Neurology Medical University of Lublin, Poland

### Monika Żybowska

ORCID: 0000-0002-3885-5907; e-mail: zybowska.m@gmail.com

Affiliation: Department of Child Neurology, Medical University of Lublin, Poland

**Prof. Magdalena Chrościńska-Krawczyk**

ORCID: 0000-0001-8121-6580; e-mail: magdalenachk@wp.pl

Affiliation: Department of Child Neurology, Medical University of Lublin, Poland

## **Abstract**

### **Introduction**

Leukodystrophies involve a diverse group of rare hereditary disorders mostly affecting the white matter of the central nervous system, which straddles nerves and glial cells. Unfortunately, these conditions are often undervalued by doctors from various specialties. The aim of the article was to present the most common leukodystrophies occurring in children

### **Material and methods**

A review of the most common leukodystrophies based on the available literature. We conducted a systematic literature review. We searched the PubMed and Google Scholar databases from 1997 to 2023.

### **Conclusions**

Leukodystrophies are rare genetic diseases that often present with non-specific symptoms, which can pose diagnostic challenges. Ocular abnormalities and psychomotor delay in the early stages of life should raise suspicion. A combination of symptoms may suggest a pyramidal-extrapyramidal form of cerebral palsy. Therefore, it is crucial to include a head MRI examination in the diagnostic workup and carefully evaluate the findings, as subtle imaging changes can indicate the presence of leukodystrophies. Currently, no causal treatment for leukodystrophies has been developed. Hence, further research is needed to enable the introduction of gene therapies.

**Key words:** leukodystrophies, hypomyelinating leukodystrophies, Pelizaeus-Merzbacher Disease, dysmyelinating leukodystrophies

## **Introduction**

Leukodystrophies involve a diverse group of rare hereditary disorders mostly affecting the white matter of the central nervous system, which straddles nerves and glial cells. Unfortunately, these conditions are often undervalued by doctors from various specialties. Diagnosis is challenging due to the non-specific nature of initial clinical symptoms, which can manifest at various ages from infancy to adulthood [1]. In regard to MRI, leukodystrophies can be classified into two groups: hypomyelinating leukodystrophy (HLD) and demyelinating leukodystrophy (LDD). HLD is marked by the complete absence, deficiency, or abnormality of myelination, whereas LDD involves progressive damage to the spinal cord. Early-stage disease characteristics can be identified through magnetic resonance imaging. The best option are sequences such as T2, T1, SWI, and DWI. In HLD, the white matter exhibits slightly higher signal intensity than the cortex on T2-weighted sequences and may appear isointense, hypointense, or hyperintense on T1-weighted sequences. Abnormal myelination is appointed by poor diversity between the cortex and subcortical regions. Additionally, there are blurry changes in the white matter presenting floating signal intensity. Reversely, demyelinating leukodystrophies manifest as highly hyperintense signals in the white matter on T2-weighted sequences and hypointense signals on T1-weighted sequences. These changes typically appear symmetrically. However, a couple of factors need to be treated during differential diagnosis. It is very important to remember that imaging findings should be always correlated with the patient's clinical presentation. [1,2,3]

## **Hypomyelinating leukodystrophies (HLD)**

As of now, 14 genes responsible for the development of HLD (Hypomyelinating Leukodystrophy) have been identified. However, there are still many disorders of unknown etiology. Early-onset forms of the disease are characterized by a very unfavorable prognosis. Children with HLD experience psychomotor delay and are generally highly hypotonic. Rapid progression leads to premature death. Late-onset forms of the disease are characterized by more nonspecific symptoms. On the other hand, forms with a later onset are characterized by more nonspecific symptoms, relatively slow progression, and motor delay caused by gradually increasing hypotonia, primarily due to damage to the central nervous system but can also result from peripheral neuropathy. Ocular ataxia is in the majority present. Extrapyrmidal symptoms are common (unlike demyelinating leukodystrophies). Initially, dyskinesias prevail, and as the disease progresses, dystonia appears. The cognitive development of children with HLD is slightly delayed, and sometimes even normal. [2]

