REVIEW

ABCD1 Gene Mutations: Mechanisms and Management of Adrenomyeloneuropathy

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Abstract: Pathogenic variants in the ABCD1 gene on the X chromosome may result in widely heterogenous phenotypes, including adrenomyeloneuropathy (AMN). Affected males typically present in their third or fourth decade of life with progressive lower limb weakness and spasticity, and may develop signs and symptoms of adrenal insufficiency and/or cerebral demyelination. Heterozygous females may be asymptomatic, but may develop a later-onset and more slowly progressive spastic paraparesis. In this review, we describe the clinical presentation of AMN, as well as its diagnosis and management. The role of rehabilitative therapies and options for management of spasticity are highlighted.

Keywords: adrenoleukodystrophy, spastic paraparesis, adrenal insufficiency

Introduction

X-linked adrenoleukodystrophy (X-ALD) is an inherited disorder characterized by the accumulation of very long-chain fatty acids (VLCFAs) in the plasma and tissues, including the nervous system, adrenal glands, and testes. It is caused by pathogenic variants in the ABCD1 gene on the X chromosome.[1,2] Those with the condition do not demonstrate any signs or symptoms at birth. It has a very variable clinical presentation, ranging from asymptomatic to a devastating fatal childhood disease. Therefore, it has been included in many state newborn screening programs across the United States. Males with X-ALD may develop adrenal insufficiency, spastic paraparesis, peripheral neuropathy, gonadal dysfunction, and/or a progressive degenerative brain disorder.[1,3]

Though relatively rare, X-ALD is the most common peroxisomal disorder.[4] Its prevalence has been estimated at 1 in 17,000 when heterozygous females are included.[5] It has been diagnosed in all ethnic groups, and ethnicity does not appear to impact one's risk for the condition. Though it is an X-linked recessive disorder, approximately half of female heterozygotes eventually develop signs of myelopathy.[2]

Neither the presentation nor course of X-ALD can be predicted by the inherited ABCD1 gene variant, plasma VLCFA levels, or family history.[6] There are three major phenotypes observed in affected males: "Addison's disease only", cerebral adrenoleukodystrophy (CALD), and adrenomyeloneuropathy (AMN). It is important to note that males that appear to have one of these phenotypic variants may subsequently develop signs of neurological and/or adrenal involvement characteristic of another form.[4] Thus, while AMN is the focus of this review, the clinical features of the other phenotypes are also described.

Clinical Phenotypes
"Addison's Disease Only"

This term refers to cases of X-ALD in which there is adrenal insufficiency without neurological signs or symptoms. It has been reported that 11 percent of males with X-ALD demonstrate this phenotype, however, in the absence of neurological involvement or additional testing, these cases may go undiagnosed as such.[7] In a study of 14 young adult males

diagnosed with primary idiopathic adrenal insufficiency, 35% exhibited elevated plasma levels of VLCFAs.[8] The treatment of adrenal insufficiency is the same for persons with idiopathic and X-ALD forms of the condition. However, the latter group of patients are at-risk for the subsequent development of AMN or CALD, for which they should be monitored. Moreover, diagnosis with a pathogenic ABCD1 gene variant has important implications for genetic counseling and family planning.[9]

Cerebral Adrenoleukodystrophy

Cerebral adrenoleukodystrophy (CALD) is the most severe phenotype of X-ALD. CALD results from demyelination within the cerebral white matter, and it is characterized by a life-threatening, rapidly progressive neurological decline. The mean age at onset is seven years, and the initial symptoms are similar to those seen in hyperactivity-attention deficit disorder.[10] Individuals with CALD may also experience seizures, visual disturbances, and/or motor symptoms including hemiparesis and/or dysarthria.[2,11] As the disease advances, it may eventually result in tetraparesis, wheelchair dependence, and/or the loss of the ability to communicate. The prognosis of CALD is very poor- when untreated, a majority of affected children die within a decade of diagnosis.[12] However, when performed early, hematopoietic stem cell transplantation slows disease progression and results in improved 5-year survival rates.[12,13]

