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Adulthood leukodystrophies

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Abstract

The leukodystrophies are a group of inherited white matter disorders with a heterogeneous genetic background, considerable phenotypic variability and disease onset at all ages. This Review focuses on leukodystrophies with major prevalence or primary onset in adulthood. We summarize 20 leukodystrophies with adult presentations, providing information on the underlying genetic mutations and on biochemical assays that aid diagnosis, where available. Definitions, clinical characteristics, age of onset, MRI findings and treatment options are all described, providing a comprehensive overview of the current knowledge of the various adulthood leukodystrophies. We highlight the distinction between adult-onset leukodystrophies and other inherited disorders with white matter involvement, and we propose a diagnostic pathway for timely recognition of adulthood leukodystrophies in a routine clinical setting. In addition, we provide detailed clinical information on selected adult-onset leukodystrophies, including X-linked adrenoleukodystrophy, metachromatic leukodystrophy, cerebrotendinous xanthomatosis, hereditary diffuse leukoencephalopathy with axonal spheroids, autosomal dominant adult-onset demyelinating leukodystrophy, adult polyglucosan body disease, and leukoencephalopathy with vanishing white matter. Ultimately, this Review aims to provide helpful suggestions to identify treatable adulthood leukodystrophies at an early stage in the disease course.

The leukodystrophies are a class of inherited white matter disorders with diverse genetic underpinnings and substantial phenotypic variability[1]. Leukodystrophies have become an important differential diagnosis in adulthood white matter diseases[2], despite the fact that white matter injury in adulthood is more often caused by acquired leukoencephalopathies with vascular, toxic, degenerative or inflammatory pathology, such as multiple sclerosis (MS), neuromyelitis optica or stroke. Making the differential diagnosis even more challenging, adulthood leukodystrophies must be differentiated from other heritable diseases

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with prominent white matter involvement that are not leukodystrophies, for example, inherited vasculopathies, which can result in white matter signal abnormalities, or later-onset or slowly progressing inborn errors of metabolism with secondary white matter involvement[3].

In this Review, we provide a comprehensive overview of the leukodystrophies that present in adulthood, focusing on those for which treatments are available. We provide information on age of onset, clinical symptoms, genetic mutations and, where available, biochemical assays that assist in diagnosis. For a summary of the leukodystrophies that rarely or never present during adulthood, which are not covered by this Review, see Supplementary information S1 (table). These conditions have also been reviewed elsewhere[4].

Classification and definitions

Leukodystrophies are defined as inherited disorders that affect the cerebral white matter. Cells involved in the axon–glia unit, such as oligodendrocytes, astrocytes, ependymal cells and microglia, are specifically affected[5]. Alterations to these non-neuronal cells lead to myelin sheath — and subsequently axonal — pathology. The underlying pathological mechanisms vary widely, involving inborn errors of metabolism, disrupted protein biosynthesis, oxidative stress and energy failure, among others. In addition to white matter involvement, some of the leukodystrophies include marked axonal pathology, either early in the disease process (though usually to a minor extent) or secondary to progressive myelin disruption in later disease stages. Involvement of the PNS is observed in some but not all leukodystrophies.

In many cases, pathological assessment is not feasible, so clinicians must rely on the molecular aetiology of the disorder and, importantly, on the appearance of the white matter on neuroimaging to define and classify the various disorders[6]. Leukodystrophies can be broadly subdivided into hypomyelinating leukodystrophies (HLDs), which are characterized by primary deficits in myelin development, and demyelinating leukodystrophies, where myelin develops normally but subsequently undergoes progressive disruption. The two groups can be easily differentiated on MRI, as individuals with HLDs show increased white matter signal on T2-weighted sequences and isointense or hyperintense white matter signal on T1-weighted sequences, whereas demyelination is characterized by increased T2 and substantially decreased T1 signals[6]. Most adulthood leukodystrophies are demyelinating in nature, and adult-onset HLDs are presumed to be very rare. However, some HLDs, such as Pol-III-related leukodystrophies with childhood or adolescent onset, can progress slowly and might be recognized only in adulthood[7]. Additional MRI features, such as calcifications, vacuolization or cysts, brainstem or basal ganglia involvement, intramyelinic oedema, or contrast enhancement, can aid MRI pattern recognition of the various leukodystrophies and are of key importance in establishing a diagnosis of an adulthood leukodystrophy[6,8].

Clinical presentation

Leukodystrophies can present across the lifespan. It is important to note that leukodystrophies rarely show precise genotype–phenotype correlation, and the same gene

defect might cause both childhood and adulthood phenotypes in the same family, as observed in X-linked adrenoleukodystrophy (X-ALD), for example[9]. Many adulthood leukodystrophies, such as the adrenomyeloneuropathy (AMN) phenotype of X-ALD[10], or adult polyglucosan body disease[11] (APBD), progress slowly over years or even decades, but rapid deterioration can occur in some diseases (for example, metachromatic leukodystrophy[12] (MLD) and cerebral presentation of X-ALD in adulthood). Others, such as megalencephalic leukoencephalopathy with subcortical cysts (MLC), can even improve with age[13]. TABLE 1 provides a complete overview of the currently known adult-onset leukodystrophies, including clinical and diagnostic signs, age of onset and mutated genes.

Neurological and psychiatric symptoms.

The most prominent symptoms in adulthood leukodystrophies tend to be motor impairment and/or varying degrees of cognitive impairment[3] (BOX 1). Pyramidal motor symptoms develop in a symmetrical fashion and may start in the lower extremities, mimicking spastic paraparesis. Gait abnormalities can be complicated by gait ataxia, as in hypomyelinating disorders or MLD, or by sensory long-tract signs, as in leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation (LBSL). Often, bulbar symptoms develop in the later stages, but they might be an early manifestation in certain disorders, including Alexander disease (AxD). Distal symmetric sensory symptoms in the lower extremities and autonomic dysfunctions such as bladder, bowel or sexual impotence, which can mimic transverse myelitis or anterior horn disease, can also be present (for example, in APBD or autosomal dominant adult-onset demyelinating leukodystrophy (ADLD)). Extrapyramidal movement disorders, such as dystonia and/or dyskinesias or seizures, are less frequent but might be a predominant manifestation in certain disorders, including progressive leukoencephalopathy with ovarian failure, various HLDs and AxD. Cognitive symptoms may initially be subtle and, thus, remain undiscovered until other neurological symptoms occur. However, in conditions such as hereditary diffuse leukoencephalopathy with axonal spheroids (HDLS) and lysosomal storage disorders, cognitive symptoms are often the presenting manifestations. In contrast to classic dementias such as Alzheimer disease, memory deficits, disorientation and psychosis are less prominent than behavioural changes, mood changes and loss of realistic assessments of daily life experiences[14].

