

INTERNATIONALE EMPFEHLUNGEN FÜR DIE DIAGNOSE UND BEHANDLUNG VON PATIENTEN MIT ADRENOLEUKODYSTROPHIEN

ENGELEN M ET AL., NEUROLOGY NOV 2022, 99 (21) 940-951; DOI:
10.1212/WNL.000000000201374

EUROPEAN REFERENCE NETWORKS
FOR RARE, LOW PREVALENCE AND COMPLEX DISEASES

Share. Care. Cure.



Haftungsausschluss:

"Die Unterstützung der Europäischen Kommission für die Erstellung dieser Veröffentlichung stellt keine Billigung des Inhalts dar, der ausschließlich die Meinung der Autoren wiedergibt, und die Kommission kann nicht für die Verwendung der darin enthaltenen Informationen verantwortlich gemacht werden."

Weitere Informationen über die Europäische Union finden Sie im Internet (<http://europa.eu>).

Luxemburg: Amt für Veröffentlichungen der Europäischen Union, 2019

© Europäische Union, 2019

Die Vervielfältigung ist unter Angabe der Quelle gestattet.

DAS EUROPÄISCHE REFERENZNETZ FÜR SELTENE NEUROLOGISCHE ERKRANKUNGEN (ERN-RND)

Das ERN-RND ist ein Europäisches Referenznetzwerk, das von der Europäischen Union eingerichtet wurde. ERN-RND ist ein Verbund der Krankenhäuser in der EU, die für die Versorgung von Menschen mit seltenen neurologischen Erkrankungen eine besondere Expertise besitzen. Ziel ist es eine verbesserte Versorgung von Patienten mit seltenen neurologischen Erkrankungen (rare neurological diseases - RND) zu erreichen. Die drei Säulen des ERN-RND sind: (I) Netzwerk bestehend aus Experten und Spezialzentren, (II) Entwicklung, Zusammenführung und Verbreitung von versorgungsrelevantem Wissen über seltene neurologische Erkrankungen, und (III) die Einrichtung und Nutzung von e-health Strukturen, die es ermöglichen, fallbezogenen Expertenwissen auszutauschen, ohne dass Patienten und Angehörige reisen müssen.

ERN-RND umfasst gegenwärtig 32 europäische Spezialzentren in 13 Mitgliedsstaaten, sowie mehrere, sehr aktive Patientenorganisationen. Die Spezialzentren befinden sich in Belgien, Bulgarien, Tschechien, Frankreich, Deutschland, Ungarn, Italien, Litauen, Niederlande, Polen, Slowenien, Spanien und Großbritannien.

ERN-RND deckt die folgenden Erkrankungsgruppen ab:

- Ataxien und hereditäre spastische Spinalparalysen (HSP)
- Atypische Parkinsonsyndrome und genetische Parkinsonerkrankungen
- Dystonien, Paroxysmale Erkrankungen und Neurodegeneration mit Eisenablagerungen im Gehirn (NBIA)
- Frontotemporale Demenz
- Huntington Erkrankung und andere Chorea
- Leukodystrophien

Mehr Informationen zum Netzwerk, den Spezialzentren und den oben genannten Erkrankungsgruppen finden Sie unter www.ern-rnd.eu.

Empfehlung für die klinische Anwendung:

Das Europäische Referenznetz für seltene neurologische Krankheiten hat diese Empfehlungen gebilligt
Leitlinien für X-ALD, um die Diagnose zu erleichtern. Das Referenznetzwerk empfiehlt die Anwendung der Leitlinien.

HAFTUNGSAUSSCHLUSS

Bei den klinischen Leitlinien, Praxisempfehlungen, systematischen Übersichtsarbeiten und anderen Leitlinien, die von ERN-RND veröffentlicht, befürwortet oder in ihrem Wert bestätigt werden, handelt es sich um die Bewertung aktueller wissenschaftlicher und klinischer Informationen, die als Bildungsangebot zur Verfügung gestellt werden.

Die Informationen (1) umfassen möglicherweise nicht alle geeigneten Behandlungen und Pflegemethoden und sollen nicht als Feststellung des Pflegestandards betrachtet werden; (2) werden nicht laufend aktualisiert und spiegeln möglicherweise nicht die neuesten Erkenntnisse wider (zwischen der Erstellung dieser Informationen und ihrer Veröffentlichung bzw. Lektüre können sich neue Informationen ergeben haben); (3) beziehen sich nur auf die spezifisch angegebenen Fragestellungen; (4) schreiben keine bestimmte medizinische Versorgung vor; (5) ersetzen nicht das unabhängige professionelle Urteil des behandelnden Arztes, da die Informationen keine individuellen Unterschiede zwischen den Patienten berücksichtigen. In jedem Fall sollte die gewählte Vorgehensweise vom

behandelnden Arzt individuell auf den jeweiligen Patienten abgestimmt werden. Die Nutzung der Informationen ist freiwillig. Die Informationen werden vom ERN-RND auf der Basis des Ist-Zustands zur Verfügung gestellt und ERN-RND übernimmt keine ausdrückliche oder stillschweigende Gewähr in Bezug auf die Informationen. ERN-RND lehnt ausdrücklich jegliche Gewähr der Gebrauchstauglichkeit und der Eignung für eine bestimmte Verwendung oder einen bestimmten Zweck ab. ERN-RND übernimmt keine Verantwortung für Personen- oder Sachschäden, die sich aus der Verwendung dieser Informationen ergeben oder damit im Zusammenhang stehen, noch für irgendwelche Fehler oder Unterlassungen.

METHODIK

Die Krankheitsgruppe für Leukodystrophien der ERN-RND hat das Übernahmeverfahren durchgeführt. Die Zustimmung zur Übernahme wurde von der gesamten Krankheitsgruppe am: 1. Februar 2023

Erkrankungsgruppe für Leukodystrophien:

Koordinatoren der Erkrankungsgruppe:

Caroline Sevin², Nicole Wolf²⁸

Mitglieder der Erkrankungsgruppe:

Experten des Gesundheitswesens:

Leonardo Ulivi¹; Nicola Giannini¹; Andrea Mignarri¹; Rosa Cortese¹; Antonio Federico¹; Odile Boespflug-Tanguy²; Giovanna De Michele³; Daniel Boesch⁴; Sylvia Boesch⁴; Pierre Kolber⁵; Kleopas Kleopa⁶; Anna Ardissonne⁸; Ettore Salsano⁸; Isabella Moroni⁸; Rachele Danti⁸; Dimitri Hemelsoet⁹; Bart Dermaut⁹; Hans Hartmann¹⁰; Mar O'Callaghan¹¹; Pedro Oliva Nacarino¹²; Ángel Martín¹³; Beata Błażejewska-Hyżorek¹⁴; Karolina Ziora-Jakutowicz¹⁴; Iwona Stępnia¹⁴; Mario Habek¹⁵; Fran Borovecki¹⁵; Thomas Klopstock¹⁶; Ales Tomek¹⁷; Johanna Uusimaa¹⁸; Arina Novasa¹⁹; Natalja Predkele¹⁹; Ieva Glazere¹⁹; Enrico Bertini²⁰; Francesco Nicita²⁰; Jørgen Erik Nielsen²¹; Lena Elisabeth Hjerminde²¹; Peter Balicza²²; Laszlo Szpisjak²³; Anneli Kolk²⁴; Klára Brožová²⁵; Ingeborg Krägeloh-Mann²⁶; Lucia Laugwitz²⁶; Ludger Schöls²⁶; Samuel Gröschel²⁶; Tom de Koning²⁷; Marjo S. van der Knaap²⁸; Marc Engelen²⁸; Wolfgang Koehler²⁹

Patientenvertreter:

Sara Hunt⁷

¹ AOU Pisana, Italien; ² Assistance Publique-Hôpitaux de Paris, Hôpital Robert-Debré, Frankreich: Referenzzentrum für Leukodystrophien; ³ Azienda Ospedaliera Universitaria Federico II Napoli, Italien; ⁴ Center for Rare Movement Disorders / Dpt. für Neurologie, Medizinische Universität Innsbruck; ⁵ Centre Hospitalier du Luxembourg; ⁶ Cyprus Foundation for Muscular Dystony Research; ⁷ ePAG; ⁸ Foundation IRCCS neurological institute Carlo Besta - Milan, Italy; ⁹ Ghent University Hospital; ¹⁰ Hannover Medical School; ¹¹ Hospital Clínic i Provincial de Barcelona y Hospital de Sant Joan de Déu, Spanien; ¹² Hospital Universitario Central de Asturias Oviedo; ¹³ Hospital Universitario La Paz Madrid; ¹⁴ Institut für Psychiatrie und Psychologie Warschau; ¹⁵ Klinički bolnišnica Zagreb; ¹⁶ Klinikum der Universität München, Deutschland; ¹⁷ Motol University Hospital, Tschechische Republik; ¹⁸ Oulu University Hospital; ¹⁹ Pauls Stradins Clinical University Hospital, Riga Lettland; ²⁰ Pediatric hospital Bambino Gesù, Rom, Italien; ²¹ Rigshospitalet Kopenhagen; ²² Semmelweis University, Ungarn; ²³ Szent-Györgyi Albert Medical School; ²⁴ Tartu University Hospital, Estland; ²⁵ Thomayer University Hospital Prague; ²⁶ Universitätsklinikum Tübingen, Deutschland; ²⁷ University Medical Center Groningen, Niederlande; ²⁸ VU University Medical Center Amsterdam, Niederlande; ²⁹ University of Leipzig Medical Center

