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Minireview

Disease specific therapies in leukodystrophies and leukoencephalopathies

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ABSTRACT

Leukodystrophies are a heterogeneous, often progressive group of disorders manifesting a wide range of symptoms and complications. Most of these disorders have historically had no etiologic or disease specific therapeutic approaches. Recently, a greater understanding of the pathologic mechanisms associated with leukodystrophies has allowed clinicians and researchers to prioritize treatment strategies and advance research in therapies for specific disorders, some of which are on the verge of pilot or Phase I/II clinical trials. This shifts the care of

Abbreviations: X-ALD, X-linked Adrenoleukodystrophy; AGS, Aicardi–Goutières Syndrome; CSF, cerebrospinal fluid; IFNα, α-interferon; RNA, ribonucleic acid; DNA, deoxyribonucleic acid; SLE, systemic lupus erythematosus; AxD, Alexander disease; GFAP, growth factor associated protein; MLD, metachromatic leukodystrophy; Pol III, polymerase III; VWM, Vanishing White Matter Disease; CTX, Cerebrotendinous Xanthomatosis; HSCT, hematopoietic stem cell transplantation; MRI, magnetic resonance imaging; CNS, central nervous system; PMD, Pelizaeus–Merzbacher Disease; APBD, Adult Polyglucosan Body Disease; NAA, N-acetyl aspartic acid; AAV2, adeno-associated virus serotype 2; SAMHD1, SAM domain and HD domain-containing protein 1; LINE1, Long Interspersed Element 1; ABCD2, ATP-binding cassette, sub-family D (ALD), member 2; ABCD1, ATP-binding cassette, sub-family D (ALD), member 1; GALC, galactosylceramidase; HBSL, hypomyelination with brain stem and spinal cord abnormalities and leg spasticity; ERT, Enzyme Replacement Therapy; rhASA, recombinant human arylsulfatase A; ZSD, Zellweger spectrum disorder; PEX, peroxisomal; HuCNS-SC, Human Central Nervous System Stem Cell; UCSF, University of California, San Francisco; DTI, diffusion tensor imaging.

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leukodystrophy patients from the management of the complex array of symptoms and sequelae alone to targeted therapeutics. The unmet needs of leukodystrophy patients still remain an overwhelming burden. While the overwhelming consensus is that these disorders collectively are symptomatically treatable, leukodystrophy patients are in need of advanced therapies and if possible, a cure.

Contents

1. Introduction

A greater understanding of the pathologic mechanisms associated with leukodystrophies has allowed clinicians and researchers to prioritize treatment strategies and advance research therapies in specific disorders. This shifts the care of leukodystrophy patients from the management of the complex array of symptoms and sequelae alone to targeted therapeutics. Herein we address the current state of existing and emerging therapies, as well as the importance of systematic research in changing the prognostic implications of these disorders.

Namely, although almost all patients with leukodystrophies have certain core features that require symptomatic management, several leukodystrophies have specific complications that require special attention (Table 1). Although our list is not exhaustive we have sought to convey the breadth of disease-specific nuance and multisystem involvement that can be seen among affected individuals. We have taken care to address specific therapeutic approaches relevant to each disorder [1–3]. While it is hoped that additional disorders will have targeted therapies in the near future, at this point it is particularly important not to miss the diagnosis of conditions such as X-linked Adrenoleukodystrophy (X-ALD), Cerebrotendinous Xanthomatosis (CTX), Metachromatic Leukodystrophy (MLD) and Krabbe because there is some evidence that early intervention in carefully selected cases may improve outcomes. Finally, there are a variety of promising, disease specific therapies currently in human trials for several leukodystrophies, including X-ALD, MLD, Krabbe disease, Peroxisomal Biogenesis Disorders, Pelizaeus–Merzbacher Disease (PMD), Adult Polyglucosan Body Disease (APBD), and Aicardi–Goutières Syndrome (AGS). These modalities include traditional pharmaceuticals as well as the manipulation of stem cells, genes, and enzymes. We have made an effort to distinguish between the strategies that currently have some evidence of efficacy and those that are at this point purely experimental (Table 2); we must acknowledge that this judgment will change as new evidence emerges. Disorders with existing symptomatic or mechanistic approaches are addressed here in an alphabetical fashion.

2. X-linked Adrenoleukodystrophy (X-ALD)

X-ALD is one of the most common leukodystrophies and disease-specific management guidelines have recently been published [4]. X-ALD is caused by mutations in *ABCD1*, encoding the adrenoleukodystrophy protein (ALDP). This is an X-linked dominant disorder that results from a deficient very long-chain fatty acid transport protein on the surface of the peroxisome. Four primary phenotypes (asymptomatic, adrenal insufficiency, cerebral ALD, and adrenomyeloneuropathy) have been identified in X-ALD patients, which may overlap during the lifespan.

Table 1
Examples of symptomatic therapies relevant to specific leukodystrophies.

Symptom	Associated disease(s)	Prevention/treatment
Adrenal insufficiency	X-ALD	Annual ACTH screening; corticosteroids. Rare in X-ALD women.
Pathological fracture	X-ALD and other non-ambulatory patients	Calcium and vitamin D supplementation for X-ALD patients on corticosteroids. Monitor bone health in all leukodystrophy patients with impaired mobility
Inflammatory cerebral demyelination	X-ALD	Occurs in 40% of ALD boys between 3–12 years. HSCT effectively halts demyelination, but only if initiated soon after lesion onset. Surveillance MRIs every 6 months can detect demyelination at a sufficiently early stage. This phenotype also affects 25% of ALD men aged 12–50 years, although comorbid symptoms of AMN in adult men can complicate HSCT. Phenotype is rare among older men as well as ALD women of any age.
Autoimmune manifestations and large vessel vasculitis	AGS	Patients with AGS have skin manifestations such as chilblains requiring specialized wound care. Additionally, hypothyroidism hypothesized to have an autoimmune mechanism is occasionally seen and TSH should be performed yearly to institute appropriate therapy as needed. AGS patients may rarely have arthropathy, autoimmune hepatitis or other systemic inflammatory features. AGS patients with mutations in SAMHD1 may have large vessel intracerebral vasculitis and this should be screened with neuroimaging.
Obstructive hydrocephalus	AxD	AxD patients should be screened and treated for obstructive hydrocephalus
Premature ovarian failure	VWM, AARS2 related leukodystrophy	None known
Episodic deterioration	VWM, mitochondrial, Pol III and more rarely in other leukodystrophies	Avoidance of triggers (e.g., head trauma, fevers, severe fright)
Cardiac dysfunction	Mitochondrial	Cardiac evaluation; pacemaker/defibrillator may be appropriate in some patients. Patients should be re-evaluated at intervals according to their needs.
Deafness	Mitochondrial and $18q^-$ in early stages; many leukodystrophies in later stages	Auditory evaluation; treatments limited
Hypogonadotropic hypogonadism, growth hormone deficiency	Pol-III	Supplemental hormonal therapies
Dental anomalies	Pol-III, ODDD, Cockayne	Dental care to prevent caries, consultation with an orthodontist as necessary. General anesthesia should be employed with caution if procedure is non-essential.
Hypercholesterolemia xanthoma formation, cataracts, psychomotor decline	CTX	Daily supplementation with chenodeoxycholic acid normalizes cholestanol levels and may prevent and/or improve other disease manifestations, statins
Gallbladder dysfunction	MLD	Patients with MLD can have gallbladder involvement leading the feeding intolerance, hematochezia, and pain. This should be considered and managed in the symptomatic patient.

All patients begin life asymptomatic and, in rare cases, may remain asymptomatic into the fourth decade in the case of men or the sixth decade in the case of women.

2.1. ALD: recognition and approach to unique clinical features

X-ALD has several, potentially overlapping phenotypes. The phenotypes include (1) asymptomatic status, (2) adrenal insufficiency, (3) inflammatory cerebral demyelination often called cerebral X-ALD, and (4) progressive spastic paraparesis and sphincter dysfunction often called adrenomyeloneuropathy. Each phenotype, in effect, describes a specific subset of symptoms with a distinct management strategy. All X-ALD gene carriers are asymptomatic for at least the first few years of life, after which males should undergo regular serologic surveillance for adrenal insufficiency and regular radiologic surveillance for cerebral demyelination; both phenotypes are life-threatening but treatable if identified in a timely fashion. Males with an X-ALD mutation should be screened via cortisol stimulation testing every 6–9 months for adrenal insufficiency. Women are typically spared adrenal insufficiency and cerebral demyelination. Patients who show signs of adrenal insufficiency should be started on corticosteroids and followed by an endocrinologist. All men and most women with an X-ALD mutation will eventually develop symptoms of spastic paraparesis and associated sphincter dysfunction during adulthood. Rehabilitation therapy and symptomatic treatment for spasticity, pain, and maintenance of ambulation can greatly enhance quality of life and prevent or mitigate early disability. Attentive urologic and gastroenterologic care may similarly help maintain comfort and independence and reduce the incidence of urinary tract infections.

