RESEARCH ARTICLE

Disease Burden in Female Patients With X-Linked Adrenoleukodystrophy

Natalie R. Grant,[1] Yedda Li,[1,2] Lizbeth De La Rosa Abreu,[1] Catherine Becker,[1] Brian D. Wishart,[3,4] Amanda Nagy,[1,2] Florian S. Eichler,[1,2,*] and Reza Sadjadi[1,2,*]

Neurology® 2025;104:e213370. doi:10.1212/WNL.0000000000213370

Correspondence
Dr. Sadjadi
rseyedsadjadi@mgh.harvard.edu

Abstract

Background and Objectives

X-linked adrenoleukodystrophy (ALD) is a neurodegenerative disease primarily affecting male patients. Female patients with ALD are also affected in adulthood, yet their disease course and symptom burden remain poorly defined. In this single-site study, we set out to characterize disease burden in female individuals with ALD and identify barriers faced by this patient population.

Methods

Adult female individuals with genetically or biochemically confirmed ALD were recruited through an outpatient specialty clinic and a patient advocacy group. We performed a retrospective chart review and conducted prospective telephone interviews to assess symptom presence and onset, interventions and management strategies, injuries, comorbidities, and quality of life (QOL). For comparison, we retrospectively gathered data from ALD diagnosis and symptom onset for adult male patients with ALD seen in our clinic.

Results

We included 127 female (median [interquartile range] age = 50.2 [39.2, 59.9]) and 82 male individuals with ALD (median [interquartile range] age = 37.5 [24.2, 43.9] years). Among our female cohort, 115 (91%) reported neurologic symptoms. The most common symptoms were urinary symptoms (74%), walking difficulty (66%), and spasticity (65%). Mental health symptoms were also common (64%). Of interest, 70 (55%) reported a history of falls, 61 (48%) had sustained injuries from falling, and 54 (43%) had a history of fractures. Compared with the male cohort, our female cohort had a significantly later age at symptom onset and diagnosis. In addition, symptom presentation was less likely to prompt a diagnosis in female individuals. Of 46 female individuals who sought clinical care for symptoms before diagnosis, 22 were initially misdiagnosed. Fifty-one (90%) of 57 female interviewees reported encountering challenges with health care access, and 49 (86%) reported a reduction in different aspects of QOL. Activities of daily living beyond walking were affected in 25 (44%) participants.

Discussion

We conclude that symptoms related to myelopathy and neuropathy are common in female individuals with ALD and that their disease burden is aggravated by the high rates of mental health problems, barriers to health care access, and injuries and complications requiring treatment. Limitations of our study include a risk for recall bias and selection bias.

Introduction

X-linked adrenoleukodystrophy (ALD) is a neurodegenerative disease due to variations in the *ABCD1* gene, resulting in impaired degradation of very long chain fatty acids (VLCFAs).[1] In male patients, the clinical spectrum has been well-studied and includes a spinal cord disease

*These authors contributed equally to this work as co-senior author.

[1]Department of Neurology, Massachusetts General Hospital, Boston; [2]Department of Neurology, Harvard Medical School, Boston, MA; [3]Department of Physical Medicine and Rehabilitation, Massachusetts General Hospital, Boston; and [4]Department of Physical Medicine and Rehabilitation, Harvard Medical School, Boston, MA.

Glossary

ALD = adrenoleukodystrophy; **AR** = androgen receptor; **cALD** = cerebral ALD; **IQR** = interquartile range; **NBS** = newborn screening; **QOL** = quality of life; **VLCFA** = very long chain fatty acid.

known as adrenomyeloneuropathy that progresses with age in all, followed in frequency by primary adrenal insufficiency in 80%, and cerebral inflammatory disease known as cerebral ALD (cALD) in 60%[2,3]. Female heterozygotes for ALD were previously believed to be unaffected and simply be carriers. While adrenal insufficiency and cALD occur in less than 1% of female patients, more than 80% are now recognized to develop progressive spinal cord disease similar to the male phenotype.[4,5] Impaired gait and balance, spasticity, urinary and bowel dysfunction, and peripheral neuropathy increase with age and significantly interfere with activities of daily living.[6-8] Symptomatic female individuals with ALD report poor quality of life (QOL) and depression, sleep disturbances, fatigue, and sexual dysfunction.[9]