REFERENZ

Internationale Empfehlungen für die Diagnose und Behandlung von Patienten mit Adrenoleukodystrophie - ein konsensbasierter Ansatz

Marc Engelen, Wouter J.C. van Ballegoij, Eric James Mallack, Keith P. Van Haren, Wolfgang Köhler, Ettore Salsano, A.S.P. van Trotsenburg, Fanny Mochel, Caroline Sevin, Molly O. Regelman, Nicholas A. Tritos, Alyssa Halper, Robin H. Lachmann, James Davison, Gerald V. Raymond, Troy C. Lund, Paul J. Orchard, Joern-Sven Kuehl, Caroline A. Lindemans, Paul Caruso, Bela Rui Turk, Ann B. Moser, Frédéric M. Vaz, Sacha Ferdinandusse, Stephan Kemp, Ali Fatemi, Florian S. Eichler, Irene C. Huffnagel

Neurologie Nov 2022, 99 (21) 940-951; DOI: 10.1212/WNL.0000000000201374

**INTERNATIONALE EMPFEHLUNGEN FÜR DIE DIAGNOSE UND
BEHANDLUNG VON PATIENTEN MIT ADRENOLEUKODYSTROPHIE 3 EIN
KONSENSORIENTIERTER ANSATZ**

International Recommendations for the Diagnosis and Management of Patients With Adrenoleukodystrophy

A Consensus-Based Approach

Marc Engelen, MD, PhD, Wouter J.C. van Ballegoij, MD, PhD, Eric James Mallack, MD, Keith P. Van Haren, MD, Wolfgang Köhler, MD, Ettore Salsano, MD, A.S.P. van Trotsenburg, MD, PhD, Fanny Mochel, MD, PhD, Caroline Sevin, MD, PhD, Molly O. Regelman, MD, Nicholas A. Tritos, MD, Alyssa Halper, MD, Robin H. Lachmann, PhD, James Davison, PhD, Gerald V. Raymond, MD, Troy C. Lund, MD, PhD, Paul J. Orchard, MD, Joern-Sven Kuehl, MD, Caroline A. Lindemans, MD, PhD, Paul Caruso, MD, Bela Rui Turk, MD, Ann B. Moser, BA, Frédéric M. Vaz, PhD, Sacha Ferdinandusse, PhD, Stephan Kemp, PhD, Ali Fatemi, MD, Florian S. Eichler, MD, and Irene C. Huffnagel, MD, PhD

Neurology® 2022;99:940-951. doi:10.1212/WNL.0000000000201374

Correspondence

Dr. Engelen
m.engelen@
amsterdamumc.nl

Abstract

Pathogenic variants in the *ABCD1* gene cause adrenoleukodystrophy (ALD), a progressive metabolic disorder characterized by 3 core clinical syndromes: a slowly progressive myelo-neuropathy, a rapidly progressive inflammatory leukodystrophy (cerebral ALD), and primary adrenal insufficiency. These syndromes are not present in all individuals and are not related to genotype. Cerebral ALD and adrenal insufficiency require early detection and intervention and warrant clinical surveillance because of variable penetrance and age at onset. Newborn screening has increased the number of presymptomatic individuals under observation, but clinical surveillance protocols vary. We used a consensus-based modified Delphi approach among 28 international ALD experts to develop best-practice recommendations for diagnosis, clinical surveillance, and treatment of patients with ALD. We identified 39 discrete areas of consensus. Regular monitoring to detect the onset of adrenal failure and conversion to cerebral ALD is recommended in all male patients. Hematopoietic cell transplant (HCT) is the treatment of choice for cerebral ALD. This guideline addresses a clinical need in the ALD community worldwide as the number of overall diagnoses and presymptomatic individuals is increasing because of newborn screening and greater availability of next-generation sequencing. The poor ability to predict the disease course informs current monitoring intervals but remains subject to change as more data emerge. This knowledge gap should direct future research and illustrates once again that international collaboration among physicians, researchers, and patients is essential to improving care.

RELATED ARTICLE

Editorial

Can We Generalize Key Principles in the Care of Rare Diseases? The Case for Adrenoleukodystrophy
Page 929

MORE ONLINE

CME Course
NPub.org/cmelist

From the Department of Pediatric Neurology/Emma Children's Hospital (M.E., W.J.C.B., I.C.H.), Amsterdam UMC, Amsterdam Leukodystrophy Center, University of Amsterdam, the Netherlands; Division of Child Neurology (E.J.M.), Department of Pediatrics, Weill Cornell Medicine/NewYork-Presbyterian Hospital, NY; Department of Neurology & Pediatrics/Lucile Packard Children's Hospital (K.P.V.H.), Stanford University School of Medicine, Palo Alto, CA 4. Department of Neurology, Leukodystrophy Clinic, University of Leipzig Medical Center, Germany; Unit of Rare Neurodegenerative and Neurometabolic Diseases (E.S.), Fondazione IRCCS Istituto Neurologico C. Besta, Milano, Italy; Department of Pediatric Endocrinology/Emma Children's Hospital (A.S.P.T.), Amsterdam UMC, University of Amsterdam, the Netherlands; AP-HP (F.M.), Department of Medical Genetics, Reference Center for Adult Neurometabolic Diseases and Leukodystrophies, and INSERM U 1127, CNRS UMR 7225, Paris Brain Institute, La Pitié-Salpêtrière University Hospital, Paris, France; Department of Pediatric Neurology/Hôpital Bicêtre Paris Sud (C.S.), France, Reference Center for Children Leukodystrophies Inserm U1127, ICM—Hôpital Pitié Salpêtrière, Paris, France; Division of Pediatric Endocrinology and Diabetes (M.O.R.), Children's Hospital at Montefiore, Albert Einstein College of Medicine of Medicine, Bronx, NY; Neuroendocrine Unit (N.A.T.), Massachusetts General Hospital, Boston, MA; Harvard Medical School (N.A.T.), Boston, MA; Division of Pediatric Endocrinology (A.H.), Department of Pediatrics, Massachusetts General Hospital, Boston, MA, and Harvard Medical School (A.H.), Boston, MA; Charles Dent Metabolic Unit (R.H.L.), National Hospital for Neurology and Neurosurgery, London, United Kingdom; Metabolic Medicine (J.D.), Great Ormond Street Hospital for Children, London United Kingdom; Department of Genetic Medicine (G.V.R.), Johns Hopkins, Baltimore, MD; Division of Pediatric Blood and Marrow Transplantation & Cellular Therapy (T.L., P.J.O.), University of Minnesota, Minneapolis; Pediatric Oncology (J.-S.K.), Hematology, Hemostaseology, University Hospital Leipzig, Germany; Pediatric Blood and Bone Marrow Transplantation (C.A.L.), Princess Maxima Center Utrecht, the Netherlands; Department of Pediatrics (C.A.L.), Wilhemina Children's Hospital, UMC Utrecht, Utrecht University, the Netherlands; Director of Pediatric Neuroimaging (P.C.), Lenox Hill Radiology and Medical Imaging Associates, New York, NY; Moser Center for Leukodystrophies (B.R.T., A.F.), Kennedy Krieger Institute, Johns Hopkins Medical Institutions, Baltimore, MD; Department of Neurogenetics (A.B.M.), Kennedy Krieger Institute, Baltimore, MD; Laboratory Genetic Metabolic Diseases (F.M.V., S.F., S.K.), Department of Clinical Chemistry and Pediatrics, Amsterdam UMC, Amsterdam Gastroenterology Endocrinology Metabolism, University of Amsterdam, the Netherlands; and Department of Neurology (F.S.E.), Massachusetts General Hospital, Boston, MA. Dr. van Ballegoij is currently at the Department of Neurology, Zaan Medisch Centrum, Zaandam.

Go to [Neurology.org/N](https://www.neurology.org/N) for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

The Article Processing Charge was funded by the UKB.

This is an open access article distributed under the terms of the Creative Commons Attribution License 4.0 (CC BY), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Glossary

ACTH = adrenocorticotropin hormone; **ALD** = adrenoleukodystrophy; **VUS** = variants of uncertain significance.

Adrenoleukodystrophy (ALD) has a variable and unpredictable clinical course.¹ It is caused by pathogenic variants in *ABCD1* causing deficient β -oxidation of saturated very-long-chain fatty acids (VLCFAs).²⁻⁴ VLCFAs in plasma are a diagnostic marker.^{5,6} Patients are asymptomatic at birth but develop symptoms as the disease progresses. There are 3 core clinical syndromes: a slowly progressive myeloneuropathy (adrenomyeloneuropathy), a rapidly progressive leukodystrophy (cerebral ALD), and primary adrenal insufficiency. Women develop myeloneuropathy; men can develop all 3 syndromes.⁷⁻⁹ Currently, it is not possible to predict the individual disease course.¹ Only supportive treatment is available for the myeloneuropathy, but early-stage cerebral ALD can be stabilized with allogeneic hematopoietic cell transplantation (HCT), and adrenal insufficiency can be treated with hormone replacement therapy. Clinical surveillance is required to monitor the emergence of treatable aspects of the disease.¹

ALD has a birth prevalence of 1:15,000 (male patients and female patients).¹⁰ The number of diagnosed patients is increasing because of newborn screening and exome sequencing in clinical practice. Management of patients with ALD varies between centers because of a lack of prospective natural history studies and controlled clinical trials. Clinical practice recommendations are needed to optimize outcomes. We aimed to reach consensus among international ALD experts on best approaches to diagnosis, clinical surveillance, and treatment of patients with ALD using a modified Delphi procedure.