Adrenomyeloneuropathy

AMN, in contrast, typically presents in adulthood and with a more insidious course. Affected males usually present with signs and symptoms of myelopathy in their third or fourth decade of life, with a mean age of onset of 27.6 years.[7] Though heterozygous women were previously thought to be asymptomatic carriers, the majority develop myelopathy and/or peripheral neuropathy by age sixty. Adrenocortical insufficiency and cerebral involvement, however, rarely occur in women with X-ALD, with reported a reported prevalence of 1 and 2% respectively.[2,14,15]

Myelopathy

Men with AMN develop a progressive myelopathy resulting from a distal axonopathy involving the dorsal column and corticospinal tract in the thoracic and lumbar spinal cord.[16] Early clinical signs include weakness, impaired vibration sensation, and mild spasticity of the lower limbs, as well as a slowed gait.[17] Impaired standing balance is common as evidenced by increased sway amplitude.[18] As the myelopathy advances, the spasticity worsens and strength declines.[17] Worsening hip flexor strength is primarily responsible for the decline in walking velocity observed.[18] Many will require an assistive mobility device for ambulation. Activity and participation levels decrease as the degree of disability increases over time.[17] In a cohort of patients with AMN, moderate handicap, as defined by the modified Rankin scale, developed over a period of 16.2 ± 8.9 years.[19]

In symptomatic women with X-ALD, the onset of myelopathy typically occurs at a later age and is more slowly progressive.[14,20] Early onset cases of severe myelopathy have, however, been reported.[21] X-ALD is believed to be underrecognized in women, who may be erroneously diagnosed with multiple sclerosis, hereditary spastic paraparesis, or spondylotic myelopathy.[22,23] Misdiagnosis with fibromyalgia is also common due to the high prevalence of chronic pain in females with X-ALD.[24] Pain was reported by 80% of heterozygous women.[25]

Neurogenic bladder and bowel are common in AMN and typically present after the onset of gait and sensory disturbances.[19] Bladder and bowel symptoms are also common in women with mutations of the ABCD1 gene, in whom they may be severe. Patients most often report symptoms of an overactive bladder, including urinary urgency and frequency. Stress incontinence and low stream have also been reported.[26] Urodynamic studies demonstrate a variety of causes of neurogenic bladder among persons with X-ALD, including detrusor overactivity, motor underactivity of the bladder, and detrusor sphincter dyssynergia.[27] Constipation is reported in half of men, and nearly half of women, with X-ALD. Fecal urgency and incontinence are also highly prevalent symptoms in this patient population.[26]

Peripheral Neuropathy

The majority of males with AMN and females heterozygous for X-ALD have peripheral neuropathy, the clinical signs of which may be difficult to differentiate from those of myelopathy. Nerve conduction studies in this population are often abnormal; evidence of both axonal loss and multifocal demyelination have been observed.[28] The lower limbs are more

commonly and severely affected, though involvement of the upper limbs may also occur.[29] Small nerve fiber dysfunction is also highly prevalent among both males and females with X-ALD.[30]

Adrenal Insufficiency

Approximately 70% of those with AMN have adrenocortical insufficiency.[7] Abnormal plasma adrenocorticotropic hormone (ACTH) and cortisol levels usually precede the onset of endocrine symptoms.[31] The presentation may be non-specific, with common symptoms including fatigue and nausea. Hyperpigmentation occurs, but may be subtle, particularly among dark-skinned individuals. Life-threatening adrenal crisis may occur and requires prompt treatment.[32]

Mineralocorticoid function often remains intact, likely because VLCFAs accumulate to a lesser degree in the zona glomerulosa than the other regions within the adrenal cortex.[31] However, aldosterone deficiency has been observed in X-ALD and manifests with salt-craving. If untreated, it causes hyponatremia, hyperkalemia, mild metabolic acidosis, and may result in hypotension.[32]

Alterations in Hair Patterns

Males with AMN demonstrate soft and scant scalp hair and half demonstrate sparse body hair.[33] Reduced hair has also been reported in a case series of two sisters heterozygous for X-ALD[34] and in two mothers of patients with AMN.[35] König et al[35] reported hair loss preceded the onset of neurological symptoms in 11 of 12 patients with AMN and observed an absence or scarcity of eyelashes among males in their cohort.