Extraneurological findings.

In the context of adulthood leukodystrophies, extraneurological symptoms can offer important clues to a specific diagnosis (BOX 2). With the exception of Addisonian crisis in X-ALD, such symptoms are usually not life-threatening. However, symptoms such as the lack of pubertal development and cosmetic dental abnormalities in Pol-III-related HLDs can adversely affect functioning and quality of life. These systemic complications are often more amenable to treatment than is the primary neurological disorder, and every effort should be made to manage these complications[15].

Epidemiology

Epidemiological data on the frequency of leukodystrophies are limited; for all leukodystrophies, estimates range from 1 in 50,000 to 1 in 7,500 (REFS 16,17), compared

with 1 in 16,800 for all X-ALD phenotypes[18]. The relative frequencies of specific adulthood leukodystrophies are unclear[19].

Although individual adulthood leukodystrophies are rare, they are increasingly recognized, probably owing to the increased use of MRI. Furthermore, phenotypes in adulthood leukodystrophies are incompletely characterized or remain unsolved in approximately 50% of all cases, resulting in a high estimated number of unreported cases and prolonged diagnostic procedures for patients and families[17]. The differential diagnosis is further complicated by the fact that other inherited and acquired disorders can present with similar clinical and radiological features[20,21].

Diagnosis of an adult-onset leukodystrophy has important implications for family planning and symptom management. In individuals presenting with white matter abnormalities, it is important to obtain a detailed three-generation family history, asking about leukodystrophy-specific symptoms (in adulthood and childhood), early deaths from unclear neurological or psychiatric diseases, and parental consanguinity, to ensure that these disorders are not missed.

Diagnosis

Differential diagnosis.

Before confirming a diagnosis of leukodystrophy, neurologists need rule out more-common causes of white matter abnormality (FIG. 1). Steps such as a family history, history of symptom onset, physical examination, laboratory studies, MRI and lumbar puncture can be helpful. In some cases, laboratory testing might point to risk factors for vascular, inflammatory, degenerative, neoplastic and toxic causes of white matter disease. In other cases, neuroimaging may be helpful to recognize specific disease patterns, for example, the subcortical infarcts in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)[22] or specific features in MS[23]. Careful consideration of treatable aetiologies, including autoimmune and antibody-mediated disorders, vitamin deficiencies and neoplasms, is warranted before determining that the patient is likely to have an inherited disorder. The adulthood leukodystrophies must also be differentiated from other inherited diseases with prominent involvement of the CNS white matter (TABLE 2).

Diagnostic algorithm.

In individuals in whom clinical symptoms are suggestive of an adulthood leukodystrophy (BOX 1) and MRI demonstrates brain white matter abnormalities, a stepwise diagnostic approach is advisable (FIG. 1). Physical examination or additional historical information, for example, from family history or involvement of extracerebral organs, may aid diagnosis in some cases. Careful review of the MRI scan by a clinician with expertise in pattern recognition for leukodystrophies might provide a specific diagnosis in certain disorders, including X-ALD[24], AxD[21] and leukoencephalopathy with vanishing white matter (also known as vanishing white matter disease, or VWMD[2,6]) (BOX 3; FIG. 2). Diagnostic confirmation is further achieved by targeted metabolic or genetic testing if the prior

investigations suggest a specific diagnosis; however, in about 50% of all adulthood leukodystrophies, these standard approaches are unlikely to yield a precise diagnosis.

Recent studies using whole-exome sequencing (WES) in leukodystrophies have shown that such next-generation sequencing techniques can increase diagnostic yields to greater than 70%[25,26], providing strong support for WES as a first-line diagnostic tool. In cases where an initial review of clinical, imaging and laboratory features does not suggest a specific diagnosis, initiation of next-generation sequencing approaches would be recommended as the next diagnostic step[25].

Brain biopsies in cases of suspected leukodystrophy should be considered only in patients with potentially treatable conditions when all other investigations have failed to provide a diagnosis, or in patients who are deteriorating rapidly.

Selected leukodystrophies

In this section, we review the main features of a selection of adulthood leukodystrophies. We have chosen to focus on those conditions for which treatments are currently available.

X-Linked adrenoleukodystrophy.

X-ALD is one of the most frequent leukodystrophies occurring in adulthood. The various phenotypes include a cerebral inflammatory demyelinating form (adult cerebral X-ALD (ACALD)), which is the primary manifestation in ~5% of affected adults, and a more frequent, slowly progressive myelopathic variant (AMN) with spastic paraplegia and bladder and sexual dysfunction[10].

X-ALD is caused by mutations in *ABCD1*, which encodes the peroxisomal membrane protein ATP-binding cassette sub-family D member 1 (ALDP)[27]. Dysfunction of ALDP results in the accumulation of very long chain fatty acids (VLCFAs) in the nervous system as well as in the adrenal glands, testis and body fluids[28]. The toxic effects from VLCFAs are thought to provoke oxidative stress phenomena, energy depletion and chronic neurodegeneration. Together, these pathological mechanisms lead to slowly progressive dyingback axonopathy in spinal cord tracts and peripheral nerves[29], typically leading to spastic–ataxic gait disturbances starting in the third to fourth decade of life. In addition to neurodegeneration, inflammatory brain demyelination occurs in up to 60% of patients[30]. The reason for this cerebral transformation remains unknown, but multiple risk factors, including head trauma, autosomal modifier genes, impaired mitochondrial function and vascular and biochemical factors, have been hypothesized.

