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Practical Approach to Longitudinal Neurologic Care of Adults With X-Linked Adrenoleukodystrophy and Adrenomyeloneuropathy

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Abstract

Although X-linked adrenoleukodystrophy (ALD) has historically been considered a childhood disease managed by pediatric neurologists, it is one of the most common leukodystrophies diagnosed in adulthood. An increase in both male and female adults reaching diagnosis due to familial cases identified by state newborn screening panels and more widespread use of genetic testing results in a large cohort of presymptomatic or early symptomatic adults. This population is in urgent need of standardized assessments and follow-up care. Adults with ALD/adrenomyeloneuropathy (AMN) may be diagnosed in a variety of ways, including after another family member is identified via genetic testing or newborn screening, presenting for symptomatic evaluation, or following diagnosis with primary adrenal insufficiency. Significant provider, patient, and systems-based barriers prevent adult patients with ALD/AMN from receiving appropriate care, including lack of awareness of the importance of longitudinal neurologic management. Confirmation of and education about the diagnosis should be coordinated in conjunction with a genetic counselor. Routine surveillance for adrenal insufficiency and onset of cerebral ALD (CALD) in men should be performed systematically to avoid preventable morbidity and mortality. While women with ALD do not usually develop cerebral demyelination or adrenal insufficiency, they remain at risk for myeloneuropathy and are no longer considered "carriers." After diagnosis, patients should be connected to the robust support networks, foundations, and research organizations available for ALD/AMN. Core principles of neurologic symptom management parallel those for patients with other etiologies of progressive spastic paraplegia. Appropriate patient candidates for hematopoietic stem cell transplant (HSCT) and other investigational disease-modifying strategies require early identification to achieve optimal outcomes. All patients with ALD/AMN, regardless of sex, age, or symptom severity, benefit from a multidisciplinary approach to longitudinal care spearheaded by the neurologist. This review proposes key strategies for diagnostic confirmation, laboratory and imaging surveillance, approach to symptom management, and guidance for identification of appropriate candidates for HSCT and investigational treatments.

Introduction

There are several key barriers to care for adult patients with X-linked adrenoleukodystrophy (ALD). These include a limited number of adult neurology providers with expertise in treating adult-onset leukodystrophies, lack of patient and practitioner awareness of medical complications

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Glossary

ACTH = adrenocorticotropic hormone; **ALD** = adrenoleukodystrophy; **AMN** = adrenomyeloneuropathy; **ATP** = adenosine triphosphate; **CALD** = cerebral adrenoleukodystrophy; **EDSS** = Expanded Disability Status Scale; **FAIR** = fluid-attenuated inversion recovery; **FDA** = Food and Drug Administration; **HSCT** = hematopoietic stem cell transplant; **LPC** = lysophosphatidylcholine; **NAA** = N-acetylaspartate; **NfL** = neurofilament light chain; **VLCFA** = very long-chain fatty acids; **VUS** = variants of uncertain significance.

and the need for long-term surveillance, and patient guilt associated with transferring a genetic disease. To assist neurologists encountering patients with ALD, international consensus-based guidelines were developed.[1] To date, most patients with ALD have been diagnosed in childhood. With the addition of ALD to newborn screening in many states, as well as more widespread use of genetic testing, more adults with pathogenic *ABCD1* variants are reaching an ALD diagnosis. In this review, we propose a framework for the longitudinal neurologic care of adults with ALD.

Of the leukodystrophies, one of the most encountered in both children and adults is ALD.[2] The predominant adult phenotype is adrenomyeloneuropathy (AMN). Although the exact incidence or prevalence of AMN is unknown, nearly all male patients who do not develop childhood cerebral ALD (CALD) and at least half of all female patients develop myeloneuropathy during adulthood. The severity of myelopathy in patients with ALD/AMN increases with age, with the most common age at onset between 20 and 40 years[3]

Although adult patients with ALD typically exhibit milder neurologic phenotypes, long-term neurologic follow-up and surveillance are crucial. These patients remain at-risk for complications with high morbidity and mortality, including adrenal insufficiency, progressive spastic paraparesis due to AMN, and at least 20% will develop CALD.[4,5] The purpose of this review was to provide a primer for all neurology providers, regardless of subspecialty practice, surveil for complications, manage progressive symptoms, refer appropriate candidates for hematopoietic stem cell transplantation (HSCT), and coordinate a multidisciplinary team for the comprehensive management of adults with ALD/AMN (Table 1).

Pathophysiology

ALD is a metabolic peroxisomal disorder that results in accumulation of saturated very long-chain fatty acids (VLCFAs) in all tissues, particularly the CNS and the adrenal cortex.[6] Monogenic pathogenic variants in the adenosine triphosphate (ATP)-binding cassette (*ABCD1*) gene, located on the X chromosome, cause ALD.[7] *ABCD1* encodes an ABC transporter that enables translocation of acylated VLCFAs into the peroxisome.[7] There is no apparent genotype/phenotype correlation with the different ALD presentations.[7]

Diagnosis of Adults

Newborn Screening and Family Member Identification

Adult relatives with pathogenic *ABCD1* variants may be identified after a positive newborn screening test. Each state has an individualized newborn screening program, and to date not all have opted to include ALD testing.