The onset of neurologic symptoms in female patients is often 10–15 years later than in male patients and female patients have been described to experience more fecal incontinence, numbness, pain, small fiber neuropathy, and restless leg syndrome.[10] In contrast to male hemizygotes, some of the phenotypic variability in female heterozygotes may arise from skewed X-inactivation patterns, which can lead to selective expression of either the allele with the pathogenic variant or the unaffected allele.[11] X-inactivation patterns have been found to correlate with neurologic manifestations in this population.[12] However, other conflicting studies have found that skewed X-inactivation is common in female patients with ALD but does not consistently correlate with clinical symptoms.[13,14]

Despite a high symptom burden, female individuals with ALD commonly face barriers to accessing medical information and receiving the care needed to manage symptoms.[15] There are often limited resources and awareness regarding ALD among medical providers, and ALD diagnoses are often not recognized in female patients who seek medical advice. In addition, there have been multiple previous reports of female patients, with ALD being misdiagnosed with other conditions such as multiple sclerosis or hereditary spastic paraplegia until a family history of ALD is detected.[16-23] There are currently no FDA-approved treatments for the adult manifestations of ALD,[24] although strategies exist to manage symptoms.[25] Clinical trials are often limited to male patients whose disease progression has been more well-studied. This is likely due in part to the slow rate of disease progression in female patients, making it difficult to detect clinically relevant changes over time.[26] The lack of treatment options and clinical trials has been previously reported as a priority need among female individuals with X-linked diseases.[15]

The goal of this study was to evaluate disease burden, define clinical characteristics, explore barriers faced, assess QOL, and better understand the daily experiences of female individuals with ALD. We aim to emphasize the unmet needs of the female ALD community and highlight sex-related disparities in diagnosis, treatment, and quality of care. By adding to the growing literature, we hope to improve disease recognition and medical care in this population. Understanding the disease course in female patients will help inform trial readiness and elucidate the pathophysiology and appropriate treatment for this disorder.

Methods

Retrospective Chart Review

We retrospectively reviewed the medical charts of all female patients ≥18 years old with genetically or biochemically confirmed ALD who were seen in the Massachusetts General Hospital Leukodystrophy clinic from 2006 through July 2023. We extracted data concerning ALD diagnosis, presence of neurologic signs and symptoms, age at symptom onset, interventions and management strategies, injuries, comorbidities, and imaging studies. Presence of signs and symptoms were recorded from standard of care neurologic examinations performed by a licensed physician and validated by a board-certified neurologist. For comparison, we gathered data from ALD diagnosis and age at symptom onset for all adult male patients with ALD seen in our clinic during the same study period.

For female patients only, we retrospectively collected laboratory results from X-inactivation studies and plasma VLCFA analysis performed during diagnostic workup. Results recorded in ug/mL were converted to umol/L by multiplying by 2.52 for C26:0, by 0.92 for C24:0/C22:0, and by 0.86 for C26:0/C22:0.[27] Normal VLCFA levels were <1.2 umol/L for C26:0, <1.0 for the ratio C24:0/C22:0, and <0.02 for the ratio C26:0/C22.0.[28] X-inactivation analysis of the androgen receptor (AR) locus was performed on DNA samples by Greenwood Genetic Center. X-inactivation patterns were determined by PCR analysis of a polymorphic CAG repeat in the AR gene before and after digestion with the methylation-sensitive restriction enzyme *HpaII* because methylation of these sites has been shown to correlate with X-inactivation.[29] X-inactivation ratios greater than 90:10 were considered highly skewed, ratios between 80:20 and 90:10 were considered moderately skewed, and ratios of less than 80:20 were considered random patterns.