In patients with cerebral X-ALD, Hematopoietic Stem Cell Transplantation (HSCT) has been shown to improve survival and stabilize or improve cognitive abilities, but only if treatment is initiated during the early stages of cerebral demyelination when the lesion is still relatively small [5–7], highlighting the importance of early diagnosis. Surveillance MRI studies are important for early identification of brain lesions, before clinical symptoms appear and in time for HSCT. Specific clinical and radiologic criteria have been established for triaging cerebral X-ALD patients who are candidates for HSCT and have been described in detail using the established clinical and radiologic criteria that have been established for triaging candidates for HSCT [5]. Factors associated with favorable treatment outcomes include low pre-transplant Loes radiographic severity score [8], limited degree of neurologic disability and high neuropsychometric measures after HSCT intervention [5,7]. The therapeutic benefits of HSCT in X-ALD patients are believed to arise, at least in part, through the replacement of the patient's genetically deficient brain microglia with genetically competent microglial progenitor cells arising from the donor blood [9].

Newborn screening for X-ALD is being implemented in a growing number of US states and is performed through the measurement of 26:0-lyso-PC levels and the ratios of 26:0-lyso-PC to 20L0-lyso-PC [10]. X-ALD males, aged 3–12 years identified through newborn screening or as relatives of a proband, should undergo gadolinium-enhanced magnetic resonance imaging (MRI) of the brain every 6 months to screen for early signs of cerebral demyelination in order to establish the need for early intervention. Annual MRI studies should be considered for adolescent boys and adults, who are at slightly lower risk for developing the cerebral ALD phenotype. Many practitioners continue to screen adult males yearly, though the incidence of development of cerebral X-ALD in adults is less well known. Among X-ALD men over 50 years and X-ALD women (heterozygotes) of any age, the onset of the cerebral and/or adrenal insufficiency phenotypes are uncommon, suggesting that routine surveillance screening for these individuals is probably unnecessary.

Table 2
Ongoing clinical trials for specific leukodystrophies.

Study title	Associated disease(s)	Intervention	Phase	NCT number
Biomarker for metachromatic leukodystrophy	MLD	N/A	N/A	NCT01536327
Imaging study of the white matter lesions in children with metachromatic leukodystrophy	MLD (late infantile)	High-field magnetic resonance imaging	N/A	NCT01325025
Intracerebral gene therapy for children with early onset forms of metachromatic leukodystrophy	MLD	Genetic: intracerebral administration of AAVrh.10cuARSA	Phase I/II	NCT01801709
Natural history study of children with metachromatic leukodystrophy	MLD	Natural History Study	N/A	NCT01963650
Gene therapy for metachromatic leukodystrophy	MLD	Genetic: autologous CD34+ stem cells transduced with ARSA encoding lentiviral vector	Phase I/II	NCT01560182
The nosology and etiology of leukodystrophies of unknown causes	All leukodystrophies and genetic leukoencephalopathies	Biorepository study	N/A	NCT00889174
Multicenter study of HGT-1110 administered intrathecally in children with Metachromatic Leukodystrophy (MLD)	MLD	Biological: recombinant human arylsulfatase A	Phase I/II	NCT01510028
The natural history of infantile Globoid Cell Leukodystrophy	Globoid Cell Leukodystrophy	N/A	N/A	NCT00983879
The natural history of infantile metachromatic leukodystrophy	MLD	N/A	N/A	NCT00639132
Open-label extension study evaluating safety and efficacy of HGT-1110 in patients with metachromatic leukodystrophy	MLD	Biological: recombinant human arylsulfatase A	Phase I/II	NCT01887938
HSCT for high risk inherited inborn errors	X-ALD; MLD; Globoid Cell Leukodystrophy	Drug: clofarabine; Procedure: total body irradiation; Drug: melphalan; Biological: hematopoietic stem cell transplantation; Drug: alemtuzumab; Drug: mycophenylate mofetil; Device: cyclosporine A; Drug: hydroxyurea	Phase II	NCT00383448
MT2013-31:Allo BMT for metabolic disorders, osteopetrosis and males with Rett syndrome	X-ALD; Peroxisomal Biogenesis Disorders; Globoid Cell Leukodystrophy; MLD; Fucosidosis	Procedure: blood stem cell transplant; Drug: rabbit anti-thymocyte globulin (ATG); Drug: Fludarabine; Drug: Busulfan; Drug: cyclophosphamide; drug: cyclosporine A (CSA); Drug: methylprednisolone; Drug: mycophenolate mofetil (MMF); Drug: granulocyte-colony stimulating factor (G-CSF); Drug: granulocyte-macrophage colony-stimulating factor (GM-CSF); Drug: N-acetylcysteine; Drug: celecoxib; Drug: vitamin E; Drug: alpha lipoic acid	Phase II	NCT02171104
UCB transplant of inherited metabolic diseases with administration of intrathecal UCB derived oligodendrocyte-like cells	X-ALD; Globoid Cell Leukodystrophy; MLD; PMD	Biological: DUOC-01	Phase I	NCT02254863
Phase I/II pilot study of mixed chimerism to treat inherited metabolic disorders	Globoid Cell Leukodystrophy; MLD; X-ALD; PMD	Biological: enriched hematopoietic stem cell transplantation/novel platform technology	Phase I	NCT01372228
Human placental-derived stem cell transplantation	X-ALD; MLD; globoid cell leukodystrophy	Drug: human placental derived stem cell	Phase I	NCT01586455
Allogeneic bone marrow transplant for inherited metabolic disorders	X-ALD; MLD; Globoid Cell Leukodystrophy; Peroxisomal Biogenesis Disorders	Drug: Campath-1H; Drug: cyclophosphamide; Drug: busulfan; Procedure: allogeneic stem cell transplantation; Drug: cyclosporine A; Drug: mycophenolate mofetil	Phase II	NCT01043640
Biomarker for Krabbe disease	Globoid Cell Leukodystrophy	N/A	N/A	NCT01425489
Lysosomal storage disease: health, development, and functional outcome surveillance in preschool children	Globoid Cell Leukodystrophy	N/A	N/A	NCT01938014
Exercise study of function and pathology for women with X-linked Adrenoleukodystrophy	X-ALD	Behavioral: exercise training		NCT01594853
Growth hormone and chromosome $18q^-$ and abnormal growth	$18q^-$ syndrome	Drug: Nutropin AQ; Procedure: arginine and clonidine stimulation testing; Procedure: growth factors laboratory testing; Procedure: neuropsychological testing	Phase III	NCT00134420

Table 2 (*continued*)

Study title	Associated disease(s)	Intervention	Phase	NCT number
A Phase 2/3 study of the efficacy and safety of hematopoietic stem cells transduced with Lenti-D lentiviral vector for the treatment of Childhood Cerebral Adrenoleukodystrophy (CCALD)	X-ALD	Genetic: Lenti-D drug product; Drug: busulfan; Drug: cyclophosphamide; Drug: filgrastim	Phase II/III	NCT01896102
Triheptanoin treatment trial for patients with Adult Polyglucosan Body Disease	APBD	Drug: triheptanoin; Dietary supplement: vegetable oil	Phase II	NCT00947960
Safety and pharmacodynamic study of sobetirome in X-linked Adrenoleukodystrophy (X-ALD)	X-ALD	Drug: sobetirome	Phase I	NCT01787578
Expanded access for Lorenzo's Oil (GTO/GTE) in adrenoleukodystrophy	X-ALD	Drug: Lorenzo's Oil	N/A	NCT02233257
Betaine and peroxisome biogenesis disorders	Peroxisomal Biogenesis Disorders	Drug: betaine	Phase III	NCT01838941
Oral Glyceryl Triacetate (GTA) in newborns with canavan	Canavan disease	Dietary supplement: GTA (glyceryl triacetate); Drug: GTA glyceryl triacetate	N/A	NCT00724802
Phase II study of cholesterol- and cholestanol-free diet, lovastatin, and chenodeoxycholic acid for Cerebrotendinous Xanthomatosis	CTX	Drug: chenodeoxycholic acid; Drug: lovastatin	Phase II	NCT00004346
Evaluation of carotid IMT and atherogenic risk factors in patients with Cerebrotendinous Xanthomatosis	CTX	Biological: blood tests	N/A	NCT01613898
Sjögren–Larsson syndrome: natural history, clinical variation and evaluation of biochemical markers	Sjögren–Larsson syndrome	N/A	N/A	NCT01971957

2.2. ALD: emerging therapies & clinical trials

In boys who have not yet developed cerebral ALD, daily consumption of Lorenzo's Oil, a mixture of oleic and erucic acid, in combination with dietary restriction of very long chain fatty acids, may help mitigate the risk of developing cerebral demyelination [11]. The oil acts as a competitive inhibitor of endogenous very long chain fatty acid production [12]. Use of Lorenzo's Oil appears to offer a modest reduction in the risk of developing cerebral X-ALD, although it has no impact on the progression of cerebral X-ALD once the disease process has begun [11]. Its consumption carries health risks [13] and it's availability in the US is currently restricted to X-ALD boys aged 3–10 under an expanded access trial (Clinical Trials.gov, NCT02233257).