ABCD1 molecular genetic testing is often used to evaluate relatives of an affected proband. Approximately 95% of diagnosed patients inherit an *ABCD1* pathogenic variant, while 4.1% have a de novo pathogenic variant.[8] In mothers of affected men, *ABCD1* molecular genetic testing is preferred over VLCFA analysis because 20% of women with ALD have normal plasma VLCFA.[3] Plasma C26:0-lysophosphatidylcholine (C26:0-LPC) has been found to be a more reliable marker in women with ALD, including those with normal plasma C26:0 and C26:0/C22:0 or false negative VLCFA.[9] C26:0-LPC testing can also be valuable in resolving genetic variants of uncertain significance (VUS). By contrast, male relatives of

Table 1 Key Recommendations

1	All male patients presenting with CALD, AMN, or presymptomatic ALD should be screened for adrenal insufficiency with a morning fasted cortisol, ACTH, and renin levels
2	Diagnostic brain MRI with and without gadolinium contrast followed by annual surveillance is recommended in men to facilitate early diagnosis of CALD
3	Regular neurologic examination can help identify and monitor myelopathy and polyneuropathy to aid in symptomatic treatment
4	As soon as a patient is diagnosed with ALD/AMN and baseline testing for CALD and adrenal insufficiency is underway, introduction to the numerous ALD/AMN foundations and support networks for leukodystrophies is encouraged for interested patients and families (Table 3)
5	Initial treatment discussions center around aggressive symptomatic management of ALD/AMN followed by sharing of resources to learn about therapeutic options for CALD if/when detected and ongoing clinical trials (refer to clinicaltrials.gov)
6	It is important to recognize myelopathy and neuropathy symptoms in women with ALD
7	Early detection of cerebral disease should lead to urgent referral for allogeneic HSCT because HSCT may lead to better outcomes if performed prior to accrual of significant disease burden

Abbreviations: ACTH = adrenocorticotropic hormone; ALD = adrenoleukodystrophy; AMN = adrenomyeloneuropathy; CALD = cerebral adrenoleukodystrophy; HSCT = hematopoietic stem cell transplantation.

newly identified heterozygous women may be evaluated by VLCFA analysis.[1,10] If a VUS in *ABCD1* is identified in a clinically unaffected individual (for instance, identified by newborn screening or as an incidental finding in whole-exome sequencing), determining plasma VLCFA (preferably C26:0-LPC) is important in variant classification. If plasma VLCFA are abnormal but not in the ALD range, functional testing in cultured skin fibroblasts is a potential next step.[11]

ALD newborn screening may identify mild variants, non-disease variants, and VUS.[12] A significant proportion of missense variants identified through newborn screening portend uncertainty regarding their pathogenicity and clinical implications.[12] Ongoing efforts to accurately classify variants and refine newborn screening protocols are needed to improve screening practices, interpret VUS, and provide prognostication for families.

In the case of pathogenic variants, the risk to siblings depends on the genetic status of the proband's parents. If a mother has the *ABCD1* pathogenic variant, the chance of transmitting the pathogenic variant for each pregnancy is 50%. A father with the pathogenic variant will pass the variant to all his female offspring and none of his male offspring. Adult family members, male and female, should be tested to determine who warrants screening and management for adrenal insufficiency, CALD, and myeloneuropathy. Variable expressivity is notable in ALD, with widely varying phenotypes often coexisting within a single family. In addition, a proband's phenotypic severity does not predict the clinical course or severity in other affected family members. Genetic evaluation with concurrent genetic counseling of at-risk family members is necessary prior to pursuing testing in the United States to consider the life-long risk of genetic discrimination regarding coverage and establishment of disability insurance, life insurance, and long-term care. The newly diagnosed parent can then be referred to an adult neurologist by a provider in a children's hospital, the child neurologist caring for the affected newborn, or a genetic counselor.

Diagnosis in the Context of Evaluation for Progressive Spastic Paraplegia

The differential diagnosis for adult patients presenting with progressive spastic paraplegia is broad, including genetic, degenerative, metabolic, nutritional, structural, infectious, inflammatory, neoplastic, and paraneoplastic etiologies. If there is no family history of a particular disorder, then genetic testing can be performed in collaboration with a genetic counselor following a comprehensive evaluation for more common disorders. We recommend pairing genetic testing with biochemical testing for fasting plasma VLCFAs, or plasma C26:0LPC, with genetic evaluation.[9] Patients presenting with spastic paraparesis should be evaluated with brain and spinal cord MRI at diagnosis to rule out other causes of myelopathy, including comorbid degenerative disk disease. In all men with spastic paraparesis due to AMN, a screening brain MRI is needed to rule out active cerebral demyelination because both AMN and adult CALD can co-occur and imaging findings may precede symptom onset.

Diagnosis in the Context of Evaluation for Adrenal Insufficiency

Adult men diagnosed with primary adrenal insufficiency may have ALD and thus may be referred to neurology from endocrinology. Primary adrenal insufficiency is the initial manifestation of ALD in 30%–40% and can be the only sign of ALD in approximately 8%–10%.[13-15] Adrenal failure in ALD is typically glucocorticoid-only, although some patients develop mineralocorticoid deficiency.[1,14] Men with ALD may have signs of adrenal insufficiency at diagnosis, although symptoms can be nonspecific (Table 2). Most patients with ALD who present with isolated adrenal insufficiency develop myelopathy by middle age (Figure 1), and conversely, adrenal dysfunction is present at onset of myelopathy in 70% of men.[3]

Diagnosis in Collaboration With a Genetic Counselor

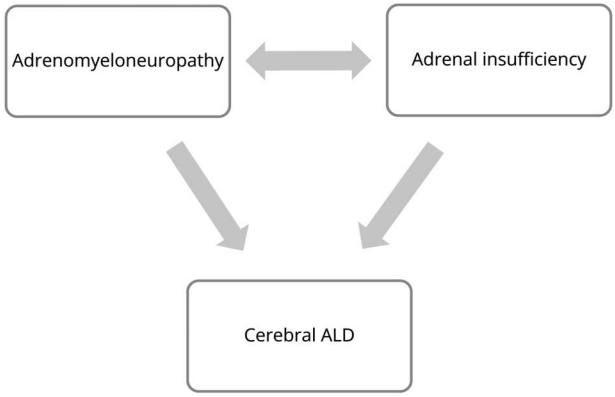
Genetic counselors may be a source of referrals and represent key members of the multidisciplinary team. We recommend that any neurologist caring for families affected by ALD/