Allogeneic haematopoietic stem cell transplantation (aHSCT) has been shown to halt cerebral inflammation in childhood cerebral X-ALD (CCALD)[31] and ACALD[32], and is currently the only available life-saving treatment option in ACALD phenotypes. However, aHSCT carries several risks, including treatment-related mortality, graft failure, graft-versus-host disease (GVHD) and opportunistic infections, due to the immunosuppression used to treat GVHD. Although full chimaerism is achieved in most aHSCT-treated patients, the biochemical abnormality is still present in nervous system cells and ultimately leads

to AMN later in life[33]. Long-term data on aHSCT in adulthood are sparse, but from our own experience, stabilization of inflammatory brain demyelination can be expected in most patients (W.K., unpublished observations). Severe disease (Expanded Disability Status Scale score >6), advanced changes on MRI (Loes score >10) and cognitive changes before transplantation seem to correlate with an unfavourable outcome of aHSCT.

As a proof of principle, an *ex vivo* lentiviral gene therapy approach in boys with cerebral inflammatory disease has shown long-term disease stabilization[34]. A multicentre phase II/III study, which was published in October 2017, assessed the efficacy and safety of *ex vivo* transduction of autologous $CD34^+$ cells with the lentiviral vector elivaldogene tavalentivec (Lenti-D) to treat CCALD. In this study, 15 of 17 boys were alive with no major functional disability 24 months after treatment[35]. Although the long-term risks and effectiveness are still under investigation, gene therapy shows promise as a treatment option with long-term benefits in patients with CCALD[36].

Prevention of neurodegeneration in patients with X-ALD seems to be more challenging[37]. Studies using high-dose biotin to promote axonal remyelination and enhance energy production[38] and studies using peroxisome proliferator-activated receptor-γ agonists to target oxidative stress and enhance mitochondrial function[39] are ongoing.

Efforts are underway to implement newborn screening for X-ALD[40,41] in an increasing number of countries — an approach that seems to be justified given the substantial progress in therapeutic research.

Metachromatic leukodystrophy.

MLD is a good example of an adulthood leukodystrophy that is frequently misdiagnosed as early-onset dementia and/or a schizophrenic disorder, as the neurological symptoms can occur late in the disease course[42,43]. MLD is caused by pathogenic mutations in *ARSA* (which encodes arylsulfatase A (ASA)) or *PSAP* (which encodes prosaposin), which result in accumulation of toxic metabolites — in particular, sulfatides — within the nervous system and visceral organs, such as the gallbladder[12,44–46].

Intravenous enzyme replacement therapy to replace the deficient or missing enzyme with an active recombinant human ASA enzyme was attempted in mice, but the therapeutic enzyme failed to cross the blood–brain barrier[47]. In a phase I/II study, intrathecal delivery of recombinant ASA is currently being researched as a therapeutic option in children with MLD[48].

Haematopoietic stem cell transplantation has been performed in patients with different MLD phenotypes at various ages and disease stages[49,50], sometimes with inconclusive or even disappointing results[51]. Currently, minimally symptomatic patients with juvenile MLD are considered to be potential candidates for aHSCT[52–55].

In an ongoing study, patients with MLD are receiving infusions of autologous haematopoietic stem cells transduced with a lentiviral vector encoding *ARSA* cDNA after myeloablative conditioning with busulfan. The investigators reported preliminary evidence of safety and therapeutic benefit[56]. The beneficial effects of this new gene therapy approach

were primarily seen in patients with early-onset MLD who received treatment in the presymptomatic or very early symptomatic stage of the disease.

Cerebrotendinous xanthomatosis.

In adulthood, cerebrotendinous xanthomatosis (CTX) typically presents with spastic paraparesis and cerebellar ataxia, followed by cognitive decline, dystonia, optic atrophy, polyneuropathy and seizures[57,58]. Early cataracts, chronic diarrhoea and the typical tendon xanthomas are additional key symptoms that can manifest during childhood. CTX is caused by homozygous or compound heterozygous mutations in the *CYP27A1* gene. *CYP27A1* encodes the mitochondrial enzyme sterol 26-hydroxylase, which is involved in the synthesis of bile acids from cholesterol[59]. The enzymatic defect leads to accumulation of large amounts of cholestanol, resulting in premature arteriosclerosis and neurotoxicity. Elevated serum cholestanol levels and the presence of urinary bile alcohols are diagnostic features of CTX[60], and the relevant biochemical investigations are highly recommended in patients with unexplained, early-onset cataracts and diarrhoea since childhood.

Treatment of CTX is predominantly preventive, so early diagnosis is crucial. Long-term replacement of bile acid, especially with chenodeoxycholic acid (CDCA; 750 mg daily) is the current best option. CDCA has been shown to improve neurological symptoms, normalize levels of cholestanol and contribute to a better prognosis, especially if initiated early[61,62].

Hereditary diffuse leukodystrophy with axonal spheroids.

HDLS primarily manifests in the fourth or fifth decade of life with behavioural changes, depression, gait ataxia and early-onset dementia[63]. Frontal gait ataxia, rigidity, bradykinesia and resting tremor are frequently observed[64]. Inheritance is autosomal dominant, although sporadic cases are common. The gene defect affects the tyrosine kinase domain of macrophage colony-stimulating factor 1 receptor, encoded by *CSF1R*[65]. An uninformative family history and emergence of clinical symptoms at an advanced age, combined with the multifocal and nonspecific MRI white matter changes that are typical of HDLS, can cause the condition to be misidentified as subcortical arteriosclerotic encephalopathy or as atypical parkinsonism in cerebrovascular disease. Therefore, HDLS is likely to be substantially underdiagnosed in adult neurology. HDLS has a worse prognosis than subcortical arteriosclerotic encephalopathy, with most patients developing severe dementia and dying within 4–6 years of diagnosis[66].

No specific treatment options for HDLS are currently available, and supportive management is of crucial importance. However, one patient, who was treated with aHSCT after misdiagnosis of MLD, showed stabilization of disease manifestations[67].