A pilot phase trial using sobetirome, thyromimetic, synthetic structural analogs of thyroid hormone that mimic tissue-restricted thyroid hormone actions [14] is in preparatory phases (ClinicalTrials.gov identifier: NCT01787578) based on the molecule's ability to upregulate ABCD2, whose genetic expression can help metabolize very long chain fatty acids [15]. Sobetirome showed efficacy and safety, indicating that it has been well tolerated at all doses studied.

Lentiviral-based gene therapy has shown early promise in X-ALD [16]. This technology involves the ex-vivo transduction of autologous HSCs with a human immunodeficiency virus type 1-derived vector. This retroviral vector targets microglial precursors, with no evidence of insertional mutagenesis, which can trigger leukemia and has the advantage of theoretically eliminating the risk of graft-versus host disease. Lentiviral ALD gene therapy has shown encouraging results in ALD patients where its use has resulted in polyclonal hematopoietic repopulation, stable transgene expression, and stabilization or reversal of demyelination [9] and is entering Phase II/III clinical trials (ClinicalTrials.gov identifier: NCT01896102).

3. Adult Polyglucosan Body Disease (APBD)

APBD is one of relatively few adult-onset leukodystrophies. Symptoms usually appear in the 5th or 6th decade with progressive spastic paraparesis, sphincter dysfunction, and ascending peripheral neuropathy. The affected gene (*GBE1*) encodes a glycogen branching enzyme whose dysfunction leads to the accumulation of polyglucosan bodies in the central and peripheral nerves. Studies into the effectiveness of anaplerotic therapy in APBD are currently ongoing (ClinicalTrials.gov identifier: NCT00947960). The implementation of triheptanonin, a 7-carbon triglyceride, is suspected to be an efficient substrate to the citric acid cycle to correct the resultant energy deficit [17]. This may be an important therapy which may prove beneficial in slowing the clinical course of these patients.

4. Aicardi–Goutières Syndrome (AGS)

AGS is a devastating neurologic disorder that primarily affects patients in the first year of life. AGS is characterized, in part, by a calcifying microangiopathy and elevated cerebral spinal fluid (CSF) α-interferon (IFNα) levels that usually presents in the first year of life. The seven AGS related genes (*TREX1*, *RNASEH2A*/*B*/*C*, *SAMHD1*, *ADAR1* and *IFIH1*) are associated with genome surveillance, integrity and damage repair. Pathogenic mutations appear to result in the aberrant accumulation of RNA:DNA (ribonucleic acid:deoxyribonucleic acid) hybrids and other immunogenic nucleic acid structures within the cell [18–21]. The discovery of elevated IFNα in CSF has prompted further research into the autoimmune complications associated with AGS.

4.1. AGS: recognition and approach to unique clinical features

AGS patients share many common features with those affected by systemic lupus erythematosus (SLE), and rare cases of SLE have been found to be associated with *TREX1* mutations. All AGS patients should be monitored and symptomatically treated for skin inflammation (e.g., chilblains), arthritis, inflammatory bowel disease, hematologic complications, and cardiomyopathy [22]. AGS patients with a *SAMHD1* mutation are at risk high risk of developing potentially life-threatening complications from large vessel vasculitis; consideration should be given for both radiologic and serologic screening in these individuals. Many AGS patients exhibit a range of endocrine dysfunction (e.g., hypothyroidism) that may benefit from periodic screening and supplementation when indicated. Systemic immunosuppressive regimens (e.g., corticosteroids) have been employed as part of symptom management for AGS, but have not yet demonstrated definite improvement in neurologic symptoms [23].

4.2. AGS: emerging therapies have not yet entered clinical trials

Experiments in the murine model of AGS have demonstrated over-accumulation of endogenous retro elements [24,25] while SAM domain and HD domain-containing protein 1 (SAMHD1) have been shown to be a dominant suppressor of Long Interspersed Element 1 (LINE-1). AGS-related mutations compromise the potency of SAMHD1 against LINE-1 retrotransposition [26]. Within the

murine model of AGS, the use of reverse transcriptase inhibitors presumably targeting production of endogenous retroelements has been studied with promising results [27]. Significant work is still necessary to better understand the mechanisms of this disorder but efforts are underway to test the use of antiretroviral therapy in AGS patients.

5. Alexander disease (AxD)

AxD results from a mutation in the gene encoding glial fibrillary acidic protein (GFAP). In classical (i.e., Type I) AxD, symptoms of macrocephaly, seizure, and spasticity appear in infancy. Substantial accumulation of the mutated GFAP may also result in obstruction of CSF pathways and hydrocephalus [28]. Routine monitoring for this complication Papilledema, headache, or changes in vision or behavior can aid in the diagnosis of this complication. Neurosurgical intervention should be considered on a case-by-case basis.

Some individuals with GFAP mutations may present in adolescence or adulthood (i.e., Type II AxD). Unique symptoms may include bulbar dysfunction (e.g., dysphonia, palatal myoclonus), autonomic dysfunction, and sleep apnea [28]. Treatment of these latter two symptoms may help alleviate encephalopathy and enhance quality of life.

6. Canavan disease

Canavan disease is characterized by progressive spongiform degeneration of the brain caused by a deficiency of the aspartoacyclase, which is necessary for brain metabolism of N-acetyl aspartic acid (NAA) [29]. Onset is typically in the first year of life and current treatment is supportive. In the first gene therapy trial in Canavan disease, intraventricular delivery of liposome-encapsulated plasmid DNA was able to produce a transient decrease in NAA accumulation, and MRI scans suggested new myelination in one of the two patients [30]. However, results of a Phase I/II clinical trial testing intraparenchymal gene delivery with a recombinant adeno-associated virus serotype 2 (AAV2) vector have been more promising. Treated children showed decreased brain NAA concentrations, MRI changes suggesting more normal myelination and stabilization of brain atrophy, and evidence for improved clinical status on long-term follow-up [31].

7. Cerebrotendinous Xanthomatosis (CTX)

CTX is an autosomal recessive inherited lipid storage disorder that results from a genetic mutation in *CYP27A1*. CTX results from a deficiency in 27-hydroxylase, a mitochondrial enzyme responsible for an early step in bile acid synthesis, and is uniquely characterized by high levels of serum cholestanol and bile acids that deposit in the brain, lens, and tendons. Clinical symptoms manifest in early childhood as cataracts and diarrhea. It is only later in life that patients show psychomotor decline, and the typical tendon xanthomas. Daily oral supplementation with 750 mg of chenodeoxycholic acid, a bile salt, typically corrects the biochemical abnormalities and may reverse some clinical symptoms [32,33]. Some experience suggests that earlier treatment initiation may correlate with better outcomes [34]. Oral statins are often included in the CTX treatment regimen, although their clinical benefit is unknown.

8. Hypomyelination with Brain Stem and Spinal cord abnormalities and leg spasticity (HBSL)

HBSL is the result of mutations in *DARS*, a cytoplasmic tRNA synthetase gene. HBSL patients present with a broad phenotypic spectrum characterized by focal cerebral white matter abnormalities and spinal cord signal abnormalities [35]. Interestingly partial responsiveness to steroids in a number of HBSL patients with subacute disease onset suggests that steroids may be a therapeutic avenue that should be further studied in this condition [35]. Certain tRNA synthetases have non-canonical functions in biological processes such as angiogenesis, regulation of gene transcription, and RNA splicing [36]. These non-canonical tRNA synthetase functions are conserved across the complete phylogeny of animals, and are now established as playing key roles in a number of pathophysiological processes [36]. DARS specifically, is one of nine cytoplasmic tRNA synthetases that make up the multi-synthetase complex (MSC) which facilitates gene-specific translational silencing of inflammation-related mRNAs. While these mechanisms and functions must be studied further to elucidate why individuals appear responsive and what their clinical response is, it provides an interesting basis for compassionate care treatment in these patients.