Table 2 Suggested Laboratory and Imaging Surveillance for Adults With X-Linked Adrenoleukodystrophy/ Adrenomyeloneuropathy

Potential complications	Clinical features	Recommended testing	Adult men	Adult women
Adrenal dysfunction	Signs can be nonspecific: • Fatigue • Vomiting • Weakness • Headaches	CBC CMP AM fasted cortisol ACTH Aldosterone	Labs at diagnosis Annually thereafter Monitor for symptomatic warning signs at each visit	Consideration of laboratory testing at diagnosis Monitor for symptomatic warning signs at each visit
Cerebral ALD	Rapidly progressive impairments in • Cognition • Behavior	MRI brain with and without gadolinium	MRI scan at diagnosis and annually thereafter Monitor for red flag clinical symptoms at each visit Consider obtaining longitudinal optical coherence tomography	Consideration of MRI scan at diagnosis Monitor for red flag clinical symptoms at each visit

Abbreviations: ACTH = adrenocorticotropic hormone; ALD = adrenoleukodystrophy; CBC = complete blood count; CMP = comprehensive metabolic panel; AM = morning.

Figure 1 Types of ALD/AMN Phenotypes Identified by Surveillance in Adult Patients



Adults with X-linked ALD can present with myeloneuropathy, adrenal insufficiency, or they may remain asymptomatic. As time progresses, adult patients with ALD can develop overlapping phenotypes, and all adults with ALD remain at risk for developing cerebral ALD thus requiring long-term surveillance. Although the neurologist caring for adult patients with ALD/AMN is likely to be more familiar with surveilling for neurologic complications of disease, monitoring adrenal function is also necessary. ALD = adrenoleukodystrophy; AMN = adrenomyeloneuropathy.

AMN partner with a genetic counselor to provide support and guidance to affected patients and their at-risk family members who may be interested in follow-up genetic testing. If a genetic counselor is not available within the neurology department's team, then referral to medical genetics is recommended.

The genetic counselor's role includes providing information to patients about genetic testing methodology, to help families make informed decisions regarding diagnostic options, inheritance patterns, implications of diagnosis, risk of genetic discrimination, and aid in the understanding of genetic testing results once received (Table 3).

Surveillance

Once an adult is diagnosed with ALD/AMN, long-term surveillance for adrenal insufficiency, CALD, and myeloneuropathy is imperative for prevention of morbidity and mortality.

Adrenal Function

One of the potentially lethal complications of ALD/AMN is unrecognized adrenal dysfunction.[14] The lifetime prevalence of adrenal disease in male patients is 80%.[14] Although the risk of developing adrenal insufficiency is age-dependent, with the highest risk in early childhood, about 30% are at risk from ages 11 to 40, and another 5% are affected ages older than 40.[14] In general, approximately 8% of all patients with known adrenal insufficiency have an adrenal crisis each year, and the rate of death is roughly 6%.[16]

Recommendation 1

All men presenting with CALD, AMN, or presymptomatic ALD should be screened for adrenal insufficiency with a morning fasted cortisol, adrenocorticotropic hormone (ACTH), and renin levels (Table 1). Adrenal insufficiency can develop over time, and annual surveillance screening is also recommended (Table 2).[1] Low or normal early morning cortisol levels with high levels of ACTH characterize adrenal insufficiency. In cases with ambiguous results, referral to endocrinology is warranted to perform synthetic ACTH stimulation testing.[1,14] Adrenal insufficiency is rare (< 1%) in women with ALD/AMN, so screening adrenal function on establishing care without surveillance unless dictated by new clinical concerns is reasonable (Table 2).[14,17] For men or women with adrenal dysfunction, referral to endocrinology is warranted for additional work-up and treatment with chronic or stress dose adrenal hormones (Table 3). Lack of adrenal insufficiency should not falsely reassure regarding the risk of myelopathy because there is no correlation between adrenal insufficiency and myelopathy course.

Cerebral ALD

CALD is the most severe form of ALD and is associated with rapidly progressive impairments in cognition, behavior, speech, vision, hearing, and motor function, as well as seizures. Devastating disability may transpire within 6 months to 2 years. Most CALD occurs in childhood, with onset most commonly in male patients between 4 and 10 years of age. Nevertheless, all men with *ABCD1* pathogenic variants are at risk for CALD during their lifetime (Figure 1). In adulthood, the risk for developing CALD is about 20%, and roughly 50%–60% of adults with AMN show cerebral involvement 10 years after onset.[4,5] Anecdotal reports suggest that brain injury due to trauma or stroke can trigger CALD in men.[18] Adult onset CALD is clinically heterogeneous, and presentation can mimic other neurologic disorders, such as rapidly progressive dementia or multiple sclerosis (MS). Of note, CALD can occur in the absence of adrenal insufficiency or AMN.[19]

Recommendation 2

Diagnostic brain MRI with and without gadolinium contrast followed by annual surveillance is recommended in men to facilitate early diagnosis of CALD (Tables 1 and 2).[1] Brain MRI is always abnormal in patients with CALD, and imaging abnormalities can occur in advance of clinical manifestations or can develop at symptom onset (Figure 2).[20] Diagnostic scans should be performed with and without gadolinium contrast because white matter T2/FLAIR signal abnormalities may be associated with blood-brain barrier breakdown and enhancement at the advancing margin of disease; contrast enhancement strongly correlates with increased likelihood of rapid disease progression.[21] Identification of CALD with gadolinium enhancement should prompt consideration of HSCT.