Interview

To supplement the data of our retrospective chart review and better understand the patient perspective, we conducted telephone interviews with female individuals with ALD (eAppendix 1). Participants were recruited from our clinic

and through a study advertisement distributed by a patient advocacy group. The interviews focused on ALD diagnosis, symptom presence and onset, interventions and management strategies, injuries, and comorbidities. We also asked participants about any specialists seen outside of neurology, barriers faced in receiving care, activities of daily living, the effect of ALD on overall QOL, and any factors contributing to QOL.

For patients who underwent both the interview and the chart review, the interview was used as the primary source of data for any patient-reported information such as symptom presentation and onset. We considered a history of injuries, comorbidities, and interventions if they were mentioned either in the interview or medical chart.

Data Analysis

Data analysis was performed using XLSTAT 2021.4.1.

We used a χ^2 test to determine the association between patient sex and what led to their ALD diagnosis. A Kaplan-Meier analysis was used to assess time to symptom onset, and a log-rank test was used to determine any differences between male and female individuals. If a range of years was provided for symptom onset age, the midpoint of that range was used for analysis. A Mann-Whitney *U* test was used to analyze the difference between age of ALD diagnosis in male and female individuals. p values <0.05 were considered significant.

Standard Protocol Approvals, Registrations, and Patient Consents

This study was reviewed and approved by the Mass General Brigham Human Research Committee. Informed consent was waived for the retrospective chart review, and verbal consent was obtained from interview participants.

Data Availability

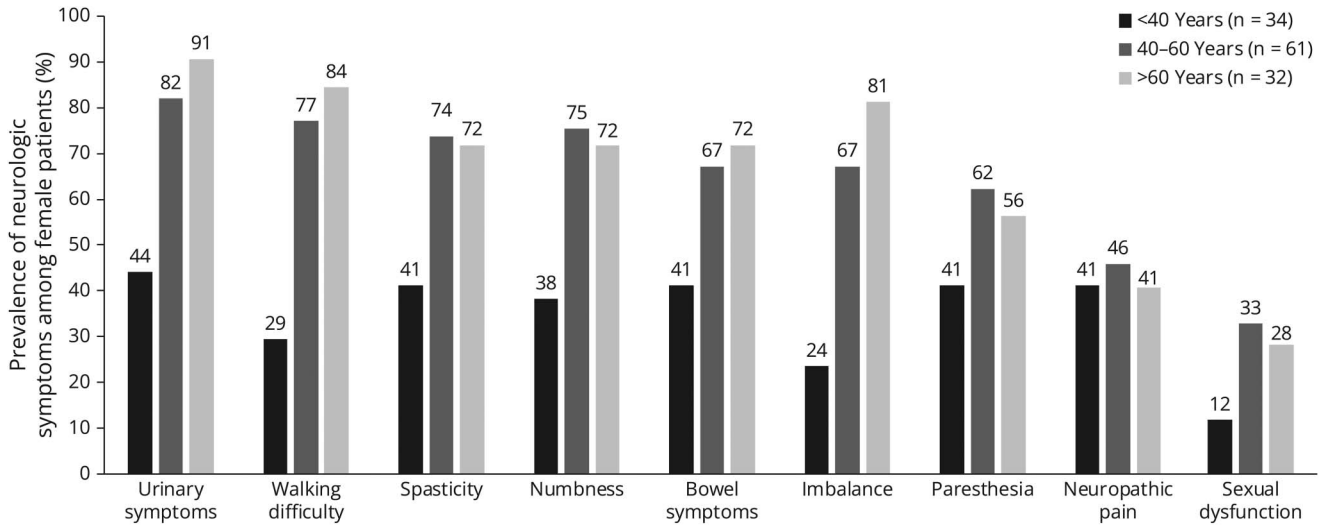
Anonymized data not published within this article will be made available by request from any qualified investigator.