9. Krabbe disease

9.1. Krabbe: recognition and approach to unique clinical features

Most individuals with Krabbe disease typically experience severe neurological disturbances. Krabbe disease results from pathogenic mutations in the *GALC* gene which encodes the lysosomal enzyme galactosylceramidase. Most Krabbe-causing mutations result in severely diminished function of the enzyme. The classical presentation of Krabbe occurs in infancy where affected individuals manifest spasticity and irritability. Less commonly, some GALC mutations appear to result in a less severe attenuation of enzyme function which may lead to a milder phenotype. Unfortunately, genotype–phenotype correlations in Krabbe disease are generally inconsistent which poses a significant hurdle for treatment selection and clinical trial design.

9.2. Krabbe: emerging therapies

Early studies suggest that in carefully selected cases (e.g., "pre-symptomatic" infants or older patients with low neurologic morbidity) HSCT may help attenuate the usually rapid neurologic deterioration [37–39]. The presymptomatic treatment paradigm constitutes the argument for newborn screening for Krabbe disease, which is currently available in a small number of US states. Among patients with later disease onset, HSCT may also prove beneficial, although the rarity of these phenotypes has limited its study [37,39]. As in MLD, these treatment recommendations are tempered by a lack of long-term outcome data and poor genotype–phenotype correlations [40–42]. The clinical staging criteria have been proposed for Krabbe disease [43] and may be useful in evaluating patients for HSCT [44].

Missense mutations, occurring in >60% of Krabbe patients, are predicted to generate misfolded proteins [45]. Misfolded proteins can be prematurely degraded and can aggregate within the cell, or trigger an unfolded protein response [46–48]. It is estimated that just 10% of normal galactosylceramidase (GALC) function is necessary to avoid the neurological symptoms associated with Krabbe disease [49]. Thus, an intervention that restores 10% of missense-causing GALC function would have the potential for impacting this disease. Pharmacological chaperones, synthetic low molecular weight molecules that can be administered orally with broad body-wide distribution (including the CNS), can rescue function of mutant proteins by directing them into a proper conformation or cellular location, or protecting them from degradation [50–52]. Pharmacological chaperones that improve the activity of misfolded GALC are currently being screened, with α-lobeline and 3′,4′,7-trihydroxyisoflavone recently identified candidates [53,54].

10. Metachromatic Leukodystrophy (MLD)

10.1. MLD: recognition and approach to unique clinical features

MLD results from a pathogenic mutation in the gene encoding either arylsulfatase A or saposin B, either of which results in the accumulation of toxic metabolites (i.e., sulfatides) within the nervous system as well

as some visceral organs. As with Krabbe disease, enzymatic activity levels tend to correlate with age of onset and severity of symptoms with age of onset ranging from infancy (most common) to adulthood (rare). Although motor symptoms dominate early life presentation of MLD, adults often manifest with increasingly severe psychiatric disturbances. The gallbladder accumulates particularly high levels of sulfatides which may result in potentially life-threatening, but treatable gall bladder pathologies (e.g., gallstones, papillomatosis, cholecystitis). In rare cases, identification of gallbladder dysfunction prior to the onset of neurologic symptoms could provide a theoretic window for early intervention to mitigate neurologic sequelae of MLD [55].

10.2. MLD: emerging therapies

MLD patients have been treated with HSCT [39,42,56,57], although its use has been widely debated due to phenotypic variability, transplant-refractory peripheral neuropathy, high treatment-related morbidity and mortality, and limited long-term outcome data. The most substantial disagreement centers on the use of HSCT among very young patients with early disease onset (i.e., late-infantile MLD); in addition to variable neurocognitive outcomes, these patients typically manifest transplant-refractory neuropathy which results in progressive flaccid paralysis [5]. Experts do agree, however, that symptomatic children with the late-infantile form of MLD are poor candidates for these therapies, as are individuals with later onset forms of the disease who have already accrued cognitive morbidity [5,39,58,59]. Bone marrow transplantation has been shown to halt demyelination in minimally symptomatic patients with juvenile or adult MLD [60]. Since the initial publication of transplant outcomes in MLD [5], the treatment regimens have improved and there are indications that morbidity rates have fallen. In addition, the use of umbilical cord blood decreases the time between diagnosis and transplantation, improving outcomes of minimally symptomatic patients with late-infantile and juvenile MLD. Outcomes vary according to clinical status, Loes score, peripheral nerve disease and neurologic examination, with the best results for those with minimally symptomatic juvenile disease [40,61–63]. Treatment recommendations are based on the limited long-term longitudinal outcome data currently available, as is the case of allogeneic HSCT for Krabbe disease patients [40–42]. The decision to pursue transplant among patients with these disorders can be complex and as a result, must be evaluated on an individual basis by a specialized and experienced center, prepared to provide the most up to date information and support patients with complex neurologic and systemic manifestations.

As therapy with HSCT has resulted in variable outcomes, Enzyme Replacement Therapy (ERT) is being studied under clinical trials in Europe, South America and Australia. ERT replaces the deficient or missing enzyme with an active enzyme, which is a recombinant human protein produced by gene activation technology. Therapeutic efficacy of ERT is thought to depend on the enzyme dose, frequency, and the disease stage at which treatment is initiated. Prior studies using a regular repeated intravenous delivery of recombinant human arylsulfatase A (rhASA) failed to show efficiency in permeating the blood–brain barrier [64]. Current Phase I/II studies, using an intrathecal delivery mechanism and a different enzyme are underway although no formal data will be available until late 2015 (ClinicalTrials.gov identifier: NCT01510028).

Lentiviral-based gene therapy for MLD have produced above-normal enzyme activity in the central nervous system and halted disease progression in the first three patients, who were presymptomatic when treated (ClinicalTrials.gov identifier: NCT01560182) [16]. Phase I/II post-therapy monitoring is underway with Phase II/III studies expected to start in 2015.

11. Pelizaeus–Merzbacher Disease (PMD)

PMD results from pathogenic mutations in a gene (*PLP1*) that encodes proteolipid protein which is one of the proteins responsible for stabilizing the myelin sheath. At the cellular level, oligodendrocytes, astrocytes, microglia, and neurons are affected through a number of mechanisms [65]. Mutations lead to a hypomyelinating leukodystrophy characterized by early onset nystagmus, hypotonia, and cognitive impairment progressing to ataxia and spasticity. The more severe, connatal form typically manifests symptoms such as seizures and/or stridor within the first two weeks of life.

Human Central Nervous System Stem Cell (HuCNS-SC) transplant for patients with the connatal form of PMD has completed one-year Phase I safety studies and is under further assessment in long-term follow-up studies at the University of California, San Francisco (UCSF) in partnership with StemCells, Inc. Pre-clinical studies with HuCNS-SC showed that transplantation in hypomyelinated *shiverer* mice generated new oligodendrocytes that produced MRI confirmed myelin [66]. The Phase I trial at UCSF transplanted HuCNS-SC directly into subcortical white matter tracts of four children with connatal PMD. MRI studies showed evidence for qualitative changes on T_1- and T_2-weighted imaging and progressive increases in fractional anisotropy on diffusion tensor imaging (DTI) [67]. Moreover, such DTI signal changes persisted after stopping immunosuppressive therapies. The preliminary clinical outcomes of the study suggest the safety of this intervention in patients with PMD. While efficacy studies for PMD are needed, this approach establishes a methodology for other leukodystrophies and leukoencephalopathies that may benefit from the application of HuCNS-SCs, or other CNS cell types (e.g., oligodendrocyte precursors), through transplantation into the brain [68].

12. Peroxisomal Biogenesis Disorders

Peroxisomal Biogenesis Disorders including Zellweger spectrum disorder (ZSD) are a heterogeneous autosomal recessive group of disorders caused by defects in at least 13 known peroxisomal (PEX) genes that are required for peroxisome assembly [69]. These gene defects result in reduced peroxisome numbers, enlarged size of remaining peroxisomes and loss of enzyme import functions, resulting in multiple peroxisomal enzyme deficiencies and multisystem defects. In general, patients with PEX gene mutations that abrogate PEX protein function cause the most severe form of the disease, Zellweger syndrome. However the presence of at least one PEX gene missense mutation, results in residual protein functions and a less severe phenotype [70].