Autosomal dominant adult-onset demyelinating leukodystrophy.

ADLD typically presents with autonomic abnormalities, such as bladder dysfunction, impotence, constipation, anhidrosis and postural hypotension, in the fourth to the sixth decade of life. The disease then progresses, and patients have a spastic–ataxic gait and mild dementia in later disease stages[68]. ADLD is caused by duplications of the *LMNB1*

gene on chromosome 5q23, which result in overexpression of lamin B1 protein, an intermediate filament protein that is expressed in the nuclear lamina within the nuclear envelope. Overexpression of this protein leads to disruption of myelin homeostasis and slowly progressive, non-inflammatory demyelination, predominantly in deep white matter structures and cerebral peduncles[69], which is occasionally mistaken for chronic progressive MS[70].

Currently, no disease-specific treatment option is available for ADLD, although supportive care for urinary dysfunction, postural hypotension and gait disturbance can substantially improve quality of life for affected patients. Identification of the gene defect allows prenatal testing and genetic counselling of family members at risk.

Leukoencephalopathy with vanishing white matter.

VWMD, also known as eIF2B-related disorder, is caused by mutations in any one of five genes (*EIF2B1–5*)[71,72]. These mutations affect the function of the eukaryotic translation initiation factor eIF2B, which has an essential role in protein synthesis, including its regulation under different stress conditions. Patients with VWMD are highly vulnerable to physiological stress factors such as minor head trauma or fever, presenting with acute motor dysfunction, ataxia or even coma[73]. In many patients with adult-onset VWMD, a common amino acid substitution (Arg113His) is found in eIF2B subunit ε, causing a milder variant with spastic paraparesis, which sometimes presents primarily with psychiatric manifestations[74]. After disease onset, symptoms accumulate over the next decade, leading to severe disability, confinement to bed and even death in almost all patients. There are some exceptions to these presentations, for example, vanishing white matter leukodystrophy with ovarian failure (ovarioleukodystrophy), an allelic disorder that is characterized by primary ovarian failure in adult women, and minimal neurological symptoms[75].

No disease-specific treatment option for VWMD can be offered to patients, and head trauma, infections and other stress factors should be strictly avoided.

Adult polyglucosan body disease.

APBD typically presents in the fifth to the sixth decade of life with a combination of upper and lower motor neuron impairment resembling amyotrophic lateral sclerosis, along with cerebellar ataxia or Parkinson disease-like symptoms with extrapyramidal movement disorders[76]. In some patients, polyneuropathic symptoms with hyporeflexia, distal symmetric sensory loss, muscle atrophy and fasciculations can be prominent, with slowed nerve conduction velocity and denervation potentials on electrophysiological testing. Cognitive deficits, reflecting white matter involvement, tend to be very mild[11].

The affected gene in APBD, *GBE1*, encodes a glycogen-branching enzyme (GBE1), dysfunction of which leads to accumulation of polyglucosan bodies in the central and peripheral nerves. The diagnosis is confirmed by detection of reduced GBE1 enzymatic activity in peripheral blood leukocytes or cultured fibroblasts[76,77]. If assays for GBE1 activity produce equivocal results, sural nerve biopsy or skin biopsy can demonstrate the presence of polyglucosan bodies, which is suggestive of APBD.

No effective treatment is available for APBD, but supportive care for the urological disturbances and gait dysfunction can considerably increase patient safety and quality of life. A randomized controlled trial to study the efficacy of anaplerotic therapy with triheptanoin, a seven-carbon triglyceride, is ongoing[78]. This approach is based on the hypothesis that decreased glycogen degradation in APBD produces a secondary energy deficit, possibly related to inadequate reserves of normal glycogen for efficient degradation to free glucose. Triheptanoin is thought to provide an efficient substrate to the citric acid cycle to correct this energy deficit. A pilot trial demonstrated arrest of clinical deterioration with limited functional recovery in patients with APBD who received triheptanoin diet therapy[79].

General treatment strategies

Despite emerging therapies for the leukodystrophies[80], few curative options are available for patients affected by these disorders. An obligation remains, however, to fully treat and manage the many disease-associated complications. To fully serve patients with these conditions, a holistic approach is necessary to improve quality of life and decrease morbidity and mortality from medical complications[15]. Treatment options in adulthood leukodystrophies should encompass psychological care and psychiatric medications, antiepileptic treatments if needed, early antibiotic treatment for recurrent infections, prevention of secondary complications such as pneumonia and urinary tract infections, attention to general medical care, cognitive and speech therapy, attention to spasticity and functional status, and nutritional support as appropriate for the individual[15]. This type of approach is best administered at a centre with specialized expertise in these disorders.

Research networks and patient advocacy

Orphan diseases such as leukodystrophies frequently pose severe problems, particularly with respect to early diagnosis and research awareness. Furthermore, development of new drugs and other treatment options for small patient groups may not be attractive for the pharmaceutical industry. Consequently, third-party funding from national and international funds, cooperation with patient groups, and international research collaborations are of major importance (see Further Information box for more information). Close partnerships between clinicians, researchers and patient organizations allow the establishment of large sample sets for genetic and natural history studies and provide high-quality platforms for both basic research and the search for new treatment options.