### **Pelizaeus-Merzbacher Disease (PMD)**

Compared to other leukodystrophies, Pelizaeus-Merzbacher disease (PMD) is relatively rare. Its prevalence ranges from 1 in 90,000 to 1 in 750,000 live births. [4,5] This disease is inherited in an X-linked recessive manner, which means it predominantly affects boys. Heterozygous girls do not exhibit neurological symptoms. Depending on the type of mutation in the PLP1 gene, PMD can manifest in various forms. The most common form is the duplication of the entire PLP1 gene. The PLP1 protein is a membrane protein, and mutations in this gene lead to abnormal protein folding, resulting in its accumulation in the endoplasmic reticulum. This accumulation is toxic to oligodendrocytes, leading to decreased myelin synthesis and axonal damage. PMD can be divided into three subtypes: the most severe form, connatal PMD, spastic paraplegia type 2 (SPG-2), and classical PMD. [6]

In MRI scans of patients with connatal PMD, a lack of myelin and oligodendrocytes is observed in most areas of the brain. However, there are no focal areas of demyelination. SPG-2 shows characteristic tiger-striped areas of myelin. Classical PMD exhibits a certain degree of myelin degradation. Internal capsules, brainstem, and cerebellum may also be affected. The rarest form is connatal PMD, which has the most severe course. During its progression, intrauterine growth restriction, significant psychomotor and physical developmental delay, extreme hypotonia including stridor, congenital microcephaly, and

nystagmus are observed. Deep reflexes are preserved. Respiratory failure and death occur rapidly. In classical PMD, nystagmus, motor developmental delay, and generalized hypotonia are predominant. Deep reflexes are often exaggerated. Dystonia may develop over time. This form progresses slowly, making it important to consider in the differential diagnosis of cerebral palsy. Spasticity develops over several years. In SPG-2, nystagmus, spasticity, ataxia, and mild cognitive impairment are present. In uncomplicated cases, life expectancy is not shortened. In children with this disease, cognitive development can be normal or significantly delayed. There is no definitive treatment for Pelizaeus-Merzbacher disease, and current management is mainly symptomatic and palliative. However, research is ongoing to investigate treatment methods targeting the molecular mechanisms responsible for PMD. [3]

### **Hypomyelination with atrophy of basal ganglia and cerebellum (HLD6, H-ABC)**

Hypomyelination with atrophy of basal ganglia and cerebellum (HLD6, H-ABC) is induced by mutation in the TUBB4 gene. The disease is extremely rare. It progresses slowly, and patients have an average life expectancy of 30 years. During the fetal period, weakened fetal movements and polyhydramnios may be noticeable. The first symptoms become apparent after birth and include nystagmus, hypotonia, and psychomotor delay. Head circumference growth is small, and microcephaly often develops. As the disease progresses, spasticity, dystonia, and exaggerated deep reflexes appear. HLD6 can sometimes be mistaken for a form of pyramidal-extrapyramidal cerebral palsy. However, a definitive diagnosis can be made through MRI, which reveals hypomyelination and atrophy of the striatum, and occasionally the cerebellum. [7]

### **Hypomyelination leukodystrophy type 7 and 8**

These leukodystrophies are caused by mutations in the POLR3A and POLR3B genes. The complete syndrome of symptoms is called 4H leukodystrophy, which consists of hypomyelination, hypodontia, and hypogonadotropic hypogonadism. [8] It is characterized by a progressive and slow course. However, the earlier the symptoms appear, the more severe the disease is. Patients present with delayed psychomotor development, with some never starting to walk or having unsteady gait. Motor ataxia, hypotonia, and diminished deep

reflexes are characteristic. Intellectual development is delayed. Other symptoms that may complicate the differential diagnosis include delayed or absent tooth eruption and lack of sexual maturation. The disease can be mistaken for panhypopituitarism or Turner syndrome. MRI imaging, which facilitates diagnosis, shows progressive corpus callosum atrophy with age and occasionally cerebellar atrophy. [9]

### **18q deletion syndrome (18q-)**

This disease is associated with a lack of eosinophil cationic protein (MBP). The clinical picture varies depending on the extent of the deletion. In addition to symptoms affecting the nervous system, such as psychomotor impairment, motor clumsiness, and microcephaly, facial and cranial dysmorphic features, particularly of the ears, as well as heart defects, may be observed. In more severe cases, extrapyramidal-pyramidal syndrome symptoms, nystagmus, and seizures can occur. In this case, MRI imaging does not always allow for a definitive diagnosis. The imaging reveals a slower rate of myelination compared to peers, and cerebellar atrophy may develop over time.[10]