Testicular Insufficiency

Men with AMN may also develop testicular deficiency and develop clinical signs of hypogonadism. Assies et al[33] reported on their findings in men with X-ALD, which included 21 subjects with AMN and 5 without neurological involvement. They observed that most had plasma testosterone levels within normal limits, but the majority had an insufficient increase after stimulation with hCG. Nearly two-thirds demonstrated low plasma levels of dehydroepiandrosterone-sulfate (DHEA-S). The majority of subjects reported erectile dysfunction, and nearly half reported reduced libido. Thirty-five percent demonstrated gynecomastia.

The impact of AMN on fertility is unclear, though hypospermatogenesis has been reported in X-ALD.[36] Stradomska et al[37] did not find a significant decrease in fertility among married adult men with AMN compared to the general population in Poland.

Cerebral Involvement

Cerebral demyelination may also develop in men with AMN who do not initially exhibit brain involvement. Signs may include hearing and/or visual disturbances, behavioral changes, impaired attention, rapid decline in intelligence, upper limb weakness, bulbar signs, and/or seizures.[19] Magnetic resonance imaging (MRI) of the brain characteristically demonstrates demyelination in the corpus callosum and the occipital periventricular white matter.[38]

While studies evaluating the prevalence of brain involvement in males with AMN have yielded very different results, it is clear that cerebral demyelination develops in a significant proportion of men with the condition. Van Geel et al[19] observed a cohort of men with AMN over time, with a mean follow-up interval of ten years. Nineteen percent developed cerebral demyelination and clinically deteriorated, with a median survival of 1.6 years after their initial manifestation of brain involvement. In a Dutch cohort of men with AMN, over sixty percent developed cerebral demyelination, with a mean onset of cerebral disease of 10.2 ± 6.9 years from the onset of myelopathy symptoms. Mean survival in this cohort was 3.4 ± 2.9 years following the onset of cerebral demyelination.[38]

Pathogenesis
The ABCD1 Gene

ABCD1 contains 10 exons and is located on the long arm of the X chromosome. It encodes for the ATP-binding cassette (ABC) subfamily D member 1 protein, a peroxisomal membrane transporter also known as the adrenoleukodystrophy protein (ALDP). ALDP imports saturated very long-chain fatty acids (VLCFAs) into the peroxisomal matrix for

degradation by peroxisomal beta-oxidation. X-ALD is caused by the ALDP deficiency that impairs the breakdown of VLCFAs.[2,39–41]

ABCD1 Variants

The ABCD1 Variant Database includes a worldwide registry of unique ABCD1 variants. As of December 2021, the database contained over 3400 cases of X-ALD with 948 pathogenic variants, 249 variants of uncertain significance, and 40 benign variants. Missense mutations are the most common type of variant (61.4%), followed by frame shift mutations (17.2%).[40]

Inheritance Pattern

X-ALD is inherited in an X-linked manner. Approximately 95% of affected individuals inherit the ABCD1 pathogenic variant from one of their parents; and an estimated 4.1% of index cases are caused by a de novo pathogenic variant.[42,43] Affected males inherit the ABCD1 pathogenic variant only from their mothers and will transmit it to all of their daughters. There is no transmission from an affected father to son. The risk of transmission of a pathogenic variant in ABCD1 in female carriers is 50% in each pregnancy. Prenatal and preimplantation genetic testing can be offered to female carriers if a pathogenic variant is identified.[42]

As previously mentioned, the phenotypic expression of the condition is unpredictable. A 1996 report of monozygotic twins with an identical point mutation in exon 8 underscores this phenomenon. One twin was asymptomatic with normal imaging, while the other twin suffered gait ataxia and visual impairment and had radiological evidence of progressive cerebral demyelination.[44] Another case report described the vast difference in phenotypes between two brothers, in which one demonstrated congenital abnormalities and died by age 25 and the other did not begin to show symptoms until 22 years of age.[45] It is thought that modifier genes and environmental influences play important roles in the variable phenotypic expression.[42]