Methods

Three centers of excellence for ALD (Amsterdam UMC, Massachusetts General Hospital, and Kennedy Krieger Institute) initiated this project. Based on their ALD-related expertise, 30 professionals ([pediatric] neurologists, endocrinologists, metabolic specialists, HCT experts, radiologists, and laboratory scientists) were invited. Experts were selected based on existing collaborations, recent publications, and attendance of relevant scientific meetings. ME, ICH, FSE, and AF formulated clinical questions on diagnosis, clinical surveillance, and treatment relevant to clinical care for patients with ALD. The questions were subsequently screened for omissions by all experts. Feedback from 3 patient advocacy groups (ALD Connect [USA], Alex TLC [UK], and “Volwassenen, Kinderen en Stofwisselingsziekten” [NL]) ensured that the clinical questions also addressed topics deemed relevant by patients. The advocacy groups provided comments in writing, and all suggestions on underrepresented topics were adopted.

We used an evidence-based and consensus-based modified Delphi approach to reach consensus among the experts.^{11,12}

First, a literature review (Figure 1) identified 132 relevant articles, which were mostly (small) retrospective and observational studies and thus insufficient for an isolated evidence-based approach.

The Delphi approach consisted of 2 questionnaire rounds and 1 consensus meeting. In the first questionnaire round, the experts rated their agreement with statements derived from the clinical questions based on a 9-point scale (1: “completely disagree” and 9: “completely agree”). Consensus was defined as follows: >80% of experts rated their “agreement” between 7 and 9 or “disagreement” between 1 and 3 (Figure 2). Statements where consensus was not reached were included in the second questionnaire round, and an anonymized overview of results derived from feedback of the first round was provided for each question alongside the experts own initial answer. Evidence tables from the literature review were provided. Experts were offered the opportunity to change their answer. The remaining statements were included in an online consensus meeting where consensus was sought by real-time discussion. The questionnaires, response numbers, and questions that did not reach consensus are listed in eAppendix 1 (links.lww.com/WNL/C362).

In this study, we summarize the recommendations that reached consensus. Twenty-eight of the 30 invited experts participated in the first questionnaire round, 26 in the second questionnaire round, and 20 in the consensus meeting. All 28 experts agreed to the final version of the recommendations. For statements concerning clinical surveillance or screening, screening was defined as clinical follow-up at predefined intervals to detect onset of symptoms or physical signs in patients who did not have any (self-reported) symptoms.

Standard Protocol Approvals, Registrations, and Patient Consents

This study is exempt from IRB approval because conclusions were reached with available data from the literature and expert opinion (Delphi procedure). No information on individual patients is included in this article.

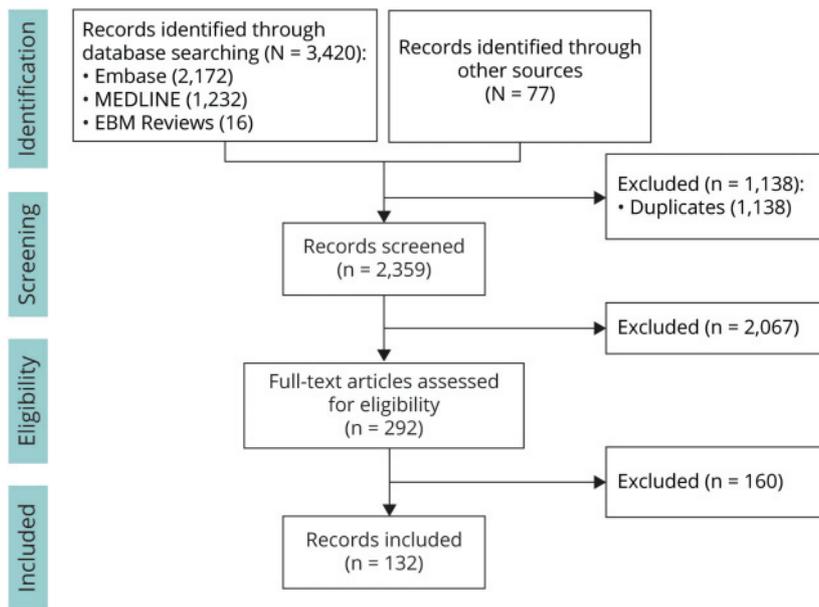
Role of the Funding Source

The health consultancy agency Adelphi Values was consulted with financial support of Bluebird Bio, SwanBio Therapeutics, and Minoryx. Adelphi Values assisted the authors with the literature search and data extraction and facilitated the consensus meeting. The financial sponsors had no influence on the content of the recommendations or this article.

Data Availability

All data on the Delphi procedure are available as supplementary data.

Figure 1 Literature Review Flowchart—Selection of Records



Results

Diagnosis

Presenting Symptoms

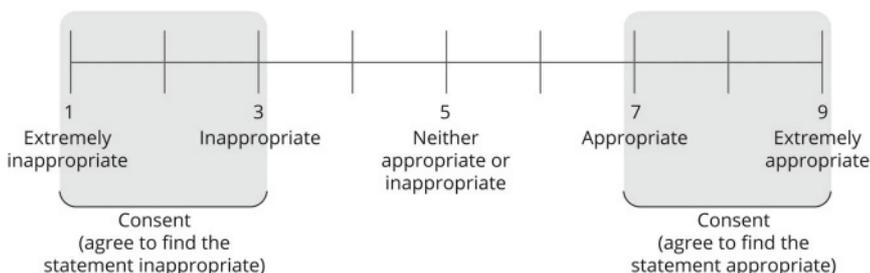
Recommendations

1. Cerebral ALD should be considered in boys and men with white matter abnormalities on brain MRI in a pattern suggestive of ALD with or without cognitive and neurologic symptoms.
2. ALD-related myelopathy should be considered in adult men and women with signs or symptoms of chronic myelopathy (gait disorder, spastic paraparesis, sphincter disturbances) with a normal MRI.
3. ALD-related adrenal insufficiency should be considered in boys and men with primary adrenal insufficiency with no detectable steroid-21-hydroxylase antibodies or other organ specific antibodies.

4. In all at-risk patients with a relative diagnosed with ALD, ALD should be considered.

Cognitive and neurologic symptoms which could indicate cerebral ALD include the new onset of attention problems, learning difficulties, onset of behavioral/mental health issues, impaired speech and vision, and progressive difficulty in walking and coordination. In boys and men with typical confluent white matter abnormalities on brain imaging—but no neurologic symptoms—cerebral ALD should still be considered as lesion development that may precede symptoms.¹³ Peripheral neuropathy is a common feature of ALD but is rarely the presenting symptom.^{7,14-16} In isolated peripheral neuropathy, other causes than ALD should be sought. Female patients with ALD remain asymptomatic in childhood and adolescence, while in adulthood, myeloneuropathy symptoms can arise.^{7,14} Cerebral ALD and primary adrenal insufficiency are extremely rare in women.

Figure 2 Scale Used to Define Consensus



Other causes of cerebral disease or adrenal insufficiency should be sought in female patients.¹⁷

Diagnostic Tests

A diagnostic algorithm is provided in Figure 3. Genetic testing (*ABCD1* analysis) is the gold standard. For biochemical testing, plasma C26:0-lysophosphatidylcholine (C26:0-lysoPC) has superior diagnostic performance.¹⁸ If unavailable, fasting plasma VLCFAs (C26:0; C26:0/C22:0; C24:0/C22:0) should be obtained.¹⁸⁻²¹ Diagnostic algorithms are sex-specific because VLCFA may be (near) normal in women. In women, the sensitivity of VLCFAs analysis is 85%, whereas C26:0-lysoPC has a sensitivity of >99%.^{18,19,22}