Table 1 Neurologic Symptoms Reported by Female Patients in Our Cohort and Median Age at Onset (Years) for Each Symptom (N = 127)

	Prevalence n (%)	Onset age median (IQR)
Myelopathy symptoms		
Urinary symptoms	94 (74.0)	42 (33, 51)
Walking difficulty	84 (66.1)	44 (37, 50)
Spasticity	82 (64.6)	43 (32,52)
Numbness	82 (64.6)	43 (34, 54)
Bowel symptoms	78 (61.4)	41 (32, 51)
Imbalance	75 (59.1)	45 (38, 53)
Paresthesia	70 (55.1)	40 (33, 52)
Neuropathic pain	55 (43.3)	38 (32, 49)
Sexual dysfunction	33 (26.0)	NA
Other symptoms		
Depression/anxiety	81 (63.8)	NA
Fatigue	79 (62.2)	NA
Insomnia	72 (56.7)	NA
Joint pain	68 (53.5)	41 (33, 51)
Restless legs syndrome	55 (43.3)	43 (33, 51)
Chronic headaches	48 (37.8)	NA
Memory difficulties	47 (37.0)	NA
Word finding difficulties	34 (26.8)	NA
Brain fog	29 (22.8)	NA
Cold/heat intolerance	21 (16.5)	NA

Abbreviations: IQR = interquartile range; NA = not assessed.

Figure 1 Prevalence of Neurologic Symptoms Among Female Individuals Stratified by Age Group (N = 127)

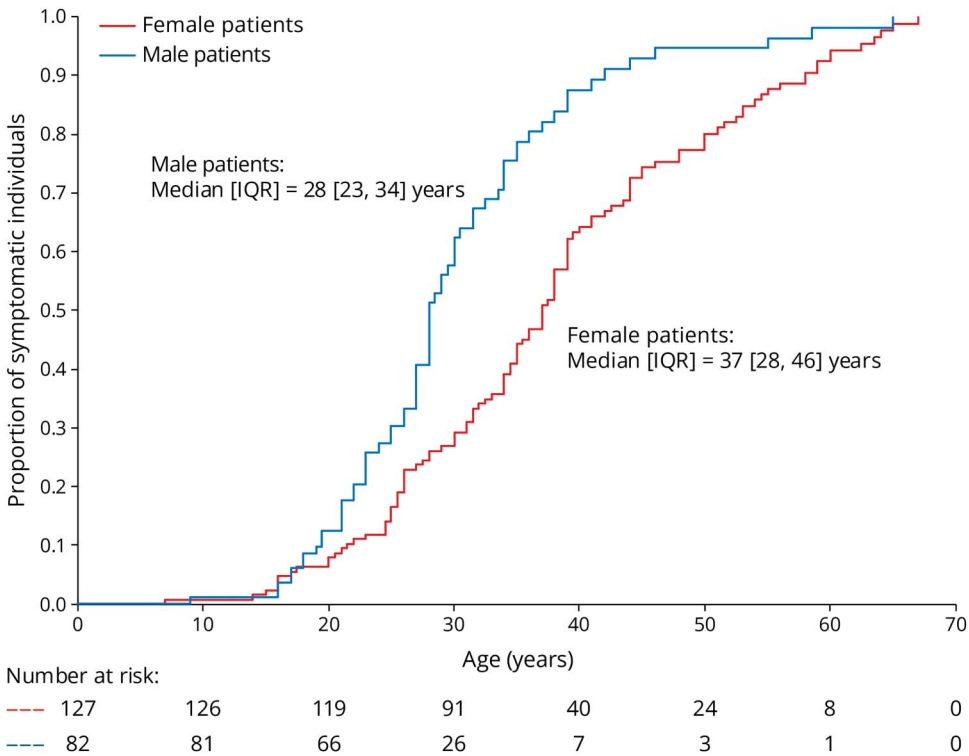


Results

Study Population

A total of 127 adult female individuals with ALD were included in our study. The median (interquartile range [IQR]) age at the most recent data point was 50.2 (39.2, 59.9) years. We identified 89 female patients in our retrospective chart review and prospectively conducted interviews with 57 participants. Nineteen participants were included in both the chart review and interview. The majority (45 [78.9%]) of interviewees were recruited through the study advertisement, and the remainder (12 [21.1%]) were recruited in our outpatient clinic. Throughout the recruitment process, no individuals declined participation or were deemed ineligible to participate. We reviewed the medical charts of 82 adult male patients with ALD (median [IQR] age = 37.5 [24.2, 43.9] years).