Very Long-Chain Fatty Acids

VLCFAs are fatty acids with a chain-length of at least 22 carbons. They serve several important functions within mammalian bodies, including essential roles in the maintenance of myelin and in the resolution of inflammation.[46] Normally, VLCFAs are degraded by being converted to VLC acyl-CoAs, which are then imported into the peroxisome to undergo beta oxidation into long-chain fatty acids.[47] However, when ALDP does not function correctly or is deficient, VLCFAs accumulate in plasma and tissues.[2] VLCFA levels are elevated in almost all tissues in males with X-ALD, including the brain, spinal cord, peripheral nerves, adrenal glands, and testes.[11] The exact means by which elevated levels of VLCFAs result in the pathology seen in persons with X-ALD has not yet been fully elucidated. The mechanisms underlying the different phenotypes observed in those with ABCD1 gene mutations appear to differ, though accumulation of these fatty acids is likely essential to the development of all of them.[47] Animal models and in vitro studies suggest oxidative stress and mitochondrial dysfunction likely play key roles in the pathogenesis.[48–53]

Diagnostic Work-Up

Plasma VLCFA Assay

The finding of elevated plasma VLCFA levels using gas chromatography allows for the definitive diagnosis of AMN in males with evidence of neurological disease and/or adrenal insufficiency.[2] Affected males demonstrate abnormally high plasma concentrations of hexacosanoic acid (C26:0) and elevated ratios of tetracosanoic acid (C24:0) and C26:0 to docosanoic acid (C22:0).[54] The application of machine learning techniques to these assays has enabled the determination that C26:0 levels between 1.61 and 3.34 μmol/l and C26/C22 ratios between 0.05 and 0.10 are diagnostic of the condition.[55] While the majority of females who are heterozygous for X-ALD have elevated plasma VLCFA levels,[56] a normal value does not exclude carrier status.[54] Accordingly, mutation analysis is recommended to identify female carriers.[7]

False positive VLCFA level results are rare, but have been reported in persons adhering to a ketogenic diet,[57,58] those with liver disease,[58] and following the ingestion of peanut butter.[59] A false positive result has also been reported in the case of a boy with new-onset autoimmune adrenal disease.[60]

Newborn screening for X-ALD has been made possible by the finding of Dr. Hugo Moser and his team of elevated C26:0 lysophophatidyl choline levels in post-natal dried venous blood spots obtained from males with X-ALD. Additional assays have since been developed. New York became the first state to begin newborn testing for the condition in 2013. Additional states have since followed. Early diagnosis enables early detection of and timely treatment for cerebral involvement and/or adrenal insufficiency.[61] False positive test results have been reported among infants with Aicardi–Goutières syndrome, a rare interferonopathy.[62]

Molecular Genetic Testing

The diagnosis of X-ALD and the carrier status of heterozygous females can be identified with molecular genetic testing. As the ABCD1 gene is the only gene associated with X-ALD, single-gene testing is usually sufficient. Sequence analysis of ABCD1 is initially performed, and is followed by gene-targeted deletion/duplication analysis if a pathogenic variant is not identified. Testing with a multigene panel may be performed to exclude other genetic disorders in one's differential diagnosis, such as hereditary spastic paraparesis.[63]

Testing of Adrenal Function

Primary adrenal insufficiency is highly prevalent in males with X-ALD, and may be detected with laboratory testing prior to the onset of symptoms, enabling prompt initiation of treatment with steroid replacement therapy. Elevated plasma levels of ACTH and low levels of cortisol are typical indicators of adrenal dysfunction in this population, however the ACTH stimulation test should also be performed to identify those who may require treatment.[3,64] Screening of asymptomatic males with X-ALD for adrenal insufficiency is recommended to occur every 6 months during childhood and annually after age 18.[65]

Mineralocorticoid function often remains intact and aldosterone deficiency is not routinely screened for. Nevertheless, aldosterone levels should be assessed in males with X-ALD in the setting of hyperkalemia, hyponatremia, and/or signs of volume depletion.[66,67]