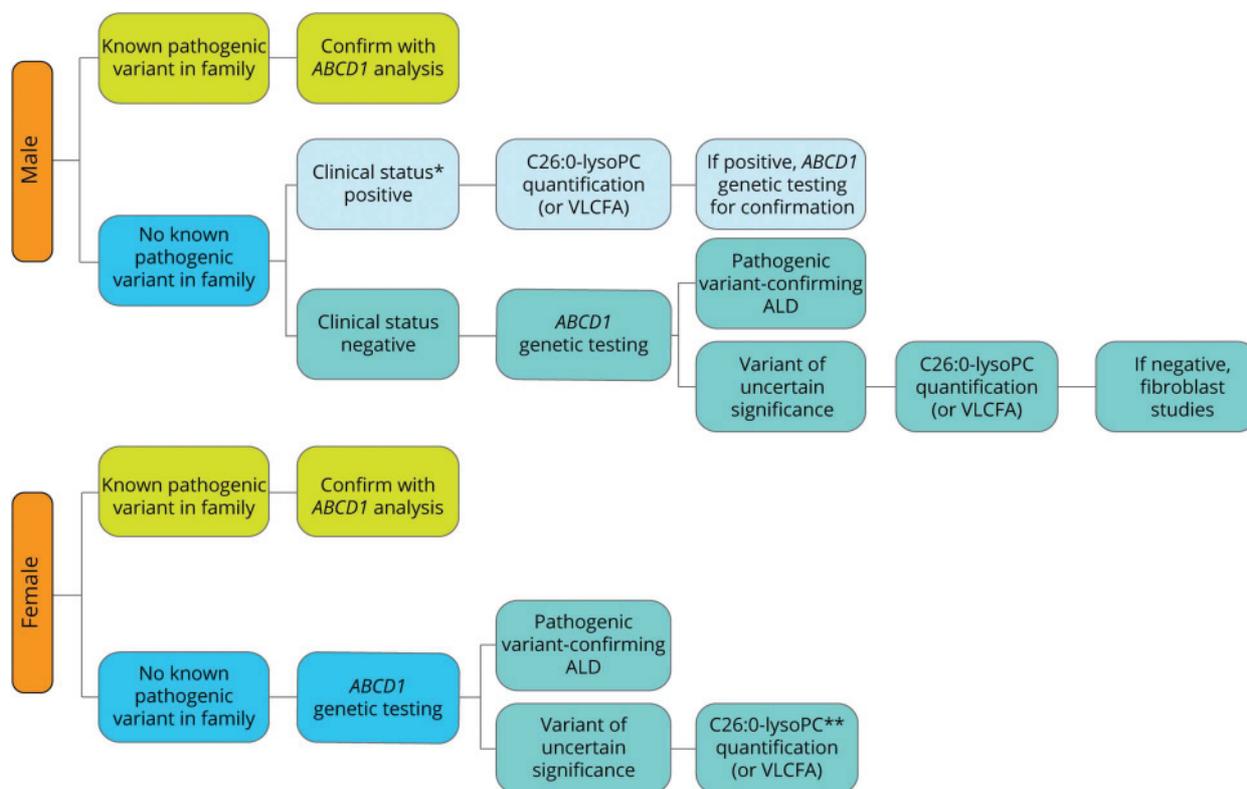
In symptomatic male patients with high suspicion for the diagnosis, biochemical testing should precede genetic testing. In asymptomatic male patients and all female patients, genetic testing is the first tier.

Detection of a known pathogenic *ABCD1* variant confirms the diagnosis of ALD in both men and women. De novo pathogenic variants and variants of uncertain significance (VUS) are common. It has been advocated that in patients in whom a previously unreported missense variant is

identified (a VUS), confirmation of a disease-causing pathogenic variant can only be established if a clinical phenotype develops or the genetic variant is proven pathogenic in another patient displaying symptoms. That is why only in boys, men, and symptomatic women with elevated biomarkers (C26:0-lysoPC or VLCFAs), a new variant in the *ABCD1* gene is considered (likely) pathogenic.²³

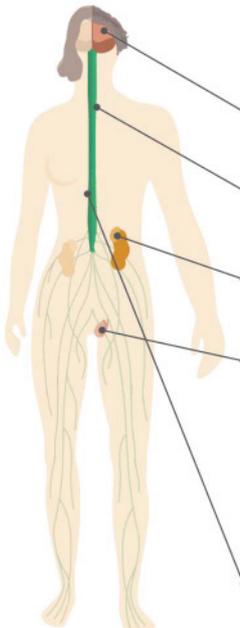
In vitro fibroblast studies are available to study the pathogenicity of a VUS in *ABCD1* and is especially recommended in asymptomatic boys and men and biomarker levels above the upper reference range of controls, but below the disease range (of the diagnostic laboratory). For women, fibroblast studies are less informative because of heterozygosity. In ambiguous cases, extended family screening may be considered although this can raise ethical questions related to testing of asymptomatic individuals. For newborn screening, positives with VUS or known benign variants in *ABCD1* and abnormal biochemistry, other peroxisomal biomarkers (i.e., plasmalogens, phytanic acid, pristanic acid, and bile acid intermediates) should be analyzed to exclude related diseases such as Zellweger spectrum disorder, *ACOX1* (or *HSD17B4*) deficiency, *CADD5*, *ACBDS* deficiency, and Aicardi-Goutières syndrome.²⁴

Figure 3 Diagnostic Algorithm



Ideally, biochemical and genetic testing are combined to establish diagnosis. *Male patients are stratified by clinical status. The clinical status of ALD is positive if any symptom or sign relatable to ALD is present. This can include cerebral ALD with symptoms, cerebral ALD based on MRI abnormalities only, myeloneuropathy, or adrenal insufficiency. If no symptoms or signs relatable to ALD are present, the clinical status is negative. **Sensitivity of C26:0-lysoPC is >99%, whereas it is 85% for VLCFA. Analyze C26:0-lysoPC in case of normal plasma VLCFA. ALD = adrenoleukodystrophy; VLCFA = very-long-chain fatty acid

Figure 4 Overview of the Management of Patients With ALD



Male	Screening or diagnostic tool	Screening protocol			Treatment
Cerebral ALD	MRI	2 years old, baseline scan	2–12 years old, every 6 months	>12 years old, yearly	HSCT or gene therapy
Myeloneuropathy	History and neurologic examination	>18 years old, only in parallel with any other testing			Supportive
Adrenal insufficiency	Morning fasted cortisol, ACTH, renin, electrolytes	0–6 months, start screening	6 months–10 years old, every 3–6 months	>10 years old, yearly	Hormone replacement therapy
Gonadal insufficiency	Symptoms biomarkers: Testosterone, LH, FSH	No screening test if symptoms			Hormone replacement therapy

Female	Screening or diagnostic tool	Screening protocol			Treatment
Myeloneuropathy	History and neurologic examination	>18 years old			Supportive

ALD = adrenoleukodystrophy

Treatment and Management

Multidisciplinary Team of Health Care Professionals

Recommendations

- A central coordinator should be assigned as the case manager.
- For male patients, a neurologist, endocrinologist, or metabolic specialist (adult or pediatric), a pediatrician, and a genetic counselor should be consulted. For female patients, this should be a neurologist, metabolic specialist, and genetic counselor.

The central coordinator may be a nurse or a (pediatric) neurologist, endocrinologist, or metabolic specialist depending on local practice and expertise. Urologists, HCT experts, rehabilitation physicians, physiotherapists, neuropsychologists, and mental health workers may be consulted. In very advanced cerebral ALD, nutritional support or speech therapy may be indicated.

An overview of the management of patients with ALD is provided in Figure 4.

Cerebral ALD

Diagnosis With MRI and the Use of Gadolinium and Sedation

Recommendations

- For the diagnosis of cerebral ALD, the minimum set of MR sequences is T1 (\pm gadolinium), T2, and FLAIR. Sedation should be used if necessary.
- Gadolinium is indicated when a new lesion or questionable lesion is identified.

- The interval between gadolinium administration and postcontrast T1-weighted image acquisition can influence study interpretation where shorter intervals can yield a false-negative result. Although the optimal timing is not known, based on our experience, we recommend an interval of at least 5 minutes.

Cerebral ALD causes severe disability and death.¹ The gold standard for the diagnosis of cerebral ALD is MRI. Gadolinium enhancement just behind the leading edge of the lesion indicates active disease.^{25–27} The extent of brain involvement on MRI can be quantified with the MR severity scoring system (Loes score), ranging from 0 (no abnormalities) to 34 (severely abnormal).²⁸ Recently published consensus guidelines on MRI surveillance in ALD recommend gadolinium administration for boys aged 3–12 years because the risk of developing cerebral ALD is deemed highest at this point.²⁹ However, new European Medicines Agency guidelines advocate restricted gadolinium use.³⁰ Therefore, our panel recommends to restrict gadolinium use to characterize newly identified or questionable lesions with 2 exceptions: (1) if sedation is required, to prevent the need for additional anesthesia exposure associated with a repeat scan, and (2) if real-time review of MR imaging is unavailable and the logistics of an additional hospital visit for gadolinium administration and repeat imaging are challenging.

Screening for Cerebral ALD

Recommendations

- All boys and men with ALD should be screened for cerebral ALD, including in the absence of neurologic or cognitive symptoms.

11. A baseline MRI scan should be obtained at age 2 years. Between 2 and 12 years, male patients should be screened every 6 months. From age 12 years, screening should be yearly.
12. We do not recommend routine screening for cerebral ALD in girls and women.

The screening protocol is presented in Figure 4. We do not recommend routine screening for cerebral disease in female patients.^{17,31,32} Irrespective of screening strategies, an MRI should be performed as soon as possible in all patients who develop potential signs or symptoms of cerebral ALD during follow-up.