Conclusions and future perspectives

Genetic leukodystrophies are gaining in importance in the adult neurology field in parallel with the diagnostic and therapeutic advances made in recent years. Diagnosing an adulthood leukodystrophy is still complex and extremely challenging. Targeted genetic testing using next-generation sequencing techniques, paired with comprehensive personal expertise in specialized leukodystrophy centres, will enable the identification of previously undetected or unknown leukodystrophies in adult patients, allowing systematic research for new therapeutic options in hitherto untreatable diseases. Early results from recent treatment studies — of gene therapy approaches, for example — are already starting to fill the

therapeutic vacuum, and the hope for new therapeutic options is now becoming a realistic goal for many leukodystrophies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key points

- Leukodystrophies are a heterogeneous group of inherited disorders with highly variable clinical manifestations and pathogenetic background
- Leukodystrophies are characterized by primary glial cell and myelin sheath pathology of variable aetiology; secondary axonal pathology can emerge as the disease progresses
- Around 20 distinct disorders are currently defined as adulthood leukodystrophies; additional involvement of grey matter structures or non-cerebral organs distinguishes these conditions from other genetic leukoencephalopathies
- Increasing numbers of individual leukodystrophies are being treated using metabolic treatment strategies, enzyme replacement or cell-based options such as allogeneic haematopoietic stem cell transplantation and gene therapy

Box 1 |

Symptoms of adulthood leukodystrophy

The leading symptoms of adulthood leukodystrophies are as follows:

- Motor symptoms, starting with clumsy gait and diplegia in lower extremities, finally leading to severe quadriplegia, dysarthria and dysphagia
- Gait ataxia
- Vegetative dysfunction, such as bladder, bowel or sexual dysfunction
- Cognitive deficits, which further progress to severe dementia

Consider leukodystrophy in young adults (aged 20–40 years) who exhibit one or more of the following features:

- Spastic paraparesis of otherwise unexplained origin (with or without brain MRI changes)
- Early onset (<40 years) of dementia
- Positive family history

Box 2 |

Extraneurological symptoms in adulthood leukodystrophies

Ophthalmological symptoms

- Cataracts: cerebrotendinous xanthomatosis (CTX)
- Optic nerve atrophy: leukoencephalopathy with vanishing white matter (VWMD), X-linked adrenoleukodystrophy (X-ALD), metachromatic leukodystrophy (MLD), globoid cell leukodystrophy (GLD; also known as Krabbe disease) and hypomyelinating leukodystrophies (HLDs)
- Macular dystrophy: Sjögren–Larsson syndrome (SLS)
- Nystagmus: Pelizaeus–Merzbacher disease, Pelizaeus–Merzbacher-like disease (HLD2) and other HLDs
- Perifoveal glistening white dots: SLS
- Cortical blindness: late-stage leukodystrophies, including X-ALD and MLD

Endocrine dysfunction

- Adrenal insufficiency: X-ALD (adrenomyeloneuropathy (AMN) phenotype)
- Testicular dysfunction: X-ALD (AMN phenotype)
- Ovarian dysfunction: VWMD, progressive leukoencephalopathy with ovarian failure
- Hypogonadotropic hypogonadism: Pol-III-related HLD
- Growth factor deficiency: Pol-III-related HLD

Polyneuropathy

- X-ALD (AMN phenotype), adult polyglucosan body disease (APBD), GLD, CTX, MLD and HLD2

Hypodontia

- Pol-III-related HLDs

Cutaneous signs

- Xanthoma: CTX
- Ichthyosis: SLS
- Melanoderma: X-ALD (AMN phenotype)

Visceral signs

- Chronic diarrhoea: CTX
- Gallbladder dysfunction: MLD

Box 3 |

MRI characteristics in adulthood leukodystrophies

Hypomyelination

Hypomyelination is characterized by increased white matter signal on T2-weighted sequences and isointense or hyperintense white matter signal on T1-weighted sequences relative to grey matter structures (FIG. 2a,b)

- Hypomyelinating leukodystrophy with atrophy of basal ganglia and cerebellum (HLD6)
- Pelizaeus–Merzbacher disease (HLD1)
- Pelizaeus–Merzbacher-like disease (HLD2)
- Pol-III-related disorders (HLD7 and HLD8)

Demyelination

Demyelination is characterized by increased white matter signal on T2-weighted sequences and substantially decreased white matter signal on T1-weighted sequences relative to grey matter structures

Diffuse cerebral (FIG. 2a,c,d):

- Leukoencephalopathy with vanishing white matter (VWMD)
- Metachromatic leukodystrophy (MLD)
- Megalencephalic leukoencephalopathy with subcortical cysts (MLC)
- End-stage demyelinating leukodystrophies

Periventricular predominance (FIG. 2d):

- MLD
- Globoid cell leukodystrophy (GLD; also known as Krabbe disease)
- Leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation (LBSL)
- Sjögren–Larsson syndrome (SLS)
- Adult polyglucosan body disease (APBD)
- Fatty acid hydroxylase-associated neurodegeneration

Asymmetric lesions (FIG. 2c,j,k):

- APBD
- Hereditary diffuse leukoencephalopathy with axonal spheroids (HDLS)
- VWMD

Cerebellum and/or middle cerebellar peduncles (FIG. 2e,n):

- Cerebrotendinous xanthomatosis (dentate nucleus)
- X-Linked adrenoleukodystrophy (X-ALD)
- Alexander disease (AxD)
- Adult-onset demyelinating leukodystrophy (ADLD)
- LBSL
- Fatty acid hydroxylase-associated neurodegeneration (atrophy)
- HLDs (atrophy)
- Progressive leukodystrophy with ovarian failure (LKENP)

Brainstem involvement (FIG. 2e,m,n,o):

- LBSL
- ADLD
- APBD
- AxD

Frontal predominance (FIG. 2d,f,j):

- AxD
- MLD
- X-ALD (frontal variant)
- HDLS

Parieto-occipital predominance (FIG. 2g,h,k):

- X-ALD
- GLD
- APBD

Temporal predominance (FIG. 2l):

- APBD
- MLC

Multifocal lesions (FIG. 2j,k,m,o):

- HDLS
- APBD
- LBSL
- AxD
- SLS

Cystic lesions (fluid-attenuated inversion recovery sequences) (FIG. 2l):

- VWMD
- MLC

Contrast enhancement (FIG. 2 h,n):

- AxD
- X-ALD

Corpus callosum thinning:

- VWMD
- ADLD
- HDLS
- LKENP

Long-tract involvement (FIG. 2i,o,p):

- Adrenomyeloneuropathy
- GLD
- LBSL

Leukoencephalopathy with ataxia (LKPAT)

- LKENP

Spinal cord atrophy (FIG. 2m):