Electrodiagnostic Testing

Electrodiagnostic testing, while not necessary to make the diagnosis of AMN, may be performed in the evaluation of affected persons to exclude other potential causes of weakness, sensory impairment, and/or spasticity. In a small study of eighteen men with AMN and five female carriers, van Geel et al[29] demonstrated decreased nerve conduction velocity (NCV) in some, but not all, subjects. Electrodiagnostic abnormalities were more commonly observed in the lower limbs. The peroneal motor NCV was below the lower limit of normal in sixteen of the subjects, and the sural sensory NCV was below the lower limit of normal in eleven. Delayed F-wave responses and soleus H reflexes were also observed in some study participants. However, only two subjects met electrodiagnostic criteria for a primary demyelinating polyneuropathy.

Imaging

MRI may be used in both the diagnosis and monitoring of males with AMN. Brain imaging is often normal or with subtle abnormalities in those without cerebral disease. Those with cerebral ALD typically demonstrate symmetric hyperintense lesions on T2-weighted and Fluid-Attenuated Inversion Recovery studies. Demyelination is most often first evident in the corpus callosum, with the parieto-occipital white matter also commonly affected.[68] Lesions may also be seen along the corticospinal, visual, and/or auditory tracts.[69,70] As MRI of the brain enables early detection of cerebral ALD, the progression of which may be prevented with hematopoietic stem cell transplantation,[13,68] it is recommended that brain MRI be repeated every 6 months until the age of 12 and annually thereafter in those with X-ALD.[4,71]

Spinal cord imaging is not currently used routinely in the monitoring of persons with X-ALD.[68] However, imaging of the spinal cord may be performed to rule out other potential causes of their neurological signs and symptoms, such as multiple sclerosis or cord compression. The finding of spinal cord atrophy, while also present in other neurodegenerative disorders, is a common finding in X-ALD patients, in whom the reduction in spinal cord cross-sectional area is most pronounced at the thoracic levels.[72] It should be noted that symptomatic female heterozygotes also commonly have abnormal spinal cord findings on MRI.[69]

Management of Adrenomyeloneuropathy

Disease-modifying therapies for AMN remain experimental at this time. For those with adrenal insufficiency, hormone replacement therapy is essential. Treatment of the condition is otherwise symptom-based, with the management of spasticity and functional impairments by physiatrists and other rehabilitation professionals.[11] As literature addressing the rehabilitation management of these specific patients is scarce, this section will incorporate discussion of some treatment strategies used in persons with other spinal cord disorders.

Rehabilitation

Males with AMN, as well as symptomatic heterozygous females, often require multidisciplinary rehabilitation. Occupational therapy is essential to help preserve one's ability to perform necessary tasks at home, school, and/or work. Physical therapy will typically address gait, balance, strength, endurance, and muscle tone, and may include evaluation for adaptive mobility devices, including gait aids and/or wheelchairs.[73] Functional electrical stimulation may help maintain the speed of and satisfaction with walking among some men with AMN.[74] Those with foot drop and/or knee buckling may benefit from the involvement of an orthotist in their care. Though most persons with AMN demonstrate normal cognitive function,[75] those who do not may benefit from cognitive rehabilitation services. Individuals with bulbar signs in the setting of cerebral involvement may benefit from evaluation and treatment by a speech-language pathologist to address dysphagia, dysphonia, and/or dysarthria. The involvement of a therapeutic recreation specialist in one's care may facilitate awareness of and participation in adaptive leisure activities and aid in one's social participation.[76]

Aquatic therapy has not yet been evaluated as a rehabilitation intervention specifically for persons with AMN, however, it may be a useful form of treatment in this patient population given beneficial effects reported in persons with spinal cord injury (SCI). Kesiktas et al[77] observed benefit in the reduction of spasm severity and oral baclofen intake among persons with SCI who received pool-based therapy. Stevens et al[78,79] reported significant improvements in leg strength, balance, preferred walking speed, 6-minute walk distance, and submaximal exercise heart rate among adults with incomplete SCI following participation in a 2 month-long underwater treadmill training program.