Patients with the most severe form of Zellweger syndrome are born with neuronal migration defects, and do not survive past 1–2 years of age. However, the majority of ZSD patients do not have neuronal migration defects and may have normal brain MRI imaging early on, but are at risk to develop a leukoencephalopathy over time. A common mutation present in at least 30% of these patients is PEX1-Gly843Asp, due to a founder effect in persons of European ancestry [71]. Studies of this allele show that it is a misfolded and degraded protein amenable to recovery at the cellular level [72]. Using a phenotype based assay with PEX1-Gly843Asp cell lines expressing a GFP-PTS1 reporter, several chaperone compounds were identified that recovered peroxisome enzyme import in a drug library screen [73]. A clinical trial was initiated, based on the nonspecific chemical chaperone, betaine (ClinicalTrials.gov identifier: NCT01838941).

13. RNA polymerase III disorders

Patients with Pol III-related leukodystrophies commonly, but not invariably, suffer from hypogonadotropic hypogonadism, which often presents as delayed puberty, but may include growth hormone failure and/or hypothyroidism. We recommend that Poll III patients be assessed and followed by an endocrinologist [74]. The decision of whether or not to treat the hormonal deficiency should be taken on

an individual basis, weighing the risks of the disease versus the potential benefits of the treatment.

14. Other unique clinical features can occur in several leukodystrophies

14.1. Episodic deterioration during acute stress or illness may occur in several disorders

Almost all leukodystrophies may manifest acute neurologic deterioration in periods of acute stress, often without full recovery to premorbid baseline, however in certain disorders this is a classic presentation. Patients with Vanishing White Matter Disease (VWM) may present following febrile illness, head trauma and/or severe fright [75]. Some mitochondrial disorders may manifest white matter abnormalities and episodic decline. Step-wise decline may also occur following infection in Pol III-related leukodystrophies [74] or in AGS [22], and after head trauma in X-ALD [76]. Therapeutic strategies for these disorders include aggressive infection prevention and treatment measures including frequent hand-washing, annual vaccinations for influenza and pneumococcus, and liberal antibiotic use. In the case of mitochondrial disorders, avoiding metabolic catabolism (i.e., nutritional fasting physiology) during periods of stress may also be appropriate [77]. Finally, greater than usual attention to avoid mild traumatic brain injury may also be warranted.

14.2. Dental anomalies occur in several hypomyelinating disorders

Pol III-related leukodystrophies, Cockayne syndrome, and Oculodentodigital Dysplasia (ODD) are three hypomyelinating leukodystrophies typically manifesting dental anomalies. For patients with these three hypomyelinating leukodystrophies, dental care is of utmost importance and regular visits to the dentist are recommended. In the Peroxisome Biogenesis Disorders, absence of enamel on the secondary teeth is a recurrent finding [78]. However, regular dental care and hygiene is important for *all* leukodystrophy patients as cavities and abscesses may go unnoticed in routine medical care and can result in severe medical morbidity. Thus, regular dental visits are recommended for all leukodystrophy patients.

15. Conclusion

As an entity, leukodystrophies are a complex, often progressive group of disorders that can manifest a wide range of symptoms and complications. A number of these disorders have severe complications that must be addressed in order to improve quality of life for these patients. The multisystem involvements that can be seen in these disorders provide challenges for clinicians and care must be designed to accommodate all of the associated symptoms.

With the absence of a cure for most leukodystrophies, the disorders that currently have specific therapies and/or active clinical trials are of great importance. In many instances, prompt recognition and early treatment initiation favor a better therapeutic response. Increased attention to the signs and symptoms of these leukodystrophies and education to promote early diagnosis is essential.

More recently, clinicians and researchers have been able to advance research therapies in specific disorders. A number of these disorders, previously untreatable, are on the verge of pilot or Phase I/II clinical trials. Next generation sequencing technologies have finally provided a way to fill gaps in diagnosis-solving cases where in the past more than half of patients never achieved an etiologic diagnosis, findings that are important in improving patient care and quality of life. Early epidemiologic research has quantified the health care burden of these disorders, which occur cumulatively as frequently as every 1/7000 births and result in significant morbidity and health care expenditures [79–81]. Finally, increased awareness of rare disorders better positions patient centered foundations and researchers to advocate for the leukodystrophy community.

The unmet needs of leukodystrophy patients still remain an overwhelming burden. While the consensus is that these disorders collectively are symptomatically treatable, leukodystrophy patients are in need of advanced therapies and if possible, a cure. Collaboration is the cornerstone of progress in the world of rare diseases. The growth of clinical research networks in the field of leukodystrophies and likewise, the increasingly common alliance of these consortiums with patient advocacy groups also bodes well, particularly in regards to the need for prioritizing and measuring patient-reported outcomes. Although the rise of patient-powered research models has arrived at a welcome time, the heavy burden of weighing safety, efficacy, and trial designs at the threshold of translational-to-clinical medicine will continue to engage clinical investigators.

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Authorship/contributions

GH, KVH, GB, NB, SAF, MP, DR, RS, FE, MS, And AV wrote the manuscript. KVH, JLB, GB, AP, DS, MCP, JL, MsvdK, SAB, SD, SAG, AM, LW, RS, FE, ME, and AV contributed to the consensus building process. AP, AT, NB, JLB, MP, DR, SAB, and ME provided expert consultation. JL, DS, and SD represented the voice of patient advocacy groups in this consensus process. GH, KVH, ME, and AV coordinated the manuscript.

Conflicts of interest

MCP: Editorial: Journal of Child Neurology, Child Neurology Open (Editor-in-Chief), Journal of Inherited Metabolic Disease (Editor). Otherwise authors report no conflict of interest.

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References

[1] S. Parikh, G. Bernard, R. Leventer, M. van der Knaap, J. Van Hove, A. Pizzino, N. McNeill, G. Helman, C. Simons, W. Rizzo, M. Patterson, R. Taft, A. Vanderver, A clinical approach to the diagnosis of patients with leukodystrophies and genetic leukoencephalopathies, Mol. Genet. Metab. (2015). http://dx.doi.org/10.1016/j.ymgme.2014.12.434 (Epub ahead of print).

[2] A. Vanderver, M. Prust, D. Tonduti, F. Mochel, H. Hussey, G. Helman, J. Garbern, F. Eichler, P. Labauge, P. Aubourg, D. Rodriguez, M. Patterson, J. Van Hove, J. Schmidt, N. Wolf, O. Boespflug-Tanguy, R. Schiffmann, M. van der Knaap, Case definition and classification of leukodystrophies and leukoencephalopathies, Mol. Genet. Metab. (2015). http://dx.doi.org/10.1016/j.ymgme.2015.01.006 (Epub ahead of print).

[3] K. Van Haren, J. Bonkowsky, G. Bernard, J. Murphy, A. Pizzino, G. Helman, D. Suhr, J. Waggoner, D. Hobson, A. Vanderver, M. Patterson, Consensus Statement on Preventive and Symptomatic Care of Leukodystrophy Patients, 2015. (in press).

[4] M. Engelen, S. Kemp, M. de Visser, B.M. van Geel, R.J. Wanders, P. Aubourg, B.T. Poll-The, X-linked adrenoleukodystrophy (X-ALD): clinical presentation and guidelines for diagnosis, follow-up and management, Orphanet J. Rare Dis. 7 (2012) 51.

[5] C. Peters, L.R. Charnas, Y. Tan, R.S. Ziegler, E.G. Shapiro, T. DeFor, S.S. Grewal, P.J. Orchard, S.L. Abel, A.I. Goldman, N.K. Ramsay, K.E. Dusenbery, D.J. Loes, L.A. Lockman, S. Kato, P.R. Aubourg, H.W. Moser, W. Krivit, Cerebral X-linked adrenoleukodystrophy: the international hematopoietic cell transplantation experience from 1982 to 1999, Blood 104 (2004) 881–888.

[6] E. Shapiro, W. Krivit, L. Lockman, I. Jambaque, C. Peters, M. Cowan, R. Harris, S. Blanche, P. Bordigoni, D. Loes, R. Ziegler, M. Crittenden, D. Ris, B. Berg, C. Cox, H. Moser, A. Fischer, P. Aubourg, Long-term effect of bone-marrow transplantation for childhood-onset cerebral X-linked adrenoleukodystrophy, Lancet 356 (2000) 713–718.

[7] W.P. Miller, S.M. Rothman, D. Nascene, T. Kivisto, T.E. DeFor, R.S. Ziegler, J. Eisengart, K. Leiser, G. Raymond, T.C. Lund, J. Tolar, P.J. Orchard, Outcomes after allogeneic hematopoietic cell transplantation for childhood cerebral adrenoleukodystrophy: the largest single-institution cohort report, Blood 118 (2011) 1971–1978.