The risk of developing cerebral disease is highest in childhood but remains present throughout life.^{1,29,33-39} The age for the baseline MRI was set at 2 years because cerebral ALD before the age of 3 years is rare, and MRI scans obtained before the age of 2 years are difficult to interpret because of incomplete myelination. Clinicians may choose to obtain an MRI at earlier time points based on clinical presentation and experience.¹⁰

For adult men, MRI surveillance should continue as long as HCT is a therapeutic option (maximum allowable age for HCT varies and was not subject to consensus here), although extended surveillance may be requested by individual patients for prognostic purposes. In patients with presumed arrested (non-progressive and nonenhancing) MRI abnormalities, imaging should initially be repeated after 3 months to confirm that lesions are nonenhancing and stable. If stable, the frequency can be expanded to 6 months and thereafter adhering to above-mentioned age-specific screening recommendations.^{13,25,39,40, e1} Scans may be repeated more frequently in individual ambiguous cases.

Alternative Methods for Screening and Diagnosis of Cerebral Disease

Recommendations

13. Nonimaging biomarkers for the diagnosis of cerebral ALD are not indicated outside of a research setting.
14. No consensus was reached on the implementation of neuropsychological testing as a screening tool for cerebral ALD.

Differentiating active from arrested white matter lesions can be challenging.^{13,25,39,40,e1} Several biomarkers (i.e., plasma neurofilament light, chitotriosidase and cytokine levels) have been studied for this purpose but require additional validation.^{e2-e5} Neuropsychological changes may precede MRI changes,^{e6,e7} and therefore, neuropsychological screening could be a useful tool to screen for cerebral ALD in parallel to MRI.

Cerebral ALD Treatment

Recommendations

15. Transplantation eligibility should be determined by an ALD transplantation expert.

16. Eligibility criteria are not exclusive. In general, boys are considered eligible for transplantation when they have demyelination with gadolinium enhancement (MR severity score [Loes score] ≤ 9) and a neurologic function score of 0 or 1 and adult men when they have demyelinating lesions with gadolinium enhancement and no or few neurocognitive impairment.
17. Genetically transduced autologous stem cell transplantation (gene therapy) should be considered (if available) in boys if allogeneic donor options are poor.

Allogeneic hematopoietic cell transplantation (HCT) is the standard treatment for cerebral ALD and can halt progression.^{34-36,38,e8-e13} Outcome is poor in advanced disease (Loes score >9 and/or neurologic function score >1).^{e14} In men, severe spinal cord disease (Expanded Disability Status Scale score >6) and bilateral internal capsule involvement are associated with poor survival.^{e15}

In boys, autologous hematopoietic stem cell transplantation after ex vivo lentiviral gene therapy has been studied as a safer alternative. Long-term safety data are not yet available.^{e15-e17} Currently, this therapy is not available for routine care. Treatment for boys or men with advanced disease or progressive lesions without gadolinium enhancement should only be considered after careful evaluation in experienced centers.

Non-Cerebral-Related Treatment Effects of Transplantation on Myeloneuropathy and Adrenal Insufficiency

HCT is unlikely to affect myeloneuropathy or adrenal insufficiency, but data are limited.^{e18,e19} For the very new ex vivo gene-corrected autologous transplantation approach, there are no data.

Lifestyle Management

Recommendation

18. Male patients should be counseled on the possible association between head injury and onset of cerebral disease so that they can make an informed lifestyle choice.

Severe head trauma has been reported as possible trigger for cerebral ALD.^{e20-e22} Definitive proof on causality is not available.

Myeloneuropathy

Screening for and follow-up of myeloneuropathy:

Recommendations

19. History and neurologic examination should be used to diagnose myeloneuropathy.
20. Asymptomatic men and women should only be screened for symptoms or physical signs of myeloneuropathy in parallel with other testing.

21. For men and women with myeloneuropathy, we recommend yearly follow-up. For men, coordinating annual visit with annual brain MRI may improve convenience and compliance.

Virtually all men and most women with ALD eventually develop symptoms and signs of myeloneuropathy.^{8,33,e23-e25} Extensive counseling on specific symptoms should be considered at the time of diagnosis of ALD. This helps prevent the incorrect attribution of unrelated symptoms to the ALD diagnosis and promotes early identification of ALD-related symptoms. Follow-up can also be used to update patients on developments in the field. Men and women presenting with new symptoms should be evaluated for myeloneuropathy. The use of standardized clinical tests and electrophysiologic testing remains restricted to research settings.^{7,14,16,17,31,e24,e26,e27}

Treatment of Myeloneuropathy

Recommendations

22. Treatment is supportive and should be aimed at reducing pain (with pharmaceuticals such as pregabalin or gabapentin) and spasticity (with spasmolytics like baclofen) and maintaining functional ability and quality of life.
23. In addition to routine neurologic care, referral to a rehabilitation specialist, continence care specialist, or pain management specialist/team may be considered.

No consensus was reached on recommendations for invasive spasticity treatments (i.e., intrathecal baclofen therapy, selective dorsal rhizotomy) or urinary incontinence.

Adrenal Insufficiency

Screening for Adrenal Insufficiency

Recommendations

24. All boys and men, but not girls and women, should be routinely screened for adrenal insufficiency with early morning cortisol and adrenocorticotropin hormone (ACTH) measurements.
25. Screening for adrenal insufficiency should be initiated in the first 6 months of life. Then, patients should be screened every 3–6 months before the age of 10 years and yearly thereafter. Screening should be performed parallel to MRI where possible.
26. All patients in whom symptoms suggestive of adrenal insufficiency manifest should undergo prompt evaluation for adrenal insufficiency to identify and prevent an adrenal crisis. If the patient is in crisis, a random cortisol and ACTH level measurement is sufficient (provided that serum specimens are drawn before glucocorticoid administration); if mildly symptomatic, early morning fasted cortisol and ACTH measurement is preferred.
27. All patients who are screened for adrenal insufficiency, or after diagnosis of adrenal insufficiency, should also be

screened for mineralocorticoid deficiency with plasma renin and serum electrolytes.

28. All patients in whom symptoms suggestive of mineralocorticoid deficiency manifest should undergo prompt evaluation with plasma renin and serum electrolytes.

Primary adrenal insufficiency is common in male patients with ALD, but rare in women.^{33,e28,e29} Screening in adult patients should continue irrespective of age because it is inexpensive, and early diagnosis offers a large potential health benefit.

Adrenal insufficiency is characterized by low or normal early morning cortisol levels with high levels of ACTH.^{1,33} For diagnosis, random cortisol and ACTH can be used when early morning measurement is not an option; however, when the results are ambiguous, patients should be retested with early morning fasted cortisol and ACTH. Synthetic ACTH stimulation testing can be restricted to ambiguous cases or when early morning fasted cortisol and ACTH are difficult to obtain. Besides glucocorticoid deficiency, some patients also develop mineralocorticoid deficiency (hypoadosteronism).^{33,e30,e31}

Treatment of Adrenal Insufficiency

Recommendations

29. If adrenal insufficiency is present, we recommend glucocorticoid replacement therapy by an endocrinologist.
30. Mineralocorticoid replacement therapy should not be initiated based on symptoms alone but should also take into account plasma renin and serum electrolyte abnormalities.
31. Routine evaluation of bone health with dual energy x-ray absorptiometry measurements in boys with adrenal insufficiency and glucocorticoid replacement therapy is not recommended.
32. No consensus was reached on the evaluation of bone health in men.

Patients with ambiguous results such as abnormal ACTH with normal or borderline cortisol values on stimulation testing should be managed per existing guidelines.^{e30,e31} Long-term glucocorticoid replacement therapy has been associated with impaired bone health.^{e32}

Gonadal Insufficiency

Screening for Gonadal Insufficiency

Recommendations

33. Boys and men should not be screened for gonadal insufficiency.
34. If symptoms manifest, gonadal insufficiency should be evaluated with biochemical testing (early morning testosterone, LH, FSH). In boys, delayed progression to puberty could indicate gonadal insufficiency (testicular volume <4 mL and/or no signs of puberty by the age of 14 years).

Abnormal hormone levels indicating gonadal insufficiency were described in boys and men with ALD.^{e33-e36} The clinical relevance of these findings remains unclear. For instance, erectile dysfunction may reflect primary gonadal insufficiency or can be caused by spinal cord disease.¹ Testing (gonadotrophins and testosterone measured in the early morning) is only recommended if there are symptoms.^{e34,e37}

Treatment of Gonadal Insufficiency

Recommendation

35. Treatment of gonadal insufficiency is restricted to endocrinologists.

Transdermal testosterone/long-acting testosterone ester injections can be used to treat gonadal insufficiency if levels are below normal and symptoms are present.

Dietary Therapy

Recommendation

36. Data to support the efficacy of Lorenzo's oil as a disease-modifying treatment in patients with ALD is insufficient.

Lorenzo's oil (oleic acid [C18:1] and erucic acid [C22:1]) in combination with a low-fat diet reduces plasma C26:0 levels to (near) normal values in most of the patients, but controlled clinical trials showing improved outcome are lacking.^{16,31-e38-e41}

Additional Management Recommendations

37. All patients who are diagnosed with ALD should be informed about the option of family screening.

38. Patients who wish to conceive must be informed regarding the potential benefits of preimplantation (preimplantation genetic diagnosis; oocyte donation) and prenatal (noninvasive fetal sex determination in maternal plasma; invasive prenatal testing) diagnostic options.