Individuals experiencing difficulty driving may benefit from specialized driver's rehabilitation services. Modifications, such as the installation of hand controls, may be necessary for the safe operation of a vehicle by persons with significant lower limb weakness.[80]

Vocational rehabilitation (VR) services may be necessary for men with AMN to prepare for, obtain, or maintain employment. The VR process includes an assessment of the individual's abilities and impairments, interests, and work potential. It may include assistance with identifying the need for and requesting job accommodations to enable one to continue to work in their own occupation. It may also include training for and placement in a new job.[81]

Men with AMN experiencing difficulty adjusting to their disability may benefit from consultation with and treatment from a rehabilitation psychologist. The psychologist may assist them in coming to terms with their changes in function and social roles, provide non-pharmacological strategies to address co-morbid anxiety and depression, and instruct them in the development of positive coping skills.[82]

Spasticity Management

The development of an individualized treatment approach for spasticity necessitates consideration of the specific goals of the patient and/or their families. Their goals may include alleviation of discomfort, prevention of contracture, improvements in activities of daily living and/or mobility, and/or reduction in caregiver burden.[83] It is also important to consider how the individual with paraparesis may be benefiting from their spasticity before devising a treatment plan, particularly with regards to standing, transferring, and ambulation.[84]

Though little has been written specifically addressing spasticity management in AMN, published case reports have highlighted the successful use of intrathecal baclofen (ITB) therapy in boys with X-ALD.[85,86] Baclofen, a GABA-B agonist, may be effective in reducing spasticity, particularly that of spinal origin. When given orally, however, it may cause significant side effects, including confusion, sedation, and dizziness.[87] ITB therapy is associated with less systemic

side effects, but greater risk for toxicity and withdrawal.[88] Among long-term users of baclofen therapy, its intrathecal administration is associated with significantly fewer and less severe spasms than is its oral use.[89]

The use of botulinum toxin therapy for spasticity has also been described in case reports of persons with ABCD1 gene mutations, including a man with AMN[73] and a woman with X-ALD.[90] Moreover, lower limb botulinum toxin injections have also been shown effective in reducing spasticity among ambulatory persons with hereditary spastic paraparesis.[91]

There are several additional treatment options for spasticity, not yet evaluated in this patient population in published studies, which may be beneficial. Non-pharmacological treatment options for spasticity include stretching, neuromuscular electrical stimulation, and splinting. While there is very little evidence for the efficacy of passive movement as a treatment for spasticity, it may be helpful in preventing contracture.[92] Tizanidine is an alpha-2 adrenergic receptor agonist administered orally that has been shown to be safe and effective in reducing muscle tone in persons with SCI without impacting their muscle strength.[93] Obturator nerve chemoneurolysis with phenol or alcohol may be used to reduce spasticity of the hip adductors.[94,95]

Medical cannabis may also help manage spasticity. Among individuals with SCI who use cannabis for therapeutic purposes, more than 40% reported doing so for reduction in spasticity.[96] Add-on treatment with a cannabinoid oromucosal spray (nabiximols) has demonstrated efficacy in the management of resistant spasticity in multiple sclerosis, and the risk of adverse reactions with this medication is low.[97] Though it is available in Canada and most of Europe, it is not yet approved for use in the United States.[98]

Pain Management

Little has been written regarding pain management in this patient population. Spasticity management, as previously discussed, may help alleviate discomfort resulting from increased muscle tone. However, other pain generators contribute to the high prevalence of chronic pain among those with ABCD1-related conditions. The pain is often, but not always, neuropathic in nature.[25] Pregabalin is indicated for the treatment of neuropathic pain secondary to spinal cord injury, as well as for peripheral neuropathy resulting from diabetes mellitus.[99] It may help to alleviate neuropathic pain in adrenomyeloneuropathy as well. High doses of pregabalin reportedly provided some relief in the case of a man with X-ALD with intractable lower limb burning pain and painful paresthesias.[100]

Winkelman et al[101] recently reported a high prevalence of restless legs syndrome (RLS) in adults with X-ALD. This may be an important cause of leg pain in this population and should be considered when the pain is worse at night, particularly if associated with the urge to move to one's legs. Treatment of RLS with iron therapy and/or dopamine agonist medication may provide some relief for those with AMN, but further research is needed.