Figure 2 Time to Myelopathy Symptom Onset in Female (N = 127) and Male (N = 82) Individuals



The y-axis represents the proportion of symptomatic individuals at each given age.

Neurologic Signs and Symptoms

Neurologic symptoms were reported by 115 (90.6%) female individuals. The most common symptoms were urinary symptoms in 74.0%, walking difficulty in 66.1%, and spasticity in 64.6% (Table 1). The symptoms with the earliest median (IQR) onset age were neuropathic pain (38 [32, 49] years) and paresthesia (40 [33, 52] years). The prevalence of most neurologic symptoms increased with age (Figure 1).

Time to symptom onset was later in our female cohort compared with our male cohort ($p < 0.001$), with a median (IQR) onset of 37 (28, 46) years in female individuals and 28 (23, 34) years in male individuals (Figure 2).

Of the 89 female patients included in our chart review, 77 (86.5%) had abnormalities on neurologic examination. Two of these patients were asymptomatic with signs only. The most common signs were impaired sensation in 83.1% and hyperreflexia in 69.7% (Table 2). Twenty-seven (30.3%) patients had poor capillary refill and/or skin discoloration, suggestive of autonomic or small fiber dysfunction.

Injuries and Comorbidities

Seventy (55.1%) of 127 female individuals had a history of falls, 61 (48.0%) had sustained injuries from falling, and 54 (42.5%) had a history of fractures. Forty (31.5%) had a diagnosis of osteoporosis or osteopenia, 52 (40.9%) had a diagnosis of arthritis, and 9 (7.1%) had Raynaud. Thirty-seven (29.1%) had recurrent UTIs. Twenty-three (18.1%) had endocrine abnormalities, most commonly hypothyroidism (n = 15), adrenal insufficiency (n = 4), hyperprolactinemia (n = 3), and hyperaldosteronism (n = 2).

Table 2 Prevalence of Neurologic Signs Observed Among Female Patients in Our Retrospective Cohort (N = 89)

	n (%)
Impaired sensation[a]	74 (83.1)
Hyperreflexia[a]	62 (69.7)
Sensory ataxia	47 (52.8)
Gait abnormality	46 (51.7)
Muscle weakness	34 (38.2)
Hypertonia[a]	31 (34.8)
Cerebellar ataxia	31 (34.8)
Action tremor	23 (25.8)
Head titubation	12 (13.5)
Dysmetria	5 (5.6)
Dysdiadochokinesia	2 (2.2)
Dystonia	12 (13.5)
Cervical dystonia	7 (7.9)
Limb dystonia	5 (5.6)

[a] Deficits were noted in the lower extremities.

Symptom Management

Female individuals in our cohort used a variety of treatments and strategies to manage symptoms (Table 3). The most common medications used were analgesics (60%) with most patients requiring them for chronic use. Among nonpharmacologic interventions, female individuals frequently sought out physical therapy, exercise, and alternative medicine to address musculoskeletal symptoms.

Laboratory Evaluation

Plasma VLCFA results were available in 53 (59.6%) medical charts and elevated in 49 (92.5%) cases. C26:0 was elevated in 44 (83.0%); the ratio C24:0/C22:0 was elevated in 43 (81.1%) and C26:0/C22:0 in 36 (67.9%). Mean VLCFA values were 1.96 ± 0.76 umol/L (C26:0), 1.18 ± 0.21 (C24:0/C22:0), and 0.03 ± 0.02 (C26:0/C22:0).

X-inactivation studies were performed on 43 (48.3%) of the 89 female patients in our chart review. Eight (18.6%) had a highly skewed pattern, 16 (37.2%) had a moderately skewed pattern, 16 (37.2%) had a random pattern, and 3 (7.0%) had an uninformative pattern.

Imaging Studies

Brain MRI data were available for 48 (53.9%) of female patients in our chart review. The median (IQR) age at brain MRI was 47.0 (38.9, 57.1) years. Twenty-three (47.9%) had nonspecific white matter changes, 21 (43.8%) had a normal MRI, 3 (6.3%) had mucosal thickening with an otherwise normal MRI, and only 1 (2.1%) had active cALD with contrast enhancement akin to the cerebral disease pattern seen in male patients.