In addition to standard brain MRI, magnetic resonance spectroscopy (MRS) should be considered if available. Decrease in the *N*-acetylaspartate (NAA) peak and elevation in the lactate peak may be detected on MRS even in cases with normal appearance of white matter on conventional MRI. As

Table 3 Multidisciplinary Team Approach for X-Linked Adrenoleukodystrophy

Specialty	Key roles
Neurology	Diagnosis Care coordination for the multidisciplinary team Routine surveillance for ALD/AMN complications Neurologic examination (including timed 25 foot walking test) Symptomatic management Coordination and access to HSCT or clinical trials if appropriate Link families to foundations and social support
Genetic counselor	Support families during diagnostic process Provide information about inheritance patterns and risk Discuss implications of diagnosis Identify methods for appropriate diagnostic genetic testing
Endocrinology	Refer patients with primary adrenal insufficiency for neurologic and genetic evaluation if ALD is suspected Management of adrenal insufficiency, hypogonadism, and bone health Prescribe stress dose steroids when indicated Assist with adrenal surveillance once adrenal insufficiency is identified
Physiatry	Spasticity management Coordination of therapies Appropriate choice of medical equipment and gait aids Botulinum toxin injections Consideration of intrathecal baclofen pumps
Physical and occupational therapy	First-line nonpharmacologic management for weakness, spasticity, gait dysfunction, pelvic floor dysfunction, falls, coordination, and balance issues Evaluation for medical equipment and gait aids
Urology	Urodynamic studies Urinary tract infection prevention Medication management of neurogenic bladder Medication management for sexual dysfunction Consideration of detrusor botulinum toxin injections or sacral neuromodulators
Gastroenterology	Medication management of neurogenic bowel
Psychiatry	Evaluation for and management of depression/anxiety Management for patients with psychiatric manifestations of CALD, including mood stabilizers and antipsychotics
Psychology	Therapeutic support for coping with diagnosis Nonpharmacologic mental health support

Abbreviations: ALD = adrenoleukodystrophy; AMN = adrenomyeloneuropathy; CALD = cerebral adrenoleukodystrophy; HSCT = hematopoietic stem cell transplantation.

such, MRS may be a more sensitive imaging biomarker for detecting early demyelination and axonal loss in ALD.[22,23]

CALD occurs in less than 1 percent of women, documented by only isolated case reports in the literature.[24] Obtaining a baseline brain MRI in a newly diagnosed female patient may be considered, without surveillance unless dictated by new symptoms (Table 2).