[8] K.A. Thibert, G.V. Raymond, D.R. Nascene, W.P. Miller, J. Tolar, P.J. Orchard, T.C. Lund, Cerebrospinal fluid matrix metalloproteinases are elevated in cerebral adrenoleukodystrophy and correlate with MRI severity and neurologic dysfunction, PLoS ONE 7 (2012) e50430.

[9] N. Cartier, S. Hacein-Bey-Abina, C.C. Bartholomae, G. Veres, M. Schmidt, I. Kutschera, M. Vidaud, U. Abel, L. Dal-Cortivo, L. Caccavelli, N. Mahlaoui, V. Kiermer, D. Mittelstaedt, C. Bellesme, N. Lahlou, F. Lefrere, S. Blanche, M. Audit, E. Payen, P. Leboulch, B. l'Homme, P. Bougneres, C. Von Kalle, A. Fischer, M. Cavazzana-Calvo, P. Aubourg, Hematopoietic stem cell gene therapy with a lentiviral vector in X-linked adrenoleukodystrophy, Science 326 (2009) 818–823.

[10] C. Theda, K. Gibbons, T.E. DeFor, P.K. Donohue, W.C. Golden, A.D. Kline, F. Gulamali-Majid, S.R. Panny, W.C. Hubbard, R.O. Jones, A.K. Liu, A.B. Moser, G.V. Raymond, Newborn screening for X-linked adrenoleukodystrophy: further evidence high throughput screening is feasible, Mol. Genet. Metab. 111 (2014) 55–57.

[11] H.W. Moser, G.V. Raymond, S.E. Lu, L.R. Muenz, A.B. Moser, J. Xu, R.O. Jones, D.J. Loes, E.R. Melhem, P. Dubey, L. Bezman, N.H. Brereton, A. Odone, Follow-up of 89 asymptomatic patients with adrenoleukodystrophy treated with Lorenzo's oil, Arch. Neurol. 62 (2005) 1073–1080.

[12] T. Sassa, T. Wakashima, Y. Ohno, A. Kihara, Lorenzo's oil inhibits ELOVL1 and lowers the level of sphingomyelin with a saturated very long-chain fatty acid, J. Lipid Res. 55 (2014) 524–530.

[13] A. Semmler, W. Kohler, H.H. Jung, M. Weller, M. Linnebank, Therapy of X-linked adrenoleukodystrophy, Expert. Rev. Neurother. 8 (2008) 1367–1379.

[14] T. Hirano, H. Kagechika, Thyromimetics: a review of recent reports and patents (2004–2009), Expert Opin. Ther. Pat. 20 (2010) 213–228.

[15] F.D. Weber, C. Wiesinger, S. Forss-Petter, G. Regelsberger, A. Einwich, W.H. Weber, W. Kohler, H. Stockinger, J. Berger, X-linked adrenoleukodystrophy: very long-chain fatty acid metabolism is severely impaired in monocytes but not in lymphocytes, Hum. Mol. Genet. 23 (2014) 2542–2550.

[16] A. Biffi, E. Montini, L. Lorioli, M. Cesani, F. Fumagalli, T. Plati, C. Baldoli, S. Martino, A. Calabria, S. Canale, F. Benedicenti, G. Vallanti, L. Biasco, S. Leo, N. Kabbara, G. Zanetti, W.B. Rizzo, N.A. Mehta, M.P. Cicalese, M. Casiraghi, J.J. Boelens, U. Del Carro, D.J. Dow, M. Schmidt, A. Assanelli, V. Neduva, C. Di Serio, E. Stupka, J. Gardner, C. von Kalle, C. Bordignon, F. Ciceri, A. Rovelli, M.G. Roncarolo, A. Aiuti, M. Sessa, L. Naldini, Lentiviral hematopoietic stem cell gene therapy benefits metachromatic leukodystrophy, Science 341 (2013) 1233158.

[17] C.R. Roe, T. Bottiglieri, M. Wallace, E. Arning, A. Martin, Adult Polyglucosan Body Disease (APBD): anaplerotic diet therapy (Triheptanoin) and demonstration of defective methylation pathways, Mol. Genet. Metab. 101 (2010) 246–252.

[18] Y.J. Crow, B.E. Hayward, R. Parmar, P. Robins, A. Leitch, M. Ali, D.N. Black, H. van Bokhoven, H.G. Brunner, B.C. Hamel, P.C. Corry, F.M. Cowan, S.G. Frints, J. Klepper, J.H. Livingston, S.A. Lynch, R.F. Massey, J.F. Meritet, J.L. Michaud, G. Ponsot, T. Voit, P. Lebon, D.T. Bonthron, A.P. Jackson, D.E. Barnes, T. Lindahl, Mutations in the gene encoding the 3′-5′ DNA exonuclease TREX1 cause Aicardi–Goutieres syndrome at the AGS1 locus, Nat. Genet. 38 (2006) 917–920.

[19] Y.J. Crow, A. Leitch, B.E. Hayward, A. Garner, R. Parmar, E. Griffith, M. Ali, C. Semple, J. Aicardi, R. Babul-Hirji, C. Baumann, P. Baxter, E. Bertini, K.E. Chandler, D. Chitayat, D. Cau, C. Dery, E. Fazzi, C. Goizet, M.D. King, J. Klepper, D. Lacombe, G. Lanzi, H. Lyall, M.L. Martinez-Frias, M. Mathieu, C. McKeown, A. Monier, Y. Oade, O.W. Quarrell, C.D. Rittey, R.C. Rogers, A. Sanchis, J.B. Stephenson, U. Tacke, M. Till, J.L. Tolmie, P. Tomlin, T. Voit, B. Weschke, C.G. Woods, P. Lebon, D.T. Bonthron, C.P. Ponting, A.P. Jackson, Mutations in genes encoding ribonuclease H2 subunits cause Aicardi–Goutieres syndrome and mimic congenital viral brain infection, Nat. Genet. 38 (2006) 910–916.

[20] G.I. Rice, J. Bond, A. Asipu, R.L. Brunette, I.W. Manfield, I.M. Carr, J.C. Fuller, R.M. Jackson, T. Lamb, T.A. Briggs, M. Ali, H. Gornall, L.R. Couthard, A. Aeby, S.P. Attard-Montalto, E. Bertini, C. Bodemer, K. Brockmann, L.A. Brueton, P.C. Corry, I. Desguerre, E. Fazzi, A.G. Cazorla, B. Gener, B.C. Hamel, A. Heiberg, M. Hunter, M.S. van der Knaap, R. Kumar, L. Lagae, P.G. Landrieu, C.M. Lourenco, D. Marom, M.F. McDermott, W. van der Merwe, S. Orcesi, J.S. Prendiville, M. Rasmussen, S.A. Shalev, D.M. Soler, M. Shinawi, R. Spiegel, T.Y. Tan, A. Vanderver, E.L. Wakeling, E. Wassmer, E. Whittaker, P. Lebon, D.B. Stetson, D.T. Bonthron, Y.J. Crow, Mutations involved in Aicardi–Goutieres syndrome implicate SAMHD1 as regulator of the innate immune response, Nat. Genet. 41 (2009) 829–832.

[21] G.I. Rice, P.R. Kasher, G.M. Forte, N.M. Mannion, S.M. Greenwood, M. Szynkiewicz, J.E. Dickerson, S.S. Bhaskar, M. Zampini, T.A. Briggs, E.M. Jenkinson, C.A. Bacino, R. Battini, E. Bertini, P.A. Brogan, L.A. Brueton, M. Carpanelli, C. De Laet, P. de Lonlay, M. Del Toro, I. Desguerre, E. Fazzi, A. Garcia-Cazorla, A. Heiberg, M. Kawaguchi, R. Kumar, J.P. Lin, C.M. Lourenco, A.M. Male, W. Marques Jr., C. Mignot, I. Olivieri, S. Orcesi, P. Prabhakar, M. Rasmussen, R.A. Robinson, F. Rozenberg, J.L. Schmidt, K. Steindl, T.Y. Tan, W.G. van der Merwe, A. Vanderver, G. Vassallo, E.L. Wakeling, E. Wassmer, E. Whittaker, J.H. Livingston, P. Lebon, T. Suzuki, P.J. McLaughlin, L.P. Keegan, M.A. O'Connell, S.C. Lovell, Y.J. Crow, Mutations in ADAR1 cause Aicardi–Goutieres syndrome associated with a type I interferon signature, Nat. Genet. 44 (2012) 1243–1248.

[22] Y.C. Crow, D. Chase, Characterization of Human Disease Phenotypes Associated With Mutations in TREX1, RNASEH2A, RNASEH2B, RNASEH2C, SAMHD1, ADAR and IFIH1, 2015. (in press).