### **Dysmyelinating leukodystrophies (LDD)**

This type of leukodystrophy involves progressive demyelination. The symptoms of these diseases are nonspecific, and the course is more severe when symptoms appear earlier. Initially, children develop normally, but they experience psychomotor regression, ataxia, and gait disturbances over time. Eventually, spastic quadriplegia, swallowing disorders, and even decerebration occur. Dementia is also often observed. Dysmyelinating leukodystrophies are progressive disorders over time. [11]

### **Metachromatic leukodystrophy (MLD)**

Metachromatic leukodystrophy (MLD) is an autosomal recessive lysosomal disorder resulting from a mutation in the ARSA gene. The defect leads to the accumulation of sulfatides in the central and peripheral nervous system (as well as in organs such as the kidneys) and damage to myelin. The estimated frequency of MLD is between 1 in 40 000 to 1 in 160 000 worldwide. It is the most common leukodystrophy in Poland. The disease can

develop at different ages and can be divided into late-infantile, juvenile, and adult forms. Generally, the earlier the symptoms appear, the more severe the course of the disease. If left untreated, it leads to death. In every form of the disease, there is damage to the peripheral nerves. After a period of normal development, regression, spasticity, and decerebration occur. Another characteristic symptom is optic nerve atrophy. If the disease manifests earlier, initial symptoms may include gait disturbances, followed by flaccidity, peripheral neuropathy, and rapid progression to spastic quadriplegia. In adolescents and adults, pyramidal signs, ataxia, and progressive dementia are present. Magnetic resonance imaging (MRI) performs a significant role in the diagnosis, revealing characteristic abnormalities—symmetrical bilateral hyperintense signals in the T2 projection starting from the corpus callosum and then involving the periventricular white matter. Within the white matter, spot patterns ("tigroid skin") and bands corresponding to preserved areas of myelin around vessels are often visible [12].

### **Globoid cell leukodystrophy (Krabbe disease, GLD)**

Krabbe disease, or globoid cell leukodystrophy (GLD), is an autosomal recessive lysosomal disorder. Mutation in the GALC gene causes a deficiency of beta-galactocerebrosidase, leading to the accumulation of galactocerebroside in the central and peripheral nervous system. It caused demyelination, brain atrophy and the formation of globoid cells. The role of pro-inflammatory cytokines in the pathogenesis of GLD is not yet fully understood. Similar to MLD, depending on the age of onset of noticeable symptoms, it can be classified into infantile (most common and most severe), juvenile, and adult forms. In the infantile form, shortly after a period of normal development, psychomotor regression occurs. Infants become hypersensitive to touch, progressive spasticity appears, and vision and hearing are lost. Children with the infantile form usually do not survive beyond the age of 2. Forms with later onset exhibit a slower and milder progression. Developmental arrest, ataxia, and demyelinating peripheral neuropathy occur, leading to spastic quadriplegia. Death occurs several years after the onset of initial symptoms. Adults with GLD experience dementia alongside the symptoms. MRI findings show changes in the white matter starting from the cerebellum and brainstem, progressing to both hemispheres over time. In adults, involvement of the parieto-occipital lobes predominates. Microscopic examination reveals globoid cells in

areas of myelin breakdown. Diagnosis can also be confirmed by evaluating the activity of beta-galactocerebrosidase in peripheral blood leukocytes.[13,14]

### **Adrenoleukodystrophy linked to the X chromosome (X-ALD):**

X-ALD is the second most diagnosed leukodystrophy in Poland. Its estimated frequency of occurrence is 1 in 14 700 births. It is caused by a mutation in the ABCD1 gene located on the X chromosome. As a result, there is a disruption in beta-oxidation processes and the accumulation of very long-chain fatty acids (VLCFA) in the central nervous system, leading to demyelination. The disease is inherited in an autosomal recessive manner. There are different forms of X-ALD, including the cerebral forms, which mainly affect boys between the ages of 3 and 10, and adrenomyeloneuropathy, which predominantly occurs in adults. Approximately, over of 60% patients has primary adrenal insufficiency. Female carriers typically exhibit a milder course of the disease with subtle symptoms. In the cerebral form, symptoms include ataxia, gait disturbances, followed by rapid progression to quadriplegia with spasticity and dementia. Behavioral disturbances and occasional psychotic symptoms may also occur. On average, patients with X-ALD survive for about 2 years from the onset of symptoms. Magnetic resonance imaging (MRI) exposes simetrically demyelinating changes with an inflammatory edge hat, which becomes more apparent after gadolinium administration. However, the initial diagnostic test is the measurement of VLCFA levels in the serum. Collecting a detailed family history is crucial in identifying discreet symptoms of adrenal insufficiency, as they may have been misattributed to other conditions. [15]