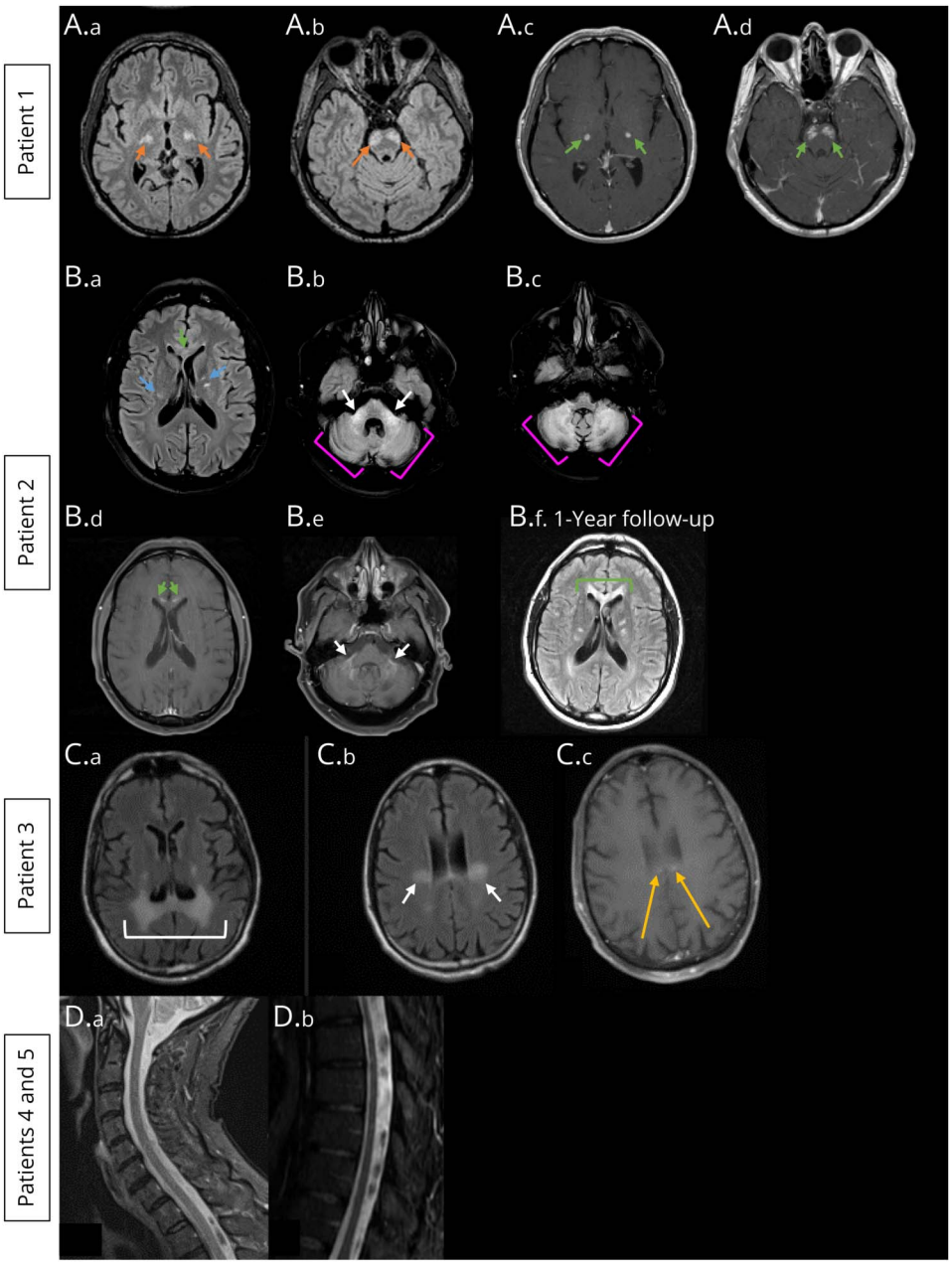
Myelopathy and Polyneuropathy

Virtually, all male and most female patients will develop myelopathy and peripheral neuropathy in adulthood, although age at onset and severity are highly variable.[14,25,26] The earliest clinical sign is usually reduced vibration sense in the hallux, followed by pyramidal tract signs causing a gait disorder. Urinary urgency with incontinence is an early burdensome symptom, and fecal incontinence is also common.[27] Even in patients aged older than 70 years, arms are not affected apart from hyperreflexia. If patients experience dysfunction of the upper extremities over time, evaluation for other diagnoses is recommended. Electrodiagnostic evaluation may help characterize large fiber axonal polyneuropathy, although it may also be normal in patients with predominantly small fiber neuropathy.[28] Signs and symptoms of peripheral neuropathy are typically overshadowed by those of myelopathy in most patients. The incidence of adults with AMN/ALD presenting with neuropathy is not known, but a diagnosis of AMN/ALD should be considered if signs of myelopathy are also present. Progression is generally slow, especially in women, occurring over years to decades.[25,26] Most male patients require a walking aid after the age of 45, and treatment is supportive.

Recommendation 3

Regular neurologic examination can help identify and monitor myelopathy and polyneuropathy to aid in symptomatic treatment (Table 1). Examination should document semiquantitative sensory examination, vibration sense in the hallux and medial malleolus, proprioception, and pinprick discrimination. Expanded Disability Status Scale (EDSS) is an acceptable clinical surrogate outcome that can supplement the history in documenting progression. When effective disease-

Figure 2 MRI of Adult Patients With X-Linked Adrenoleukodystrophy



(A) Patient 1: axial FLAIR sequences (A.a, A.b) and T1 postgadolinium images (A.c, A.d) from a man in his mid-40s with ALD/AMN with EDSS of 4 who was found to have T2/FLAIR hyperintense (orange arrows) and enhancing (green arrows) lesions in the corticospinal tract extending to the pons and brainstem. He developed frontal disinhibition and worsening gait, requiring a wheelchair within 1 year after the images presented. (B) Patient 2: axial FLAIR (B.a, B.b, B.c) and T1 postgadolinium images (B.d, B.e) of a man in his mid-40s with rapidly progressive cerebral ALD involving multiple brain regions, including the corticospinal tract (B.a, blue arrows), cerebellar white matter (B.b, B.c, pink brackets) and cerebellar peduncles (B.b, B.e, white arrows). Note the subtle FLAIR signal increase also in the genu of corpus callosum (B.a, green arrow) associated with gadolinium enhancement (B.d, green arrows). Follow-up imaging after 1 year showed bright signal hyperintensity in the genu on FLAIR sequences (B.f, green bracket). (C) Patient 3: axial FLAIR sequences (C.a and C.b) from a man in his late 40s with cerebral ALD demonstrating symmetric periventricular T2/FLAIR hyperintensities (white bracket and arrows). There is associated gadolinium enhancement on axial T1 postcontrast images in the periventricular white matter and splenium (C.c, yellow arrows). (D) Patients 4 and 5: sagittal short tau inversion recovery (STIR) images demonstrating mild spinal cord atrophy of the cervical spine (D.a) in a man in his late 60s and lower thoracic spine (D.b) in a man in his late 30s with AMN. There are no parenchymal lesions in the spinal cord and no gadolinium enhancement (not shown). ALD = adrenoleukodystrophy; AMN = adrenomyeloneuropathy; EDSS = Expanded Disability Status Scale; FLAIR = fluid-attenuated inversion recovery.

modifying therapies become available, monitoring for longitudinal efficacy will become more important. Clinimetric and patient-reported outcome measures are under investigation to quantify disease severity and include body sway, timed walk tests, and gait analysis with wearable sensors. Plasma biomarkers such as neurofilament light chain (NfL) may become useful in monitoring AMN but are still under investigation. Myelopathy can correlate with a normal or atrophic spinal cord on MRI (Figure 2). After initial spine MRI is completed at the time of diagnosis, routine surveillance MRIs of the spinal cord are unlikely to change management and are not recommended unless a new clinical concern arises.[29-31]

Treatment

Management After Diagnosis

Recommendation 4

As soon as a patient is diagnosed with ALD/AMN and baseline testing for CALD and adrenal insufficiency is underway, introduction to the numerous ALD/AMN foundations and support networks for leukodystrophies is encouraged for interested patients and families (Table 1). These organizations are excellent resources for patient advocacy, medical system navigation, connection to other affected families, coping with a rare and progressive neurodegenerative disease, providing

Table 4 Clinical Trial Opportunities and Foundations That Support the X-Linked Adrenoleukodystrophy Community

	Organization	Role	Contact
Research opportunities			
	ClinicalTrials.gov	Provides patients, family members, health care professionals, researchers, and the public with information on publicly and privately supported clinical studies	clinicaltrials.gov
	National Stem Cell Foundation	Nonprofit organization that funds adult stem cell and regenerative medicine research; connects children with limited resources to clinical trials for rare diseases	nationalstemcellfoundation.org
ALD-specific foundations			
	ALD Connect	Nonprofit organization that brings together patients, families, physicians, scientists, advocates, and industry	aldconnect.org
	The Stop ALD Foundation	Focuses on accelerating the process of developing new knowledge and therapies for ALD/AMN	stopald.org
	Fight ALD	Brings awareness through education to the community and medical professionals about early ALD symptoms and the importance of newborn screening	fightald.org
	ALD Info	Provides information on all aspects of ALD, written and maintained by ALD researchers and physicians	adrenoleukodystrophy.info
	ALD Alliance	Provides resources to families newly diagnosed with ALD	aldalliance.org
	Navigating ALD	Assists with building an ALD care team	navigatingald.com
Leukodystrophy-specific initiatives			
	Global Leukodystrophy Initiative	Shared research infrastructure that supports collection and analysis of clinical data and biological specimens to pave the way for transformative therapeutic trials across the leukodystrophies	theglia.org
	United Leukodystrophy Foundation	Nonprofit, voluntary health organization dedicated to funding cutting-edge research and to providing patients and their families with disease information and medical referrals	ulf.org
	Alex, The Leukodystrophy Charity	Originally established as "ALD Life," an internationally recognized center of excellence for those affected by ALD/AMN. Later the charity expanded to support all genetic leukodystrophies	alextlc.org
Female-specific organization			
	Remember The Girls	Raises awareness of the many issues facing girls and women with X-linked genetic disorders including ALD	rememberthegirls.org