Individuals with paraparesis, especially those who use assistive walking devices or wheelchairs, are also at risk for painful musculoskeletal conditions. Persons with SCI commonly develop upper extremity overuse syndromes, particularly when they rely on their upper limbs for transfers and locomotion. This may be more pronounced in persons with comorbid obesity, for whom weight management is key.[102] Shoulder pain is highly prevalent among wheelchair users and may be caused by a number of different pathologies. This is commonly treated conservatively with therapeutic exercise, including a regimen of stretching and strengthening.[103] Neck and low back pain are also common in wheelchair users. In addition to analgesics and therapeutic exercise, modifications to one's wheelchair and/or cushion may allow for improved posture and pain.[104]

Bladder and Bowel Management

Bladder issues significantly impact the health-related quality of life in males with AMN, as well as female carriers of ABCD1 gene mutations, and may improve with appropriate treatment.[26] Urodynamic studies best identify the cause of an individual's neurogenic bladder, thereby enabling a more targeted management strategy.[27]

A number of treatment options are available for neurogenic detrusor overactivity (NDO), a common finding among those with X-ALD.[27] Conservative management may include timed voiding and adapting or restricting one's fluid intake. Anticholinergic medications, including oxybutynin and tolterodine, are very effective, but their use may be limited by side effects, such as constipation, drowsiness, and dry mouth.[105] Mirabegron is a beta-3 agonist that is approved for the treatment of overactive bladder. It has been shown to be safe and effective for the management of NDO in persons with

SCI.[106] Intra-detrusor botulinum toxin injections are also effective in the treatment of NDO with a typical duration of response of 6–9 months.[105]

Some with X-ALD demonstrate detrusor sphincter dyssynergia (DSD) on urodynamic studies.[27] This condition often necessitates catheterization to prevent complications from high intravesical pressures, which include urinary tract infections, hydronephrosis, and renal failure. Clean intermittent self-catheterization is generally preferable, though indwelling catheters may be necessary in those unable or unwilling to perform it.[107] Injections of botulinum toxin A into the external sphincter may provide temporary benefit in persons with DSD. Surgical treatment options include urinary diversion procedures and urethral sphincterotomy.[108]

Detrusor underactivity has also been observed in some with X-ADL[27] and may also necessitate bladder catheterization. Parasympathomimetics, such as bethanechol, have been widely used in the treatment of underactive bladder, though the evidence supporting their use is lacking and side effects are common.[109] The use of alpha-adrenergic blockers such as tamsulosin may be beneficial. Timed and/or double voiding may be a helpful adjunctive therapy. Sacral neuromodulation, while not evaluated in published studies of AMN, is efficacious in the treatment of non-obstructive underactive bladder.[110]

Bowel symptoms in X-ALD are commonly treated with fiber supplements and/or laxatives.[27] A bowel program performed at a consistent time 20–30 minutes following a meal, daily or every other day, may help facilitate stooling and prevent accidents.[80]

Hormone Replacement Therapy

Once diagnosed with adrenal insufficiency, men with AMN require glucocorticoid replacement therapy. While this may be a life-saving intervention, steroids do not significantly impact patients' neurological signs or symptoms. Treatment is typically with cortisone or hydrocortisone given in the early morning and a second smaller dose given in the late afternoon. Intravenous methylprednisolone may be used when oral administration of steroids is not feasible. Stress-dose steroids are essential during times of increased physiologic stress. In the event of persistent orthostatic hypotension, hyperkalemia, and/or hyponatremia, fludrocortisone may be added to their steroid regimen.[66,111]

The evidence for long-term supplementation with DHEA in persons with adrenal insufficiency is relatively weak and it is not routinely used.[112] However, men with AMN who demonstrate hypogonadism in the setting of low serum testosterone levels should receive supplemental androgen therapy.[111]