- Adrenomyeloneuropathy
- APBD
- AxD

DATABASES

Online Mendelian Inheritance in Man: http://www.omim.org/

FURTHER INFORMATION

ALD Charity (Switzerland): http://www.ald-charity.ch/

ALD Connect: http://aldconnect.org/

ALD Life (UK): http://www.aldlife.org/

European Leukodystrophy Association: http://ela-asso.com/en/

German Leukodystrophy Network (Leukonet): http://www.leukonet.de/10/?L=1

Global Leukodystrophy Initiative: http://theglia.org/

Leukodystrophy Care Network: http://www.huntershope.org/

LeukoTreat Network: http://www.leukotreat.eu/

StopALD (US): http://www.stopald.org/

The Myelin Project: http://myelin.org/

United Leukodystrophy Foundation: http://ulf.org/

World Leukodystrophy Alliance: http://leukodystrophyalliance.org/

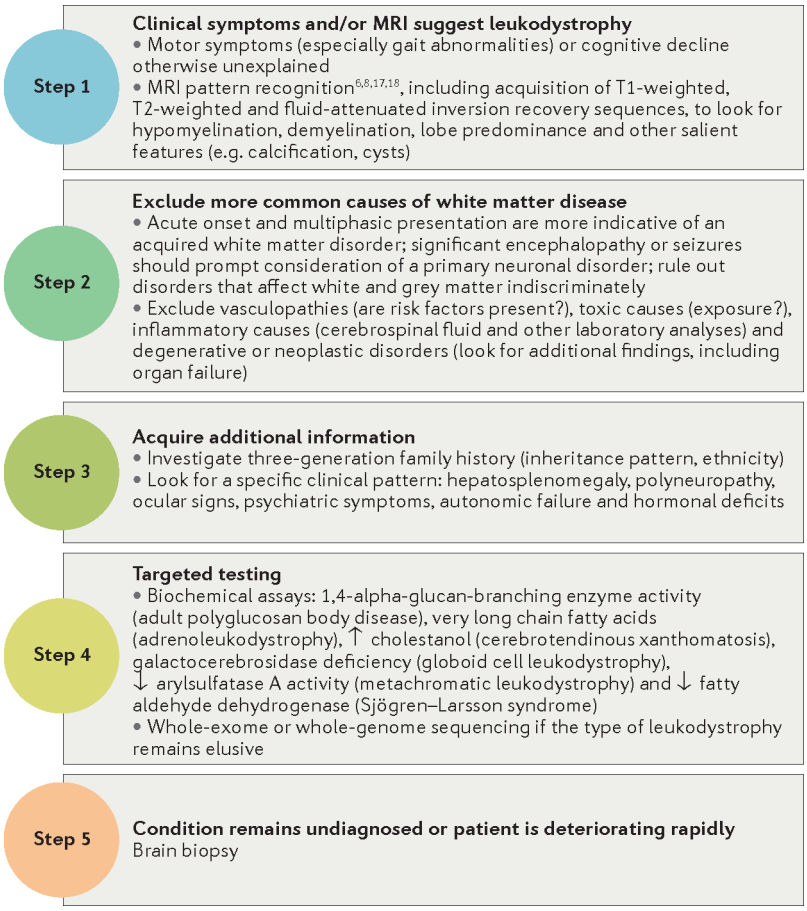

Figure 1 |. Diagnostic pathway for adulthood leukodystrophies.