39. We recommend classifying female patients with an *ABCD1* pathogenic variant as "asymptomatic/presymptomatic" or "symptomatic women with ALD" and to refrain from using terms as heterozygotes or carriers.

Discussion

We provide recommendations on diagnosis, clinical surveillance, and treatment of ALD. Our consensus-based approach among ALD experts across the world allowed us to formulate recommendations despite limited scientific evidence. Still, on some topics, consensus could not be reached (for instance, the exact timing of adrenal testing in the first year of life). Furthermore, this approach is at risk for bias because of panelist selection and repeat review. We aimed to include all relevant specialists with experience in the field of ALD, but this group is small, and the clinical experience of panelists varied from smaller regional to larger international cohorts

with more than 100 patients. Experts were instructed to withhold from voting on recommendations outside their field of expertise, but no additional correction was applied for differences in clinical experience. Moreover, consensus was defined as >80% agreement. Therefore, some panelists did not agree with specific recommendations although consensus was reached. The screening protocol for cerebral ALD and lifestyle management are examples of topics that remain subject of discussion. Nonetheless, this guideline addresses a need in the ALD community because of the worldwide increase in diagnoses and the number of presymptomatic individuals because of newborn screening and improved diagnostic procedures. Moreover, we highlight knowledge gaps that can direct future research and illustrates that international collaboration among physicians, researchers, and patients is essential to improve care.

Panel 1: Search Strategy and Selection Criteria

We searched Embase, MEDLINE, and Evidence-Based Medicine Reviews for relevant publications on diagnosis, clinical surveillance, and treatment of patients with ALD. No medical librarian was involved. The search was limited to full-text availability in English and a publication date between 1990 to the year 2019. The search terms used were "adrenoleukodystrophy" or "x-linked adrenoleukodystrophy" or "X-ALD." For the syntax of the search, refer to page 9 of the literature review report provided as supplementary data (eMethods, links.lww.com/WNL/C364). In addition, we conducted a gray literature search of internet-based sources and extended the search with snowballing. The gray literature search included GeneReviews, UpToDate, ClinicalKey, The International Leukodystrophy Association (or Global Leukodystrophy Initiative), ALD.info, and the Society for the Study of Inborn Errors of Metabolism. To provide up to date published data that were not captured in full-text publications, we also included recent conference proceedings and summits, that is, the ALD Connect annual meeting, the European Pediatric Neurology Society meeting, the American Society of Gene and Cell Therapy annual meeting, the United Leukodystrophy Foundation conference, and the American Academy of Neurology annual meeting. All articles on ALD involving human participants were included, and nonhuman (animal) studies were excluded. Detailed inclusion and exclusion criteria can be found in the literature review report (eMethods, links.lww.com/WNL/C364). Two reviewers of Adelphi Values (A.V.) independently screened all abstracts and where applicable concomitant full text for their eligibility. After completion, the results were reviewed and compared by a third senior reviewer (A.V.), to resolve discrepancies and reach consensus on inclusion in the literature review. The results of this consensus process and the results of the data extraction are summarized in the data extraction form that is available as eAppendix 2 (links.lww.com/WNL/C363). The study quality was assessed using the Newcastle-Ottawa Scale for Assessing the Quality of Nonrandomized Studies in Meta-analysis, and the results are available as eTable 1 (links.lww.com/WNL/C366).

Panel 2: Summary of Recommendations

Presenting Symptoms—When to Consider ALD

1. In boys and men with confluent white matter abnormalities on brain MRI in a pattern suggestive of ALD with or without cognitive and neurologic symptoms;
2. In adult men and women with symptoms and signs of chronic myelopathy with a normal MRI;
3. In boys and men with primary adrenal insufficiency with no detectable steroid-21-hydroxylase antibodies or other organ specific antibodies;
4. In all at-risk patients with a relative diagnosed with ALD.

Diagnostic Tests

A diagnostic algorithm is provided in Figure 3.

Screening, Diagnosis, and Treatment of Cerebral ALD

7-12. Screen all boys and men for cerebral ALD with MRI, including in the absence of neurologic or cognitive symptoms. Screening frequency is discussed in Figure 4. Gadolinium is indicated when a new lesion or questionable lesion is identified, or sedation is used.

15-17. To treat cerebral ALD, consult an ALD transplantation expert who can determine allogeneic or genetically transduced autologous stem cell transplantation eligibility.

Screening, Diagnosis, and Treatment of Myeloneuropathy

19. Use history and neurologic examination to diagnose myeloneuropathy.
20. Solely screen apparently asymptomatic men for symptoms or physical signs of myeloneuropathy in parallel to any other testing.
21. Schedule yearly follow-up for men and women with myeloneuropathy
22. Treatment is supportive. Aim treatment at reducing pain and spasticity and maintaining functional ability and quality of life.

Screening, Diagnosis, and Treatment of Adrenal Insufficiency

24-28. Screen all boys and men for adrenal insufficiency with early morning cortisol, ACTH, plasma renin, and serum electrolytes. If symptoms suggestive of adrenal insufficiency manifest, evaluate adrenal insufficiency promptly to prevent an adrenal crisis.

29-30. Consult a (pediatric) endocrinologist for glucocorticoid replacement therapy when adrenal insufficiency is present. Do not initiate mineralocorticoid replacement therapy based on symptoms alone but also take into account plasma renin and serum electrolyte abnormalities.

Dietary Therapy

36. Data to support the efficacy of Lorenzo's oil as a disease-modifying treatment in patients with ALD are insufficient.

Acknowledgment

We thank Richard Perry, Daisy Bridge, Laila Bankousli, and Ben Rousseau (all from Adelphi Values) for their valuable contributions, including the literature search and moderating the expert meetings.

Study Funding

Research grant from Blue Bird Bio, SwanBio Therapeutics, Minoryx.

Disclosure

M. Engelen has received research support from Minoryx, Autobahn Therapeutics, BlueBirdBio and SwanBio; consultation fees from Minoryx, BlueBirdBio, Autobahn Therapeutics and Poxel. W.J.C. van Ballegoij: has received funding from Minoryx Therapeutics. E. Mallack: has received funding from the NIH for ALD-related work (K12NS066274, K23NS118044), and has received grant support from Bluebird Bio and Orchard Therapeutics for leukodystrophy education and awareness. K. van Haren: consulting fees from Autobahn, Bluebird Bio, Minoryx, Orpheris, Poxel, and Viking Therapeutics. Research support from Bluebird Bio and Minoryx. W. Köhler: has received funding for ALD-related work from Bluebird Bio, MedDay, Minoryx, SwanBio and European Leukodystrophy Association. Non-ALD-related honoraria and consultation fees from Alexion, Celgene, Grifols, Novartis, Roche, Vigil and Dresden International University. All are unrelated to the present manuscript. A.S.P. van Trotsenburg: honoraria from Ferring, Merck and Pfizer. F. Mochel: consultancy fees from Minoryx. C. Sevin: received consultancies and/or honoraria from Bluebird Bio, Orchard Therapeutics and Takeda M.O. Regelmann: consultant for Bluebird Bio and has received compensation to speak on their behalf regarding ALD awareness. N.A. Tritos: recipient of institution-directed research support from Ipsen and Novartis and occasional consulting fees from Novo Nordisk and Sandoz (all for work unrelated to the content of this manuscript) A. Halper: consultant for Eton Pharmaceuticals. R. Lachmann: consultant for Sanofi, Biomarin, Takeda, Amicus, Nestle Health Sciences and Arcturus. Has received travel expenses to attend investigator meetings from Minoryx Therapeutics. All are unrelated to the present manuscript. J. Davison: has undertaken advisory board/consultancy work for Bluebird Bio*, Orchard Therapeutics, Sanofi Genzyme, Biomarin, Recordati RRD, Chiesi. He is a medical advisor (unpaid) to Alex TLC*. He has received honoraria for educational activities from Recordati RRD and FYMCA Medical Ltd. (* Interest directly related to X-ALD). G.V. Raymond: consultant for Minoryx, Bluebird Bio, and Viking. Serves on DSMBs for Ionis and Retrophin. T. Lund: is a primary investigator on the Bluebird Bio trial and paid consultant for Swan Bio. P. Orchard: Clinical trial support from bluebird bio, Immusoft. Honoraria from Orchard Therapeutics, Sanofi Genzyme, Avrobio, Rocket Pharmaceuticals J.S. Köhl: Honoraria from bluebird bio, JAZZ and Sobi. Travel grants from Neovii. C.A. Lindemans: consultancy expert advisory boards: Bluebird Bio, Orchard therapeutics, Sobi, ExCellThera Inc P. Caruso: no conflict of interest. B. Turk: Coinventor of Compositions and Methods for Treatment of Peroxisomal Disorders and Leukodystrophies, US Patent Provisional

Application No. 62/248,163, Int. Application Nr. PCT/US2016/059,697 A.B. Moser: no conflict of interest. F.M. Vaz: no conflict of interest. S. Ferdinandusse: no conflict of interest. S. Kemp: reports serving as consultant to Poxel Pharma and SwanBio Therapeutics and receives unrestricted research grants from SwanBio Therapeutics. A. Fatemi: has Institutional Research contracts with Minoryx, Viking Therapeutics, Autobahn Therapeutics, Poxel, SwanBio Therapeutics. Served as a member of Bluebirdbio DSMB. Is convector on a patent licensed to Ashvattha Therapeutics. F. Eichler: reports serving as consultant to AutoBahn Therapeutics, Bluebird Bio, Ionis Pharmaceuticals, Minoryx, Poxel Pharma, Takeda Therapeutics, Taysha Gene Therapies and SwanBio Therapeutics I.C. Huffnagel: consulting fees from Minoryx Therapeutics and Vertex. Go to [Neurology.org/N](https://www.neurology.org/N) for full disclosures.