### **Leukoencephalopathy with brainstem and spinal cord involvement and elevated lactate levels (LBSL)**

LBSL is a rare autosomal recessive inherited disorder caused by mutations in the DARS2 gene. The disease manifests in various forms, with the classic form characterized by a slow progression. Initial symptoms include ataxia and a combination of extrapyramidal and pyramidal features. A distinctive "stork-like" gait resulting from posterior column damage in the spinal cord is also observed. Intellectual development and dementia are generally unaffected. MRI shows numerous round lesions in the deep white matter, and T2-weighted

sequences reveal hyperintense changes in the posterior columns of the spinal cord. Magnetic resonance spectroscopy (MRS) demonstrates an elevated lactate peak. [16]

### **Vanishing white matter disease (VWM)**

VWM is inherited in an autosomal recessive manner and is caused by mutations in the EIF2B gene. The pathomechanism of the disease is not fully understood. Unlike the previous leukodystrophies, VWM develops gradually. However, as the disease progresses, patients become disabled due to generalized hypotonia. VWM can develop in the early infancy period or later in life. Severe cases may exhibit initial symptoms in the last trimester of pregnancy, including oligohydramnios and intrauterine growth retardation. However, in the majority of cases, the first noticeable symptoms occur between 1 and 5 years of age. After an initial period of normal development, there is a delay in motor development, accompanied by spasticity and ataxia. Intellectual developmental disorders are generally absent or mild. Disease progression is non-uniform with periods of exacerbation. The characteristic MRI finding is bilateral gradual disappearance of the periventricular white matter. The white matter signal gradually resembles that of cerebrospinal fluid over time. Currently, there is no effective treatment for VWM. [17,18]

### **Alexander Disease (ALXDRD)**

One of the few leukodystrophies inherited in an autosomal dominant manner. It is caused by a mutation in the GFAP gene, resulting in a defect in astrocyte cells. Pathological protein accumulates in the cytoplasm and processes of astrocytes in the form of Rosenthal fibers. ALXDRD can present as neonatal, infantile, juvenile, or adult forms. Progression is slowly. In individuals with the neonatal form, the first symptoms occur within the first 30 days of life and manifest as hydrocephalus and various neurological symptoms such as hypotonia, hyperactivity, and myoclonus. The infantile form is characterized by a slow progression of spasticity affecting mainly the lower limbs. Seizures may also occur. In the juvenile form, initially normal development and subtly emerging symptoms such as morning vomiting, choking, clumsiness, or nasal speech are common. After years, the development of a combined pyramidal-extrapyramidal syndrome may occur. In the adult form, the first symptoms often resemble a pseudo-bulbar palsy syndrome, including dysarthria, dysphagia,

dysphonia. Motor disturbances and pyramidal features may also be present. In adults, ALXDRD can manifest as spastic paraparesis or dementia. The MRI findings are not specific to this disease but may show asymmetric demyelinating changes in the white matter of the brain. [19]

### **Canavan Disease (CD)**

Caused by a mutation in the ASPA gene inherited in an autosomal recessive manner. The genetic defect leads to the accumulation of N-acetylaspartic acid (NAA) in the brain, resulting in oligodendrocyte dysfunction and myelin degeneration. Symptoms typically occur early and include macrocephaly, generalized hypotonia, and progressive psychomotor regression, as well as the development of a combined pyramidal-extrapyramidal syndrome. The MRI image reveals white matter degeneration starting from subcortical areas. A notable feature is megalencephaly, an enlarged brain. Diagnosis is mainly based on symptoms, imaging studies, and significantly elevated levels of NAA in the urine. [20]