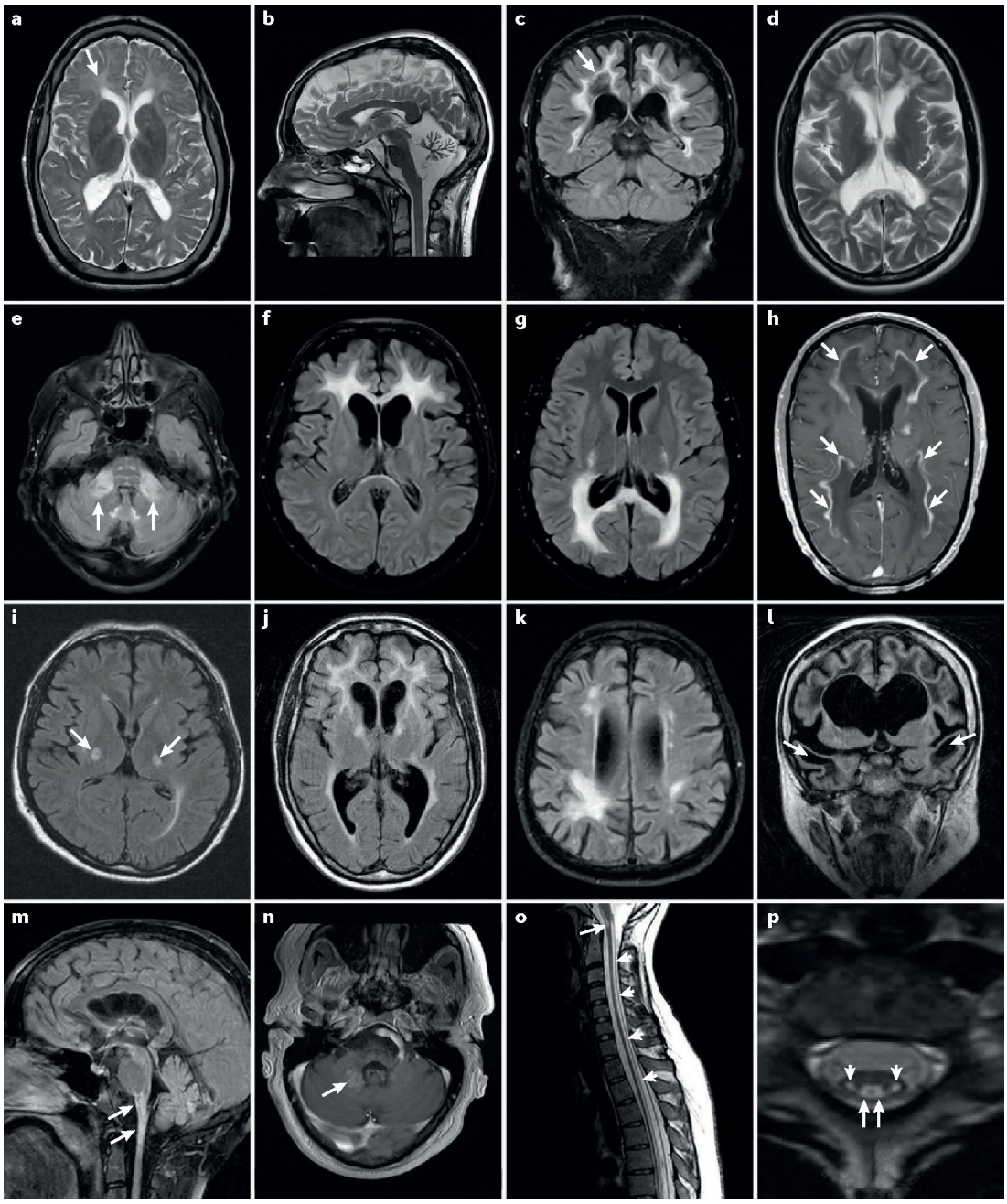

Figure 2 |. Characteristic MRI features of adult leukodystrophies.

a | Hypomyelination in an adult with a Pol-III-related leukodystrophy. Arrow indicates moderately increased T2-weighted signal in affected white matter. Note relative atrophy, which is common in adults with hypomyelination. **b** | Severe cerebellar atrophy in a 24-year-old female with Pol-III-related hypomyelinating leukodystrophy. **c** | Diffuse cerebral white matter changes in a 61-year-old male with vanishing white matter disease. Note rarefaction of affected white matter (arrow) on fluid-attenuated inversion recovery images. **d** | Periventricular predominance of diffuse white matter changes in a 24-year-old female with metachromatic leukodystrophy. **e** | Middle cerebellar peduncle involvement (arrows) as well

as the characteristic brainstem signal abnormalities in autosomal dominant leukodystrophy with autonomic symptoms. **f**–**h** | Cerebral inflammatory demyelinating variants of X-linked adrenoleukodystrophy (X-ALD) with frontal (part **f**) or parieto-occipital (part **g**) predominance. Note the contrast enhancement marginal to the demyelinated areas (arrows) (part **h**). **i** | Adrenomyeloneuropathy variant of X-ALD with bilateral T2-signal changes in degenerating corticospinal tracts (arrows). **j** | Large multifocal white matter lesions in a 41-year-old patient with hereditary diffuse leukoencephalopathy with spheroids. Note mild frontal atrophy, which is common in this condition. **k** | Multifocal lobar white matter changes in a 55-year-old patient with adult polyglucosan body disease. **l** | Frontotemporal cystic lesions (arrows) in a 33-year-old female with megalencephalic leukoencephalopathy with subcortical cysts. **m**,**n** | Alexander disease (AxD) in adulthood. Brainstem and spinal cord atrophy and lesions are shown (arrows in part **m**). A partially contrast enhancing area is shown (arrow in part **n**) in a 35-year-old male with AxD. **o**,**p** | Long-tract involvement seen in *DARS*-mutated leukoencephalopathy with brainstem and spinal cord involvement and elevated cerebrospinal fluid lactate. Sagittal images (part **o**) show T2-signal elevation in the brainstem (arrow) and along spinal tracts (small arrows). Axial sequences (part **p**) show bilateral involvement of the corticospinal (small arrows) and spinothalamic (arrow) tracts.

Table 1 |

Leukodystrophies with major prevalence and/or onset in adulthood

Disease	Age of onset	OMIM entries	Gene(s)	Clinical signs	Biochemical findings
Hypomyelinating leukodystrophies					
Hypomyelinating leukodystrophy with atrophy of basal ganglia and cerebellum (HLD6)[81]	Infancy to adulthood	612438	*TUBB4A*	• Child: dystonia, nystagmus, mild cognitive deficit, ataxia and spasticity • Adolescent or adult: spastic ataxia or dystonia	None
Pelizaeus-Merzbacher disease (HLD1)[82]	Infancy to adolescence	312080	*PLP1*	• Child: dystonia, nystagmus, ataxia, spasticity, mild cognitive deficit and polyneuropathy in some cases • Adolescent: spastic ataxia	None
Pelizaeus-Merzbacher-like disease (HLD2)[83]	Infancy to adolescence	608804	*GJC2*	• Child: dystonia, nystagmus, ataxia, spasticity and mild cognitive deficit • Adolescent: spastic ataxia	None
Pol-III-related disorders (HLD7 and HLD8)[84]	90%: 2–6 years; 10%: ≥10 years	• 607694 • 614381	• *POLR3A* • *POLR3B*	Dystonia, nystagmus, ataxia, spasticity, mild cognitive deficit, hypodontia and delayed or absent puberty	None
Demyelinating leukodystrophies					
Progressive leukodystrophy with ovarian failure (LKENP)[85]	Childhood to adulthood	615889	*AARS2*	Ataxia, spasticity and cognitive decline; all female patients have ovarian failure	None
X-Linked adrenoleukodystrophy (X-ALD)[10]	• Adrenomyeloneuropathy (AMN): 14–60 years • Adulthood cerebral adrenoleukodystrophy (ACALD): ≥21 years	300100	*ABCD1*	• AMN: spastic paraparesis, sensory signs, and bladder and sexual dysfunction • ACALD: behavioural changes and psychosis; later: spastic paraparesis, ataxia and dementia	Elevated saturated very long chain fatty acids in serum
Adult polyglucosan body disease (APBD)[77]	50–60 years	263570	*GBE1*	Spastic paraparesis, distal sensory neuropathy, bladder dysfunction and cerebellar ataxia; Parkinson-like syndrome and amyotrophic lateral sclerosis-like appearance in patients with predominant polyneuropathy; later: cognitive deficits	• Deficient glycogenbranching enzyme • Pathology: polyglucosan accumulation in skin and nerves
Alexander disease (AxD)[86]	Childhood to adulthood	203450	*GFAP*	• Child: macrocephaly, dementia or developmental delay, spasticity, seizures and feeding difficulties and/or recurrent vomiting • Adult: bulbar signs, spasticity, cerebellar ataxia, oculomotor signs, palatal myoclonus and autonomic dysfunction	• Elevated glial fibrillary acidic protein in cerebrospinal fluid • Pathology: Rosenthal fibres
Autosomal dominant adult-onset demyelinating leukodystrophy (ADLD)[68]	40–60 years	169500	*LMNB1* duplication	Autonomic dysfunction, spastic-ataxic gait and cognitive impairment	None
Cerebrotendinous xanthomatosis (CTX)[61]	Childhood to adulthood	213700	*CYP27A1*	• Child: Cataracts, chronic diarrhoea and xanthomas • Adult: Cerebellar ataxia, spasticity, seizures, mild cognitive deficits, polyneuropathy and xanthomas	Elevated serum cholestanol and bile alcohols; reduced mitochondrial sterol 26-hydroxylase activity in leukocytes