Sexual Dysfunction

Men with AMN with erectile dysfunction (ED) may benefit from treatment with a phosphodiesterase inhibitor. Oral sildenafil and tadalafil have both been shown to improve erectile function among men with ED caused by traumatic SCI.[113,114]

Dietary Management

It should be noted that dietary interventions may result in reduced plasma levels of VLCFAs but are not sufficient to alter the course of X-ALD, in which most VLCFAs are of endogenous origin. Foods rich in VLCFAs include vegetable oils, fruit peels and seeds, grains, nuts, and fatty fish and meat.[115] Consuming a low-fat diet and daily doses of so-called "Lorenzo's oil", a combination of oleic and erucic acids, neither resulted in improvement nor prevented progression of disease among subjects with AMN.[116]

Males with adrenal insufficiency secondary to AMN may require modifications to their usual diets for optimal health. Consumption of licorice and grapefruit juice should be avoided as they result in transient increases in the availability of cortisol to the tissues following cortisone administration.[117] Patients with mineralocorticoid deficiency should be advised against restricting their salt consumption.[118] Intermittent fasting should generally be avoided, though it may be an important part of some religious observances. Clinical complications are common among individuals with adrenal insufficiency who engage in intermittent fasting during Ramadan.[119]

Hematopoietic Stem Cell Gene Therapy

Hematopoietic stem cell transplantation (HSCT) is the standard of care in persons with early-stage cerebral adrenoleukodystrophy, in whom it has been shown to prevent disease progression, resulting in improved functional status and

survival.[120,121] HSCT does not, however, halt progression of adrenal dysfunction nor does it prevent myelopathy in X-ALD.[122,123]

Experimental Treatments

Recombinant adeno-associated viral (AAV) vector-mediated gene therapy is under investigation for the treatment of AMN. Intrathecal AAV vector gene delivery via an osmotic pump in a mouse model resulted in widespread gene expression in the central nervous system as well as a significant decrease in spinal cord VLCFA levels.[124]

Leriglitazone is a peroxisome proliferator-activated receptor gamma agonist and the primary metabolite of pioglitazone, a drug used in the treatment of diabetes mellitus. It has been granted orphan drug status for the treatment of X-ALD. It has been shown to have neuroprotective effects in animal models of the disease, as well as a dose-dependent efficacy in improving motor impairment. It was safely tolerated by humans in a Phase 1 trial of healthy volunteers.[125] Men with X-ALD who received the drug in a subsequent trial demonstrated improvements in body sway as well as in blood and imaging biomarkers compared with those who received placebo. Potential adverse effects of the drug include weight gain, edema, hypersecretion of tears, and cardiac events, including angina and tachycardia.[126]

Genetic Counseling

Genetic counseling provides one with information about the risks for and implications of genetic disorders. Identification of female carriers may help inform their family planning decisions and may facilitate prenatal and/or preimplantation genetic testing. The testing of undiagnosed at-risk male relatives of an individual with X-ALD may facilitate early diagnosis and treatment of adrenal insufficiency and/or cerebral involvement.[63]

Conclusion

X-linked adrenoleukodystrophy results from the accumulation of very long-chain fatty acids in the plasma and tissues observed in persons with ABCD1 gene mutations. Though it is an x-linked recessive disorder, the majority of females heterozygous for X-ALD develop signs of myelopathy and/or neuropathy. Adrenomyeloneuropathy is a form of X-ALD in which affected males develop progressive spastic paraparesis, most often in their third or fourth decade of life, with the majority also developing adrenal insufficiency and/or peripheral neuropathy. Those with adrenal insufficiency require glucocorticoid replacement therapy. A significant proportion of affected males eventually develop cerebral involvement, which carries a very poor prognosis, though early identification and treatment with stem cell gene therapy may prevent its progression. No treatment options currently exist to prevent progression nor treat the myelopathy of AMN, though research is ongoing. Thus, rehabilitation therapies and symptom-based management remain the mainstays of treatment for males with AMN and symptomatic females with X-ALD.

Disclosure

The authors report no conflicts of interest in this work.

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