Abbreviations: ALD = adrenoleukodystrophy; AMN = adrenomyeloneuropathy.

educational materials, and keeping families abreast of therapeutic advancements (Table 4). A referral to a leukodystrophy specialist should be considered, particularly with ambiguous findings on genetic testing (i.e., VUS in *ABCD1*), or atypical neurologic examination or MRI findings.

Recommendation 5

Initial treatment discussions center around aggressive symptomatic management of ALD/AMN followed by sharing of resources to learn about therapeutic options for CALD if/when detected and ongoing clinical trials (refer to clinicaltrials.gov) (Table 1). Current disease-modifying therapies are directed toward treating CALD; no existing US Food and Drug Administration (FDA)–approved treatments target AMN. Studies for experimental therapies for adults with AMN are currently in process.

Neurologic Symptom Management

While some adults with ALD/AMN may remain presymptomatic or minimally symptomatic for years, others will progressively accrue disability. In addition to surveilling for potentially life-threatening complications as outlined above, it is the neurologist's role to identify and manage symptoms in male and female patients. In the absence of disease-specific evidence-based guidelines, management principles mirror comprehensive care strategies often used with other inherited or acquired progressive myelopathies, such as due to MS, neuromyelitis optica spectrum disorder, or hereditary spastic

paraplegias. The neurologist spearheads the large multidisciplinary care team that comes together for comprehensive symptomatic management (Table 3).

Spasticity

There are no disease-specific therapeutic strategies for AMN-associated spasticity. As with other etiologies, therapies aimed toward reducing discomfort, maintaining functional ability, and optimizing quality life are recommended.[1] First-line management consists of nonpharmacologic strategies including stretching, exercise, and early referral to physical and occupational therapies. Pharmacologically, baclofen or tizanidine can be considered. Starting medication at a low dose at bedtime is recommended to help offset potential sedation. Refractory spasticity should prompt referral to physiatry. Physiatrists can assist with more advanced management strategies such as consideration for focal injections of botulinum toxin or intrathecal baclofen pump placement (Table 3).[32,33]

Sensory Ataxia

Proprioceptive loss and imbalance are among the earliest symptoms in both male and female patients with AMN. Sensory ataxia can result in significant gait impairment and falls. The use of assistive devices should be discussed early in the disease course to prevent falls and avoid significant injuries. Referral to physical therapy to work on balance and gait stabilization with the use of assistive devices such as braces and canes should be considered (Table 3).

Neurogenic Bladder and Bowel

Common symptoms of bladder dysfunction may include urinary frequency, urgency, hesitancy, and nocturia. Myelopathic patients can have an increased risk for urinary tract infections, although they may not detect typical symptoms such as dysuria. Whenever a patient reports sudden worsening in urinary or neurologic symptoms, infection should be ruled out with urinalysis and culture. Treatment of bladder dysfunction in ALD/AMN mirrors standard therapeutic approaches in other etiologies of spinal cord injury. Nonpharmacologic strategies such as regimented bathroom breaks with timed voiding and dietary modifications to avoid "bladder irritating" foods/drinks are first-line. Pharmacologic treatment includes beta-3 adrenergic agonists (mirabegron) and antimuscarinic agents (oxybutynin). Older adults may be more susceptible to anticholinergic side effects of antimuscarinics, so use of medications that do not cross the blood brain barrier, including trospium chloride, or that selectively block the M3 muscarinic receptor, such as darifenacin, may be preferential.[34] Many patients with neurogenic bladder benefit from urology referral to facilitate urodynamic testing, which can help define the pathophysiologic etiology for urinary dysfunction.[35] Urologists may also consider advanced management strategies including detrusor botulinum toxin injections or placement of sacral neuromodulators (Table 3).[36,37]

Neurogenic bowel symptoms most commonly include constipation, poor evacuation, or incontinence. Decreased motility related to progressive myelopathy may contribute to bowel dysfunction. Initial nonpharmacologic interventions include dietary changes, such as increasing fluid and fiber intake. There are numerous medication options, including laxatives, stool softeners, and prokinetic agents.[35] Referral to a gastroenterologist for refractory cases should be considered (Table 3). Referral to physical therapy for pelvic floor strengthening is also an option.[27]

Hypogonadism and Sexual Dysfunction

Clinical signs of sexual dysfunction in men with ALD/AMN can include erectile dysfunction, diminished libido, failure of the testes to descend, small testes, diminished body hair, and gynecomastia.[38] Fertility is not typically affected.[39] Routine screening regarding sexual dysfunction and symptoms of hypogonadism during clinical neurology follow-up visits may uncover issues that significantly affect quality of life. Pharmacologic management, in collaboration with a urologist, can be considered for erectile dysfunction. Symptoms such as weakness and loss of sensation may also affect female patients' sexual function, and referral to physical therapy for pelvic floor strengthening exercises can be considered. For complex or refractory cases, referral to a urologist or endocrinologist may be helpful (Table 3).