Disease	Age of onset	OMIM entries	Gene(s)	Clinical signs	Biochemical findings
Leukoencephalopathy with ataxia (LKPAT)[87,88]	Childhood to adulthood	615651	*CLCN2*	Cerebellar ataxia, visual problems, optic neuropathy, cognitive deficits and headaches	None
Leukoencephalopathy with vanishing white matter (VWMD)[71–75]	Childhood to adulthood	603896	*EIF2B1–5*	• Child: progressive spastic ataxia • Adult: spastic paraparesis, psychiatric symptoms, ataxia and ovarian failure	None
Fatty acid hydroxylase-associated neurodegeneration[89]	10–20 years	612319	*FA2H*	Spasticity, dystonia and cognitive dysfunction	None
Globoid cell leukodystrophy (GLD; also known as Krabbe disease)[90]	Childhood to adulthood	245200	*GALC*	• Child: irritability, encephalopathy, polyneuropathy and spastic quadriplegia • Juvenile or adult: spastic tetraparesis, ataxia, polyneuropathy and cognitive impairment; later: blindness and deafness	Galactocerebrosidase deficiency in leukocytes or fibroblasts
Demyelinating leukodystrophies (cont.)					
Hereditary diffuse leukoencephalopathy with spheroids (HdLS)[63]	40–70 years	221820	*CSF1R*	Cognitive and psychiatric disturbances, spastic-ataxic gait, seizures and bladder dysfunction	None
Leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation (LBSL)[91]	Childhood to adulthood	611105	*DARS2*	Child or adult: cerebellar and sensory ataxia, spasticity and dorsal column dysfunction	None
Megalencephalic leukoencephalopathy with subcortical cysts (MLC)[13]	Childhood to adulthood	• 604004 • 613925 • 613926	• *MLC1* • *HEPACAM* • *HEPACAM*	• Early-onset macrocephaly, mild cognitive deficits, spasticity and ataxia of variable severity, dysarthria and epilepsy • Mild motor and cognitive delay (40%), clinical improvement possible; early-onset macrocephaly and delayed-onset neurological deterioration, including cerebellar ataxia, spasticity, epilepsy and mild cognitive decline	None
Metachromatic leukodystrophy (MLD) and its biochemical variants[12]	Childhood to adulthood	• 250100 • 249900	• ARSA • PSAP	• Child: gait abnormalities, spasticity, ataxia and polyneuropathy • Juvenile or adult: psychosis, cognitive decline and polyneuropathy; later: spastic-ataxic gait and bladder dysfunction	Decreased arylsulfatase A activity, elevated urinary sulfatides
Sjögren-Larsson syndrome (SLS)[92]	Birth to 30 months, but it might not be recognized until adulthood	270200	*ALDH3A2*	Child: spastic paraparesis, mental retardation, macular dystrophy and ichthyosis	Low fatty aldehyde dehydrogenase levels in fibroblasts

OMIM, Online Mendelian Inheritance in Man.

Table 2 |

Differential diagnoses for adulthood leukodystrophies

Disease	OMIM entries	Gene(s)
Inherited vasculopathies with white matter involvement		
Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)[22]	125310	*NOTCH3*
Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL)[93]	600142	*HTRA1*
Brain small vessel disease with or without ocular anomalies[94]	607595	*COL4A1*
Fabry disease[95]	301500	*GLA*
Retinal vasculopathy with cerebral leukodystrophy (RVCL)[96]	192315	*TREX1*
Polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy (PLOSL)[97]	221770	*TREM2, TYROBP*
Inherited CNS diseases with grey and white matter involvement		
Dentatorubral-pallidoluysian atrophy (DRPLA)[98]	125370	*ATN1*
Fragile X tremor/ataxia syndrome (FXTAS) [99]	300623	*FMR1*
Inborn errors of metabolism with white matter involvement		
Aspartylglucosaminuria (AGU)[100]	208400	*AGA*
Methylmalonic aciduria, isovaleric acidaemia and propionic acidaemia[101]	251000	*MUT*
	243500	*IVD*
	606054	*PCCA, PCCB*
Disorders of glycoprotein degradation, including α-mannosidosis (MANSA)[102], β-mannosidosis (MANSB)[103] and neuraminidase deficiency[104]	248500	*MAN2B1*
	248510	*MANBA*
	256550	*NEU1*
Galactosaemia[105]	230400	*GALT*
GM1-gangliosidosis, type III[106]	230650	*GLB1*
GM2-gangliosidosis, AB variant[107]	272750	*GM2A*
Hereditary homocystinurias[108], such as methylenetetrahydrofolate reductase deficiency[109] or cystathionine β-synthase deficiency[110]	236250	*MTHFR*
	236200	*CBS*
Phenylketonuria (PKU)[111]	261600	*PAH*
Organic acidurias, such as L-2-hydroxyglutaric aciduria (L2HGA)[112] or 3-hydroxy-3-methylglutaryl-CoA lyase deficiency (HMGCLD)[113]	236792	*L2HGDH*
	246450	*HMGCL*
Other diseases with white matter involvement		
Wilson disease[114]	277900	*ATP7B*

The table lists a selection of inherited diseases with involvement of CNS white matter that should be considered in the differential diagnosis of adulthood leukodystrophies. OMIM, Online Mendelian Inheritance in Man.