### **Megalencephalic Leukoencephalopathy with Subcortical Cysts (MLC)**

The disease is autosomal recessive inheritance. It is caused by a mutation in the MLC1 or HEPACAM gene. A characteristic feature of MLC is rapid head growth starting in the first year of life. The disease develops very slowly, with initially normal or slightly delayed psychomotor development. Typically, initial symptoms such as ataxia and mild mental regression occur after a head injury. Over time, features of a combined pyramidal-extrapyramidal syndrome appear. The MRI shows demyelination features, and as the disease progresses, subcortical cysts appear in the temporal and frontal lobes. [21]

### **Adult-Onset Autosomal Dominant Leukodystrophy (ADLD)**

The reason of ADLD is duplication of the LMNB1 gene. The first symptoms appear in the fourth or fifth decade of life and mainly involve the autonomic nervous system (sphincter disturbances, orthostatic hypotension). The predominant neurological symptom is slowly progressive spastic paraparesis. MRI examination reveals symmetrical involvement of the white matter of the cerebral hemispheres. [22]

## **Hereditary Diffuse Leukoencephalopathy with Spheroids (HDLS)**

Hereditary Diffuse Leukoencephalopathy with Spheroids (HDLS) is an autosomal dominant inherited disease that typically manifests in the fifth or sixth decade of life. It is caused by a mutation in the CSF1R gene. The predominant symptoms include apraxia, parkinsonism, dementia, depression, and pyramidal syndrome. HDLS progresses intensely, and death usually occurs around 6 years after the onset of symptoms. On MRI, there are bilateral, asymmetric white matter involvement in the cerebral hemispheres, with a predominance of frontal and temporal lobe affection. [23]

## **Treatment**

In most cases of leukodystrophies, the only available form of treatment is symptomatic management, along with rehabilitation, occupational therapy, and nutritional support. In specific types such as Metachromatic Leukodystrophy (MLD), Globoid Cell Leukodystrophy (GLD), and X-linked Adrenoleukodystrophy (X-ALD), there is a potential for disease-modifying treatment in the pre-symptomatic phase through allogeneic bone marrow transplantation. However, this treatment option is often limited to the affected individual's first-degree siblings, as the preparatory process for transplantation can be too burdensome for individuals with central nervous system involvement during the symptomatic phase. In recent years, there have been ongoing research efforts into gene therapies, although the results have not been satisfactory thus far. Further research is needed to explore possible treatment approaches for leukodystrophies, particularly in the pre-symptomatic period. [24]

## **Conclusions**

Leukodystrophies are rare genetic diseases that often present with non-specific symptoms, which can pose diagnostic challenges. Ocular abnormalities and psychomotor delay in the early stages of life should raise suspicion. A combination of symptoms may suggest a pyramidal-extrapyramidal form of cerebral palsy. Therefore, it is crucial to include a head MRI examination in the diagnostic workup and carefully evaluate the findings, as subtle imaging changes can indicate the presence of leukodystrophies. Currently, no causal

treatment for leukodystrophies has been developed. Hence, further research is needed to enable the introduction of gene therapies.

## **Disclosures**

### **Author's contribution:**

Conceptualization, Sielwanowska W., Syzdoł B., Chrościńska-Krawczyk M., Żybowska M., Rzewuska A.; methodology, Sielwanowska W., Syzdoł B., Chrościńska-Krawczyk M.; software, Żybowska M., Rzewuska A.; check, Syzdoł B.; formal analysis, Chrościńska-Krawczyk M.; investigation, Sielwanowska W., Syzdoł B.; resources, Sielwanowska W., Syzdoł B., Chrościńska-Krawczyk M., Żybowska M., Rzewuska A.; data curation, Sielwanowska W., Syzdoł B., Chrościńska-Krawczyk M., Żybowska M., Rzewuska A.; writing - rough preparation, Sielwanowska W., Syzdoł B., Żybowska M., Rzewuska A.; writing - review and editing, Sielwanowska W., Syzdoł B., Chrościńska-Krawczyk M.; visualization, Sielwanowska W., Syzdoł B., Chrościńska-Krawczyk M.; supervision, Sielwanowska W., Chrościńska-Krawczyk M.; project administration, Sielwanowska W., Chrościńska-Krawczyk M.;

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