Osteopenia

While no systematic data exists, osteopenia is common among individuals with AMN who are walker or wheelchair-dependent. Special attention should be paid toward bone health, and vitamin D supplementation to maintain adequate levels should be recommended.

Polyneuropathy

Neuropathic symptoms, mainly numbness and dysesthesias, are common in adults with AMN. Patients may also experience muscle cramps, spasms, and restless leg syndrome.[40] Physical therapy with emphasis on core strengthening, balance training, and appropriate assistive devices remain the mainstay of management (Table 3). Nonpharmacologic interventions often include advice on proper socks, footwear and bracing, and regular foot examination for injuries. Patients may find topical options such as lidocaine and capsaicin cream helpful. Other pharmacologic options can be considered, but with the trade-off for potential cognitive side effects. A first-line choice is often gabapentinoid drugs due to their favorable safety profile.[41] Alternatives to consider include tricyclic antidepressants and duloxetine.[41] Patients may experience considerable musculoskeletal pain in the back and lower extremities due to undertreated spasticity and impaired gait, or severe neuropathic pain due to polyneuropathy. Standard treatments are unfortunately not always effective, and referral to a pain service might be indicated.

Cognitive Function and Mental Health

The prevalence of psychiatric symptomatology in adults with ALD/AMN is unknown, although case series and our experience suggest that mood symptoms are common. Cerebral

demyelination in adults with ALD is known to affect processing speed and contribute to deficits in attention and learning.[42] Even in the absence of cerebral demyelination, adult patients with AMN may have risk for anxiety and depression, although the mechanism by which AMN relates to these mental health problems is not clear. For all patients with ALD/AMN, we recommend open discussion about adjustment to and implications of the diagnosis. Many patients benefit from targeted psychosocial support toward coping with a slowly progressive lifelong neurodegenerative disease. Routine check-ins regarding emotional well-being at each neurology follow-up appointment is recommended, with a low threshold for referral to psychology and psychiatry for additional expertise and consideration of medical management with antidepressants or anxiolytics (Table 3).

It is important that the adult form of CALD can present with nonspecific psychiatric symptoms prior to other neurologic deficits. One study reviewing 109 reported cases of ALD showed that 39% presented with a psychiatric manifestation and 17% presented exclusively with a psychiatric problem.[43] Presentation can mimic the symptoms of schizophrenia or bipolar disorder, and signs/symptoms of mania are often present, although frank psychosis and cognitive impairment are other possibilities.[44,45] Partnering with a psychiatrist for titration and monitoring of antipsychotics and mood stabilizers is recommended (Table 3).

Treatment of Symptomatic or Asymptomatic Women With ALD

Recommendation 6

It is important to recognize myelopathy and neuropathy symptoms in women with ALD (Table 1).[14,46] While it is very rare for women with ALD to develop cerebral demyelination or adrenal insufficiency, a screening brain MRI and serum ACTH can provide reassurance (Table 2). Family members and other clinicians in a woman's care team should be educated that heterozygous ALD status does not equate to an asymptomatic clinical course. Pain and other neuropathy symptoms should be addressed similarly to symptomatic men, and alternative etiologies should be ruled out.

Although data are lacking regarding the role of stigma affecting families affected by ALD/AMN, attention should be given to guilt and blame when providing genetic counseling to families affected by all X-linked disorders.[47] In our clinical practice, we have noted that guilt surrounding the inheritance of ALD/AMN can act as a barrier to establishing care with a neurologist, even as affected women develop bothersome and debilitating symptoms of progressive myelopathy. In addition, women with ALD are often the caregivers to other affected family members and may deprioritize their own medical care. These emotions should be addressed and normalized by both the neurologist and genetic counselor for comprehensive mental health support and to facilitate longitudinal care.

Mortality and Burden of Illness

Recent analysis of large national commercial insurance databases revealed a higher rate of health care resource utilization by adults with AMN compared with age-matched peers.[48] Surprisingly, the mortality rates and burden of illness were significantly higher in adult patients with AMN; this may not be explained by the occurrence of adult CALD alone. Future research is needed to elucidate the comorbidities and etiology behind organ dysfunction beyond the CNS. This may be important for future risk stratification of more invasive procedures such as HSCT.

Disease-Modifying Therapy

Current disease-modifying therapies in ALD are targeted toward the treatment of CALD. There are no approved therapies that slow or prevent progression of AMN or reverse endocrine manifestations of the disease. New disease-modifying experimental strategies are under investigation, and other therapeutic options for AMN may be available in the coming years. It is the primary neurologist's role to keep patients with ALD/AMN informed as new therapeutic opportunities arise, consider referral to nearby leukodystrophy or trial centers, and keep abreast of ongoing clinical trials (Table 3).

Hematopoietic Stem Cell Transplant

To date the only effective treatment capable of interrupting destructive inflammatory demyelination in CALD is allogeneic HSCT.

Recommendation 7

Early detection of cerebral disease should lead to urgent referral for allogenic HSCT because HSCT may lead to better outcomes if performed prior to accrual of significant disease burden (Table 1).

Data detailing the outcomes of HSCT in adult ALD populations are limited. Two recent studies in adults indicate that HSCT has the potential to arrest inflammatory demyelination, stabilize the enlargement of brain lesions, and potentially improve brain lesions if performed at early stages of disease. A retrospective study of 14 men with adult CALD treated with HSCT in 4 European centers was the first to support feasibility, outline complications, and describe potential long-term neurologic benefits of HSCT in adult patients. This cohort showed an overall survival of 57% at median follow-up of 65 months. Poor survival was associated with severe motor deficits (EDSS > 6) and bilateral involvement of the internal capsule on brain MRI prior to HSCT. Radiologic arrest of cerebral demyelination and neurocognitive stability was seen in the 8 survivors, although 5 of 8 had ongoing deterioration in motor function.[49] In a more recent prospective study from a cohort in Tokyo, 12 patients with adolescent-/adult-onset CALD underwent HCST. Notably, all patients enrolled had Loes scores (an MRI severity score for CALD) up to 13, and none had severe neuropsychiatric symptoms.[50] All patients undergoing