Publication History

Received by *Neurology* February 3, 2022. Accepted in final form August 23, 2022. Submitted and externally peer reviewed. The handling editor was Renee Shellhaas, MD, MS.

Appendix Authors

Name	Location	Contribution
Marc Engelen, MD, PhD	Department of Pediatric Neurology/Emma Children's Hospital, Amsterdam UMC, Amsterdam Leukodystrophy Center, University of Amsterdam, Amsterdam, the Netherlands	Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data
Wouter J.C. van Ballegoij, MD, PhD	Department of Pediatric Neurology/Emma Children's Hospital, Amsterdam UMC, Amsterdam Leukodystrophy Center, University of Amsterdam, Amsterdam, the Netherlands	Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data
Eric James Mallack, MD	Division of Child Neurology, Department of Pediatrics, Weill Cornell Medicine/NewYork-Presbyterian Hospital, New York City, NY	Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data
Keith P. Van Haren, MD	Department of Neurology & Pediatrics/Lucile Packard Children's Hospital, Stanford University School of Medicine, Palo Alto, CA	Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data
Wolfgang Köhler, MD	Department of Neurology, Leukodystrophy Clinic, University of Leipzig Medical Center, Leipzig, Germany	Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data
Ettore Salsano, MD	Unit of Rare Neurodegenerative and Neurometabolic Diseases, Fondazione IRCCS Istituto Neurologico C. Besta, Milano, Italy	Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data

Appendix (continued)

Name	Location	Contribution
A.S.P. van Trotsenburg, MD, PhD	Department of Pediatric Endocrinology/Emma Children's Hospital, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands	Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data
Fanny Mochel, MD, PhD	AP-HP, Department of Medical Genetics, Reference Center for Adult Neurometabolic Diseases and Leukodystrophies; and INSERM U 1127, CNRS UMR 7225, Paris Brain Institute, La Pitié-Salpêtrière University Hospital, Paris, France	Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data
Caroline Sevin, MD	Department of pediatric neurology/Hôpital Bicêtre Paris Sud, France, Reference Center for Children Leukodystrophies Inserm U1127, ICM - Hôpital Pitié Salpêtrière, Paris, France	Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data
Molly O. Regelman, MD	Division of Pediatric Endocrinology and Diabetes, Children's Hospital at Montefiore, Albert Einstein School of Medicine, Bronx, NY	Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data
Nicholas A. Tritos, MD	Neuroendocrine Unit, Massachusetts General Hospital, Boston, MA; and Harvard Medical School, Boston, MA	Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data
Alyssa Halper, MD	Division of Pediatric Endocrinology, Department of Pediatrics, Massachusetts General Hospital, Boston, and Harvard Medical School, Boston, MA	Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data
Robin H. Lachmann, PhD	Charles Dent Metabolic Unit, National Hospital for Neurology and Neurosurgery, London, United Kingdom	Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data
James Davison, PhD	Metabolic Medicine, Great Ormond Street Hospital for Children, London United Kingdom	Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data
Gerald V. Raymond, MD	Department of Genetic Medicine, Johns Hopkins, Baltimore, MD	Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data
Troy Lund, MD, PhD	Division of Pediatric Blood and Marrow Transplantation & Cellular Therapy, University of Minnesota, Minneapolis, MN	Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data

Continued

Appendix (continued)

Name	Location	Contribution
Paul J. Orchard, MD	Division of Pediatric Blood and Marrow Transplantation & Cellular Therapy, University of Minnesota, Minneapolis, MN	Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data
Joern-Sven Kuehl, MD	Pediatric Oncology, Hematology, Hemostaseology, University Hospital Leipzig, Leipzig, Germany	Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data
Caroline A. Lindemans, MD, PhD	Pediatric Blood and bone marrow Transplantation, Princess Maxima Center Utrecht, the Netherlands; and Department of Pediatrics, Wilhemina Children's hospital, UMC Utrecht, Utrecht University, Utrecht, the Netherlands	Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data
Paul Caruso, MD	Director of Pediatric Neuroimaging, Lenox Hill Radiology and Medical Imaging Associates, New York, NY	Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data
Bela Rui Turk, MD	Moser Center for Leukodystrophies, Kennedy Krieger Institute, Johns Hopkins Medical Institutions, Baltimore, MD	Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data
Ann B. Moser, BA	Department of Neurogenetics, Kennedy Krieger Institute, Baltimore, MD	Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data
Frederic M Vaz, PhD	Laboratory Genetic Metabolic Diseases, Department of Clinical Chemistry and Pediatrics, Amsterdam UMC, Amsterdam Gastroenterology Endocrinology Metabolism, University of Amsterdam, Amsterdam, the Netherlands	Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data
Sacha Ferdinandusse, PhD	Laboratory Genetic Metabolic Diseases, Department of Clinical Chemistry and Pediatrics, Amsterdam UMC, Amsterdam Gastroenterology Endocrinology Metabolism, University of Amsterdam, Amsterdam, the Netherlands	Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data
Stephan Kemp, PhD	Laboratory Genetic Metabolic Diseases, Department of Clinical Chemistry and Pediatrics, Amsterdam UMC, Amsterdam Gastroenterology Endocrinology Metabolism, University of Amsterdam, Amsterdam, the Netherlands	Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data

Appendix (continued)

Name	Location	Contribution
Ali Fatemi, MD	Moser Center for Leukodystrophies, Kennedy Krieger Institute, Johns Hopkins Medical Institutions, Baltimore, MD	Drafting/revision of the manuscript for content, including medical writing for content; Study concept or design; Analysis or interpretation of data
Florian S. Eichler, MD	Department of Neurology, Massachusetts General Hospital, Boston	Drafting/revision of the manuscript for content, including medical writing for content; Study concept or design; Analysis or interpretation of data
Irene C. Huffnagel, MD, PhD	Department of Pediatric Neurology/Emma Children's Hospital, Amsterdam UMC, Amsterdam Leukodystrophy Center, University of Amsterdam, Amsterdam, the Netherlands	Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data

References

- Kemp S, Huffnagel IC, Linthorst GE, Wanders RJ, Engelen M. Adrenoleukodystrophy - neuroendocrine pathogenesis and redefinition of natural history. *Nat Rev Endocrinol.* 2016;12(10):606-615.
- Mosser J, Douar AM, Sarde CO, et al. Putative X-linked adrenoleukodystrophy gene shares unexpected homology with ABC transporters. *Nature.* 1993;361(6414):726-730.
- Singh I, Moser AE, Moser HW, Kishimoto Y. Adrenoleukodystrophy: impaired oxidation of very long chain fatty acids in white blood cells, cultured skin fibroblasts, and amniocytes. *Pediatr Res.* 1984;18(3):286-290.
- Wanders RJ, van Roermund CW, van Wijland MJ, et al. Peroxisomal very long-chain fatty acid beta-oxidation in human skin fibroblasts: activity in Zellweger syndrome and other peroxisomal disorders. *Clin Chim Acta.* 1987;166(2-3):255-263.
- Moser HW, Moser AB, Frayer KK, et al. Adrenoleukodystrophy: increased plasma content of saturated very long chain fatty acids. *Neurology.* 1981;31(10):1241-1249.
- Igarashi M, Schaumburg HH, Powers J, Kishimoto Y, Kolodny E, Suzuki K. Fatty acid abnormality in adrenoleukodystrophy. *J Neurochem.* 1976;26(4):851-860.
- Engelen M, Barbier M, Dijkstra IM, et al. X-linked adrenoleukodystrophy in women: a cross-sectional cohort study. *Brain.* 2014;137(Pt 3):693-706.
- Huffnagel IC, Dijkgraaf MGW, Janssens GE, et al. Disease progression in women with X-linked adrenoleukodystrophy is slow. *Orphanet J Rare Dis.* 2019;14(1):30.
- Habekost CT, Schestatsky P, Torres VF, et al. Neurological impairment among heterozygote women for X-linked Adrenoleukodystrophy: a case control study on a clinical, neurophysiological and biochemical characteristics. *Orphanet J Rare Dis.* 2014;9:6.
- Moser A, Jones RO, Hubbard WC, et al. Newborn screening for X-linked adrenoleukodystrophy. *Int J Neonatal Screen.* 2016;2(4):1-5.
- Powell C. The Delphi technique: myths and realities. *J Adv Nurs.* 2003;41(4):376-382.
- Fink A, Kosecoff J, Chassin M, Brook RH. Consensus methods - characteristics and guidelines for use. *Am J Public Health.* 1984;74(9):979-983.
- Moser HW, Loes DJ, Melhem ER, et al. X-Linked adrenoleukodystrophy: overview and prognosis as a function of age and brain magnetic resonance imaging abnormality. A study involving 372 patients. *Neuropediatrics.* 2000;31(5):227-239.
- Horn MA, Nilsen KB, Jorum E, Mellgren SI, Tallaksen CM. Small nerve fiber involvement is frequent in X-linked adrenoleukodystrophy. *Neurology.* 2014;82(19):1678-1683.
- Rattay TW, Just J, Roben B, et al. Nerve ultrasound characterizes AMN polyneuropathy as inhomogeneous and focal hypertrophic. *Orphanet J Rare Dis.* 2018;13(1):194.
- van Geel BM, Assies J, Haverkort EB, et al. Progression of abnormalities in adrenomyeloneuropathy and neurologically asymptomatic X-linked adrenoleukodystrophy despite treatment with "Lorenzo's oil". *J Neurol Neurosurg Psychiatry.* 1999;67(3):290-299.
- Schmidt S, Traber F, Block W, et al. Phenotype assignment in symptomatic female carriers of X-linked adrenoleukodystrophy. *J Neurol.* 2001;248(1):36-44.
- Jaspers YRJ, Ferdinandusse S, Dijkstra IME, et al. Comparison of the diagnostic performance of C26:0-lysophosphatidylcholine and very long-chain fatty acids analysis for peroxisomal disorders. *Front Cell Dev Biol.* 2020;8:690.