[23] C. Chahwan, R. Chahwan, Aicardi–Goutieres syndrome: from patients to genes and beyond, Clin. Genet. 81 (2012) 413–420.

[24] D.B. Stetson, Endogenous retroelements and autoimmune disease, Curr. Opin. Immunol. 24 (2012) 692–697.

[25] D.B. Stetson, J.S. Ko, T. Heidmann, R. Medzhitov, Trex1 prevents cell-intrinsic initiation of autoimmunity, Cell 134 (2008) 587–598.

[26] K. Zhao, J. Du, X. Han, J.L. Goodier, P. Li, X. Zhou, W. Wei, S.L. Evans, L. Li, W. Zhang, L.E. Cheung, G. Wang, H.H. Kazazian Jr., X.F. Yu, Modulation of LINE-1 and Alu/SVA retrotransposition by Aicardi–Goutieres syndrome-related SAMHD1, Cell Rep. 4 (2013) 1108–1115.

[27] G.B. Beck-Engeser, D. Eilat, M. Wabl, An autoimmune disease prevented by antiretroviral drugs, Retrovirology 8 (2011) 91.

[28] M. Prust, J. Wang, H. Morizono, A. Messing, M. Brenner, E. Gordon, T. Hartka, A. Sokohl, R. Schiffmann, H. Gordish-Dressman, R. Albin, H. Amartino, K. Brockman, A. Dinopoulos, M.T. Dotti, D. Fain, R. Fernandez, J. Ferreira, J. Fleming, D. Gill, M. Griebel, H. Heilstedt, P. Kaplan, D. Lewis, M. Nakagawa, R. Pedersen, A. Reddy, Y. Sawaishi, M. Schneider, E. Sherr, Y. Takiyama, K. Wakabayashi, J.R. Gorospe, A. Vanderver, GFAP mutations, age at onset, and clinical subtypes in Alexander disease, Neurology 77 (2011) 1287–1294.

[29] R. Matalon, K. Michals, D. Sebesta, M. Deanching, P. Gashkoff, J. Casanova, Aspartoacylase deficiency and N-acetylaspartic aciduria in patients with Canavan disease, Am. J. Med. Genet. 29 (1988) 463–471.

[30] P. Leone, C.G. Janson, L. Bilaniuk, Z. Wang, F. Sorgi, L. Huang, R. Matalon, R. Kaul, Z. Zeng, A. Freese, S.W. McPhee, E. Mee, M.J. During, Aspartoacylase gene transfer to the mammalian central nervous system with therapeutic implications for Canavan disease, Ann. Neurol. 48 (2000) 27–38.

[31] P. Leone, D. Shera, S.W. McPhee, J.S. Francis, E.H. Kolodny, L.T. Bilaniuk, D.J. Wang, M. Assadi, O. Goldfarb, H.W. Goldman, A. Freese, D. Young, M.J. During, R.J. Samulski, C.G. Janson, Long-term follow-up after gene therapy for canavan disease, Sci. Transl. Med. 4 (2012) (165ra163).

[32] V.M. Berginer, G. Salen, S. Shefer, Long-term treatment of cerebrotendinous xanthomatosis with chenodeoxycholic acid, N. Engl. J. Med. 311 (1984) 1649–1652.

[33] Y. Tokimura, M. Kuriyama, K. Arimura, J. Fujiyama, M. Osame, Electrophysiological studies in cerebrotendinous xanthomatosis, J. Neurol. Neurosurg. Psychiatry 55 (1992) 52–55.

[34] B. Pilo-de-la-Fuente, A. Jimenez-Escrig, J.R. Lorenzo, J. Pardo, M. Arias, A. Ares-Luque, J. Duarte, S. Muniz-Perez, M.J. Sobrido, Cerebrotendinous xanthomatosis in Spain: clinical, prognostic, and genetic survey, Eur. J. Neurol. 18 (2011) 1203–1211.

[35] N.I. Wolf, C. Toro, I. Kister, K.A. Latif, R. Leventer, A. Pizzino, C. Simons, T.E. Abbink, R.J. Taft, M.S. van der Knaap, A. Vanderver, DARS-associated leukoencephalopathy can mimic a steroid-responsive neuroinflammatory disorder, Neurology 84 (3) (2015) 226–230.

[36] P. Yao, K. Poruri, S. Martinis, P. Fox, Non-catalytic regulation of gene expression by aminoacyl–tRNA synthetases, in: S. Kim (Ed.), Aminoacyl–tRNA Synthetases in Biology and Medicine, Springer Netherlands, 2014, pp. 167–187.