HSCT survived with a median follow-up period of 28.6 months. Six of 8 patients who did not undergo HSCT died. Neurologic deficits attributable to cerebral disease stabilized or partially improved in all patients, and improvement was also noted on neuroimaging.[51] These outcomes indicate that ideal adult candidates for HSCT have evidence of inflammatory brain lesions on MRI but are without corresponding symptoms. Adult patients with symptomatic and advanced cerebral disease are not considered good candidates for HSCT because it will not reverse symptoms and HSCT is a procedure associated with high morbidity. There are long-term sequelae related to immunosuppression, infection, and graft-versus-host disease, and transplant-related mortality in adult patients may be as high as 30%.[49] The leading cause of death following HSCT is ALD progression. Therefore, adults with a high burden of neurologic symptoms and neuroimaging severity (Loes score > 13) are poor candidates for HSCT.[51]

A major challenge in the care of adults with CALD is determining where the neurologist can refer patients for HSCT given that the procedure is not commonly performed in this population. Options include referral to research-based opportunities recruiting for HSCT trials on clinicaltrials.gov or foundation websites (Table 4), or consideration of tertiary care centers already performing HSCT for refractory MS. Another challenge in this population is identifying candidate HSCT donors, given that family members may also be affected by *ABCD1* pathogenic variants. This warrants collaboration with a genetic counselor for testing of asymptomatic family members.

Currently, HSCT is not recommended for treatment of AMN alone because there is no evidence that it modifies AMN onset or reverses axonal damage.[52,53] Although the underlying mechanisms of AMN and adrenal insufficiency are not fully understood, neither are associated with infiltration of inflammatory cells like cerebral lesions in CALD; this may explain, at least in part, the differential benefits of HSCT for CALD.[54] As such, it is important that adults who have received HSCT (even in childhood) undergo longitudinal monitoring and management of adrenal insufficiency (Table 2) and AMN manifestations.[54]

Gene Therapy

Gene therapy for childhood-onset CALD was recently approved by the FDA, but no data are available in adults; at present, gene therapy is restricted to boys aged 4 to 17 years. In the pediatric population, a multicenter study reported 17 patients who received infusion of CD34+ cells transduced with a lentiviral vector containing normal *ABCD1* complementary DNA.[55] FDA approval was based on additional data from 2 uncontrolled studies involving a total of 67 children with early CALD. Preclinical studies using an in vivo adeno-associated virus 9 (AAV9)-based gene therapy approach have shown that various delivery routes, including intrathecal, may reach target cells and correct VLCFA metabolism in mice.[56,57] At the time of this publication, a similar approach is under investigation for treatment of AMN. Adeno-associated viral vector (AAV)-based gene therapy aims to reduce VLCFA levels by establishing *ABCD1* expression in the spinal cord after lumbar intrathecal administration. Initial evaluation in mouse models demonstrated improvement in AMN markers and was shown to be well-tolerated in nonhuman primate models. Refer to clinicaltrials.gov for the most up-to-date information using gene therapy in adults with ALD/AMN.

Another novel therapy under investigation is leriglitazone, a selective agonist for peroxisome proliferator-activated receptor gamma (PPAR-γ). PPAR-γ regulates expression of key gene pathways that contribute to neuroinflammatory and neurodegenerative processes implicated in ALD/AMN pathophysiology.[58,59] A 96-week randomized, double-blind, placebo-controlled, phase 2–3 trial (ADVANCE) showed no change in progression of AMN symptoms (measured by 6-minute walk test distance), so the primary end point was not attained.[58] However, because so few treated men developed CALD, there is an ongoing randomized study to determine whether leriglitazone alters CALD progression (NCT05819866).

Dietary Modifications and Supplements

Based on the available evidence, dietary interventions, including Lorenzo's oil, have not been shown to halt or slow disease progression in ALD/AMN. Routine use of these interventions is not recommended because of the lack of proven efficacy in several open-label studies.[60]

Progressive Spastic Paraplegia

Just as symptomatic management strategies for AMN are mirrored in the care of patients with other etiologies of progressive myelopathy, disease-modifying strategies that are under investigation for other neurologic disorders may ultimately be translatable to adult patients with AMN. We recommend that the neurologist stay abreast of updates on clinicalTrials.gov and ALD/AMN foundation websites for potential opportunities (Table 4).

Conclusion

ALD/AMN is a lifelong disease with a broad spectrum of clinical manifestations. Adult male and female patients are reaching diagnosis at growing rates due to more widespread genetic testing, expanded newborn screening, and increased identification of ALD/AMN in asymptomatic family members. Establishing care with a neurologist is recommended at diagnosis, regardless of symptom severity, to begin lifelong laboratory and neuroimaging surveillance, allow for early symptomatic intervention, and identify appropriate candidates for potential life-saving interventions. Recently published consensus-based guidelines for ALD provide guidance, but further evidence is needed to support longitudinal management of adults.[1] In particular, it is not known whether all

missense variants identified on newborn screening will have the same risk of developing adrenal insufficiency, AMN, or CALD as previously described for pathogenic variants.[12] Further studies examining the utility of advanced imaging (including MRS) and blood-based biomarkers (such as NfL) for both AMN and CALD in adults will be key to inform future screening guidelines and treatment outcomes. As more women with pathogenic variants are identified, a more nuanced understanding of the AMN natural history will be forthcoming. The development of disease-specific symptomatic treatments will improve quality of life for both men and women with AMN. Finally, disease-modifying therapies that alter outcomes in adults will be key additions to future management guidelines. With the guidance provided here, neurologists are well-poised to coordinate multidisciplinary comprehensive and longitudinal care of adult men and women with ALD/AMN.

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