19. Huffnagel IC, van de Beek MC, Showers AL, et al. Comparison of C26:0-carnitine and C26:0-lysophosphatidylcholine as diagnostic markers in dried blood spots from newborns and patients with adrenoleukodystrophy. *Mol Genet Metab.* 2017;122(4):209-215.
20. Sandlers Y, Moser AB, Hubbard WC, Kratz LE, Jones RO, Raymond GV. Combined extraction of acyl carnitines and 26:0 lysophosphatidylcholine from dried blood spots: prospective newborn screening for X-linked adrenoleukodystrophy. *Mol Genet Metab.* 2012;105(3):416-420.
21. Lee S, Clinard K, Young SP, et al. Evaluation of X-linked adrenoleukodystrophy newborn screening in North Carolina. *JAMA Netw Open.* 2020;3(1):e1920356.
22. Moser AB, Kreiter N, Bezman L, et al. Plasma very long chain fatty acids in 3,000 peroxisome disease patients and 29,000 controls. *Ann Neurol.* 1999;45(1):100-110.
23. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med.* 2015;17(5):405-424.
24. Barendsen RW, Dijkstra IME, Visser WF, et al. Adrenoleukodystrophy newborn screening in The Netherlands (SCAN study): the X-factor. *Front Cell Dev Biol.* 2020;8:499.
25. Melhem ER, Loes DJ, Georgiades CS, Raymond GV, Moser HW. X-linked adrenoleukodystrophy: the role of contrast-enhanced MR imaging in predicting disease progression. *AJNR Am J Neuroradiol.* 2000;21(5):839-844.
26. Van der Knaap MSV, *J. Resonance of Myelination and Myelin Disorders.* In: Heilmann U, ed.: Springer;2005:176-190.
27. Powers JM, Liu Y, Moser AB, Moser HW. The inflammatory myelinopathy of adrenoleukodystrophy: cells, effector molecules, and pathogenetic implications. *J Neuropathol Exp Neurol.* 1992;51(6):630-643.
28. Loes DJ, Hite S, Moser H, et al. Adrenoleukodystrophy: a scoring method for brain MR observations. *AJNR Am J Neuroradiol.* 1994;15(9):1761-1766.
29. Mallack EJ, Turk BR, Yan H, et al. MRI surveillance of boys with X-linked adrenoleukodystrophy identified by newborn screening: Meta-analysis and consensus guidelines. *J Inher Metab Dis.* 2021;44(3):728-739.
30. Agency EM. *EMA's Final Opinion Confirms Restrictions on Use of Linear Gadolinium Agents in Body Scans Recommendations Conclude EMA's Scientific Review of Gadolinium Deposition in Brain and Other Tissues;*2017.
31. Aubourg P, Adamsbaum C, Lavallard-Rousseau MC, et al. A two-year trial of oleic and erucic acids ("Lorenzo's oil") as treatment for adrenomyeloneuropathy. *N Engl J Med.* 1993;329(11):745-752.
32. Fatemi A, Barker PB, Ulug AM, et al. MRI and proton MRSI in women heterozygous for X-linked adrenoleukodystrophy. *Neurology.* 2003;60(8):1301-1307.
33. Huffnagel IC, Laheji FK, Aziz-Bose R, et al. The natural history of adrenal insufficiency in X-linked adrenoleukodystrophy: an international collaboration. *J Clin Endocrinol Metab.* 2019;104(1):118-126.
34. Baumann M, Korenke GC, Weddige-Diedrichs A, et al. Haematopoietic stem cell transplantation in 12 patients with cerebral X-linked adrenoleukodystrophy. *Eur J Pediatr.* 2003;162(1):6-14.
35. Kuhl JS, Suarez F, Gillett GT, et al. Long-term outcomes of allogeneic haematopoietic stem cell transplantation for adult cerebral X-linked adrenoleukodystrophy. *Brain.* 2017;140(4):953-966.
36. Mahmood A, Raymond GV, Dubey P, Peters C, Moser HW. Survival analysis of haematopoietic cell transplantation for childhood cerebral X-linked adrenoleukodystrophy: a comparison study. *Lancet Neurol.* 2007;6(8):687-692.
37. Vargas CR, Coelho DD, Barschak AG, et al. X-linked adrenoleukodystrophy: clinical and laboratory findings in 15 Brazilian patients. *Genet Mol Biol.* 2000;23(2):261-264.
38. Raymond GV, Aubourg P, Paker A, et al. Survival and functional outcomes in boys with cerebral adrenoleukodystrophy with and without hematopoietic stem cell transplantation. *Biol Blood Marrow Transpl.* 2019;25(3):538-548.
39. Liberato AP, Mallack EJ, Aziz-Bose R, et al. MRI brain lesions in asymptomatic boys with X-linked adrenoleukodystrophy. *Neurology.* 2019;92(15):e1698-e708.
40. Mallack EJ, van de Stadt S, Caruso PA, et al. Clinical and radiographic course of arrested cerebral adrenoleukodystrophy. *Neurology.* 2020;94(24):e2499-e507.
41. Access eReferences here: links.lww.com/WNL/C365

Neurology® Online CME Program

Earn CME while reading *Neurology*. This program is available to AAN members and to online *Neurology* subscribers. Read the articles marked CME, go to [Neurology.org](https://www.neurology.org), and click on the CME link. The American Academy of Neurology (AAN) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to sponsor continuing medical education for physicians. *Neurology* is planned and produced in accordance with the ACCME Essentials. For more information, contact AAN Member Services at 800-879-1960.

Share Your Artistic Expressions in *Neurology* 'Visions'

AAN members are urged to submit medically or scientifically related artistic images, such as photographs, photomicrographs, and paintings, to the "Visions" section of *Neurology*®. These images are creative in nature, rather than the medically instructive images published in the NeuroImages section. The image or series of up to six images may be black and white or color and must fit into one published journal page. Accompanying description should be 100 words or less; the title should be a maximum of 140 characters including spaces and punctuation.

Please access the Author Center at [NPub.org/authors](https://www.npub.org/authors) for full submission information.

Neurology®

International Recommendations for the Diagnosis and Management of Patients With Adrenoleukodystrophy: A Consensus-Based Approach

Marc Engelen, Wouter J.C. van Ballegoij, Eric James Mallack, et al.

Neurology 2022;99:940-951 Published Online before print September 29, 2022

DOI 10.1212/WNL.0000000000201374

This information is current as of September 29, 2022

Updated Information & Services	including high resolution figures, can be found at: http://n.neurology.org/content/99/21/940.full
References	This article cites 38 articles, 8 of which you can access for free at: http://n.neurology.org/content/99/21/940.full#ref-list-1
Citations	This article has been cited by 1 HighWire-hosted articles: http://n.neurology.org/content/99/21/940.full##otherarticles
Subspecialty Collections	This article, along with others on similar topics, appears in the following collection(s): All Clinical Neurology http://n.neurology.org/cgi/collection/all_clinical_neurology Leukodystrophies http://n.neurology.org/cgi/collection/leukodystrophies Metabolic disease (inherited) http://n.neurology.org/cgi/collection/metabolic_disease_inherited Peroxisomes http://n.neurology.org/cgi/collection/peroxisomes
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://www.neurology.org/about/about_the_journal#permissions
Reprints	Information about ordering reprints can be found online: http://n.neurology.org/subscribers/advertise

Neurology® is the official journal of the American Academy of Neurology. Published continuously since 1951, it is now a weekly with 48 issues per year. Copyright © 2022 The Author(s). Published by Wolters Kluwer Health, Inc. on behalf of the American Academy of Neurology. All rights reserved. Print ISSN: 0028-3878. Online ISSN: 1526-632X.





https://ec.europa.eu/health/ern_en



European
Reference
Network

for rare or low prevalence
complex diseases

 **Network**
Neurological Diseases
(ERN-RND)

 **Coordinator**
Universitätsklinikum
Tübingen — Deutschland

www.ern-rnd.eu

Co-funded by the European Union