[37] W. Krivit, Allogeneic stem cell transplantation for the treatment of lysosomal and peroxisomal metabolic diseases, Springer Semin. Immunopathol. 26 (2004) 119–132.
[38] M.L. Escolar, M.D. Poe, J.M. Provenzale, K.C. Richards, J. Allison, S. Wood, D.A. Wenger, D. Pietryga, D. Wall, M. Champagne, R. Morse, W. Krivit, J. Kurtzberg, Transplantation of umbilical-cord blood in babies with infantile Krabbe's disease, N. Engl. J. Med. 352 (2005) 2069–2081.
[39] W. Krivit, C. Peters, E.G. Shapiro, Bone marrow transplantation as effective treatment of central nervous system disease in globoid cell leukodystrophy, metachromatic leukodystrophy, adrenoleukodystrophy, mannosidosis, fucosidosis, aspartylglucosaminuria, Hurler, Maroteaux–Lamy, and Sly syndromes, and Gaucher disease type III, Curr. Opin. Neurol. 12 (1999) 167–176.
[40] H.R. Martin, M.D. Poe, J.M. Provenzale, J. Kurtzberg, A. Mendizabal, M.L. Escolar, Neurodevelopmental outcomes of umbilical cord blood transplantation in metachromatic leukodystrophy, Biol. Blood Marrow Transplant. 19 (2013) 616–624.
[41] A. Kohlschutter, Lysosomal leukodystrophies: Krabbe disease and metachromatic leukodystrophy, Handb. Clin. Neurol. 113 (2013) 1611–1618.
[42] P.K. Duffner, V.S. Caviness Jr., R.W. Erbe, M.C. Patterson, K.R. Schultz, D.A. Wenger, C. Whitley, The long-term outcomes of presymptomatic infants transplanted for Krabbe disease: report of the workshop held on July 11 and 12, 2008, Holiday Valley, New York, Genet. Med. 11 (2009) 450–454.
[43] M.L. Escolar, M.D. Poe, H.R. Martin, J. Kurtzberg, A staging system for infantile Krabbe disease to predict outcome after unrelated umbilical cord blood transplantation, Pediatrics 118 (2006) e879–e889.
[44] M.L. Escolar, M.D. Poe, J.K. Smith, J.H. Gilmore, J. Kurtzberg, W. Lin, M. Styner, Diffusion tensor imaging detects abnormalities in the corticospinal tracts of neonates with infantile Krabbe disease AJNR, Am. J. Neuroradiol. 30 (2009) 1017–1021.
[45] D.A. Wenger, M.A. Rafi, P. Luzi, Molecular genetics of Krabbe disease (globoid cell leukodystrophy): diagnostic and clinical implications, Hum. Mutat. 10 (1997) 268–279.
[46] W. Bueter, O. Dammann, A. Leviton, Endoplasmic reticulum stress, inflammation, and perinatal brain damage, Pediatr. Res. 66 (2009) 487–494.
[47] M. D'Antonio, M.L. Feltri, L. Wrabetz, Myelin under stress, J. Neurosci. Res. 87 (2009) 3241–3249.
[48] E. Herczenik, M.F. Gebbink, Molecular and cellular aspects of protein misfolding and disease, FASEB J. 22 (2008) 2115–2133.
[49] E. Conzelmann, K. Sandhoff, Partial enzyme deficiencies: residual activities and the development of neurological disorders, Dev. Neurosci. 6 (1983) 58–71.
[50] T.K. Chaudhuri, S. Paul, Protein-misfolding diseases and chaperone-based therapeutic approaches, FEBS J. 273 (2006) 1331–1349.
[51] R.E. Boyd, G. Lee, P. Rybczynski, E.R. Benjamin, R. Khanna, B.A. Wustman, K.J. Valenzano, Pharmacological chaperones as therapeutics for lysosomal storage diseases, J. Med. Chem. 56 (2013) 2705–2725.
[52] K.J. Valenzano, R. Khanna, A.C. Powe, R. Boyd, G. Lee, J.J. Flanagan, E.R. Benjamin, Identification and characterization of pharmacological chaperones to correct enzyme deficiencies in lysosomal storage disorders, Assay Drug Dev. Technol. 9 (2011) 213–235.
[53] A.S. Berardi, G. Pannuzzo, A. Graziano, E. Costantino-Ceccarini, P. Piomboni, A. Luddi, Pharmacological chaperones increase residual beta-galactocerebrosidase activity in fibroblasts from Krabbe patients, Mol. Genet. Metab. 112 (4) (2014) 294–301.
[54] J. Ribbens, G. Whiteley, H. Furuya, N. Southall, X. Hu, J. Marugan, M. Ferrer, G.H.B. Maegawa, A high-throughput screening assay using Krabbe disease patient cells, Anal. Biochem. 434 (2013) 15–25.
[55] A. Agarwal, P.J. Shipman, Gallbladder polyposis in metachromatic leukodystrophy, Pediatr. Radiol. 43 (2013) 631–633.
[56] R.G. Bredius, L.A. Laan, A.C. Lankester, B.J. Poorthuis, M.J. van Tol, R.M. Egeler, W.F. Arts, Early marrow transplantation in a pre-symptomatic neonate with late infantile metachromatic leukodystrophy does not halt disease progression, Bone Marrow Transplant. 39 (2007) 309–310.
[57] G. Malm, O. Ringden, J. Winiarski, E. Grondahl, P. Uyebrant, U. Eriksson, H. Hakansson, O. Skjeldal, J.E. Mansson, Clinical outcome in four children with metachromatic leukodystrophy treated by bone marrow transplantation, Bone Marrow Transplant. 17 (1996) 1003–1008.
[58] K.I. Weinberg, Early use of drastic therapy, N. Engl. J. Med. 352 (2005) 2124–2126.
[59] W. Krivit, L.A. Lockman, P.A. Watkins, J. Hirsch, E.G. Shapiro, The future for treatment by bone marrow transplantation for adrenoleukodystrophy, metachromatic leukodystrophy, globoid cell leukodystrophy and Hurler syndrome, J. Inherit. Metab. Dis. 18 (1995) 398–412.
[60] C. Sevin, P. Aubourg, N. Cartier, Enzyme, cell and gene-based therapies for metachromatic leukodystrophy, J. Inherit. Metab. Dis. 30 (2007) 175–183.
[61] T.M. Pierson, C.G. Bonnemann, R.S. Finkel, N. Bunin, G.I. Tennekoon, Umbilical cord blood transplantation for juvenile metachromatic leukodystrophy, Ann. Neurol. 64 (2008) 583–587.
[62] C. Cable, R.S. Finkel, T.J. Lehky, N.M. Biassou, E.A. Wiggs, N. Bunin, T.M. Pierson, Unrelated umbilical cord blood transplant for juvenile metachromatic leukodystrophy: a 5-year follow-up in three affected siblings, Mol. Genet. Metab. 102 (2011) 207–209.
[63] M.E. van Egmond, P.J. Pouwels, J.J. Boelens, C.A. Lindemans, F. Barkhof, M.D. Steenwijk, P.M. van Hasselt, M.S. van der Knaap, N.I. Wolf, Improvement of white matter changes on neuroimaging modalities after stem cell transplant in metachromatic leukodystrophy, JAMA Neurol. 70 (2013) 779–782.
[64] F. Matthes, S. Stroobants, D. Gerlach, C. Wohlenberg, C. Wessig, J. Fogh, V. Gieselmann, M. Eckhardt, R. D'Hooge, U. Matzner, Efficacy of enzyme replacement therapy in an aggravated mouse model of metachromatic leukodystrophy declines with age, Hum. Mol. Genet. 21 (2012) 2599–2609.
[65] S. Appikatla, D. Bessert, I. Lee, M. Huttemann, C. Mullins, M. Somayajulu-Nitu, F. Yao, R.P. Skoff, Insertion of proteolipid protein into oligodendrocyte mitochondria regulates extracellular pH and adenosine triphosphate, Glia 62 (2014) 356–373.
[66] N. Uchida, K. Chen, M. Dohse, K.D. Hansen, J. Dean, J.R. Buser, A. Riddle, D.J. Beardsley, Y. Wan, X. Gong, T. Nguyen, B.J. Cummings, A.J. Anderson, S.J. Tamaki, A. Tsukamoto, I.L. Weissman, S.G. Matsumoto, L.S. Sherman, C.D. Kroenke, S.A. Back, Human neural stem cells induce functional myelination in mice with severe dysmyelination, Sci. Transl. Med. 4 (2012) 155ra136.
[67] A. Trepanier, L. Bennett, J. Garbern, Paper Presented at the American College of Medical Genetics, 2010 (Albuquerque, NM).
[68] N. Gupta, R.G. Henry, J. Strober, S.M. Kang, D.A. Lim, M. Bucci, E. Caverzasi, L. Gaetano, M.L. Mandelli, T. Ryan, R. Perry, J. Farrell, R.J. Jeremy, M. Ulman, S.L. Huhn, A.J. Barkovich, D.H. Rowitch, Neural stem cell engraftment and myelination in the human brain, Sci. Transl. Med. 4 (2012) (155ra137).
[69] N.E. Braverman, M.D. D'Agostino, G.E. Maclean, Peroxisome biogenesis disorders: biological, clinical and pathophysiological perspectives, Dev. Disabil. Res. Rev. 17 (2013) 187–196.
[70] N. Preuss, U. Brosius, M. Biermanns, A.C. Muntau, E. Conzelmann, J. Gartner, PEX1 mutations in complementation group 1 of Zellweger spectrum patients correlate with severity of disease, Pediatr. Res. 51 (2002) 706–714.
[71] C.S. Collins, S.J. Gould, Identification of a common PEX1 mutation in Zellweger syndrome, Hum. Mutat. 14 (1999) 45–53.
[72] C. Walter, J. Gootjes, P.A. Mooijer, H. Portsteffen, C. Klein, H.R. Waterham, P.G. Barth, J.T. Epplen, W.H. Kunau, R.J. Wanders, G. Dodt, Disorders of peroxisome biogenesis due to mutations in PEX1: phenotypes and PEX1 protein levels, Am. J. Hum. Genet. 69 (2001) 35–48.
[73] R. Zhang, L. Chen, S. Jiralerspong, A. Snowden, S. Steinberg, N. Braverman, Recovery of PEX1-Gly843Asp peroxisome dysfunction by small-molecule compounds, Proc. Natl. Acad. Sci. U. S. A. 107 (2010) 5569–5574.
[74] G. Bernard, A. Vanderver, Pol III-Related Leukodystrophies, in: R.A. Pagon, M.P. Adam, T.D. Bird, C.R. Dolan, C.T. Fong, K. Stephens (Eds.),GeneReviews, 1993 (Seattle (WA)).
[75] M.S. van der Knaap, J.C. Pronk, G.C. Scheper, Vanishing white matter disease, Lancet Neurol. 5 (2006) 413–423.
[76] G.V. Raymond, R. Seidman, T.S. Monteith, E. Kolodny, S. Sathe, A. Mahmood, J.M. Powers, Head trauma can initiate the onset of adreno-leukodystrophy, J. Neurol. Sci. 290 (2010) 70–74.
[77] S. Parikh, A. Goldstein, M.K. Koenig, F. Scaglia, G.M. Enns, R. Saneto, G. for the Mitochondrial Medicine Society Clinical Directors Working, G. Clinical Director's Work, Practice patterns of mitochondrial disease physicians in North America. Part 2: treatment, care and management, Mitochondrion 13 (6) (2013) 681–687.
[78] B.S. Acharya, P. Ritwik, G.M. Velasquez, S.J. Fenton, Medical–dental findings and management of a child with infantile Refsum disease: a case report, Spec. Care Dentist. 32 (2012) 112–117.
[79] J.L. Bonkowsky, C. Nelson, J.L. Kingston, F.M. Filloux, M.B. Mundorff, R. Srivastava, The burden of inherited leukodystrophies in children, Neurology 75 (2010) 718–725.
[80] P. Heim, M. Claussen, B. Hoffmann, E. Conzelmann, J. Gärtner, K. Harzer, D.H. Hunneman, W. Köhler, G. Kurlemann, A. Kohlschütter, Leukodystrophy incidence in Germany, Am. J. Med. Genet. 71 (1997) 475–478.
[81] A. Vanderver, H. Hussey, J.L. Schmidt, W. Pastor, H.J. Hoffman, Relative incidence of inherited white matter disorders in childhood to acquired pediatric demyelinating disorders, Semin. Pediatr. Neurol. 19 (2012) 219–223.