Spine MRI data were available for 46 (51.7%) female patients. The median (IQR) age at spine MRI was 50.0 (39.0, 57.9) years. Only 2 (4.3%) had a normal MRI, and the remainder (95.7%) had abnormal findings. The most common abnormal findings were degenerative changes (n = 31%, 67.4%), disk herniation (n = 21%, 45.7%), spinal stenosis (n = 17%, 37.0%), facet joint disease (n = 12%, 26.1%), spinal cord atrophy (n = 7%, 15.2%), signal abnormality (n = 6%, 13.0%), spondylosis (n = 5%, 10.9%), spinal curvature (n = 5%, 10.9%), and edema (n = 3%, 6.5%).

Thirty-three (37.0%) female patients had undergone EMG and/or nerve conduction studies at a median (IQR) age of 46.3 (39.2, 54.4) years. Seventeen (51.5%) had normal studies, and 16 (48.5%) had abnormal findings. Specifically, 10 patients had electrophysiologic evidence of peripheral neuropathy, 3 radiculopathy, and 3 reduced motor or sensory response with unclear significance.

Table 3 Interventions and Management Strategies Used Among Female Individuals in Our Cohort (N = 127)

Medications/procedures		Nonpharmacologic	
Type of therapy/strategy	**n (%)**	**Type of therapy/strategy**	**n (%)**
Spasticity and gait management			
Antispasmodics	47 (37.0)	Mobility devices[a]	45 (35.4)
Oral medications	43 (33.9)	Unilateral walking aid	35 (27.6)
Intrathecal baclofen pump	4 (3.1)	Ankle-foot orthotics	25 (19.7)
Orthopedic surgery	41 (32.3)	Bilateral walking aid	22 (17.3)
Botox (lower extremities)	20 (15.7)	Wheelchair	8 (6.3)
Electrical muscle stimulation	4 (3.1)	Physical therapy	69 (54.3)
		Yoga/stretching	50 (39.4)
		Strength training[b]	48 (37.8)
		Resting splints	2 (1.6)
Pain management			
Analgesics	77 (60.6)	Chiropractic adjustments	34 (26.8)
Chronic analgesic use	46 (36.2)	Acupuncture/dry needling	20 (15.7)
Acute analgesic use	31 (24.4)	Heating pads	18 (14.2)
Steroid injection into joints	39 (30.7)	Massage therapy	8 (6.3)
Restless legs syndrome medications	25 (19.7)	Orthopedic belt	2 (1.6)
Nerve block or ablation	9 (7.1)	Leg compression stockings/cuffs	4 (3.1)
Intravenous immunoglobulins	3 (2.4)		
Urinary/bowel symptom management			
Bladder medications	36 (28.3)	Leak protection pads	46 (36.2)
Bowel medications	34 (26.8)	Limiting fluid/diuretic intake	25 (19.7)
Botox (bladder)	5 (3.9)	Pelvic floor therapy	21 (16.5)
		Self-catheterization	9 (7.1)
		Enema	2 (1.6)
Mental/emotional care			
Antidepressants/anti-anxiety medications	61 (48.0)	Emotional support therapy	9 (7.1)
Sleep medications	45 (35.4)		

[a] Twenty-nine individuals used more than 1 type of device in different situations or environments.
[b] Strength training included regular exercise (n = 43%, 33.9%), pilates (n = 12%, 9.4%), aquatic therapy (n = 8%, 6.3%), and tai chi (n = 3%, 2.4%).

Diagnostic Delay

Female individuals were diagnosed with ALD later than male patients. The median (IQR) age of ALD diagnosis was 37.0 (30.4, 46.2) years in our female cohort and 23.9 (15.0, 33.7) years in our male cohort ($p < 0.001$). Male patients were more likely to be diagnosed because of symptom presentation. Where the majority (53.7%) of male patients obtained a diagnosis due to symptom presentation, the majority (83.5%) of female individuals were diagnosed because of family screening ($p < 0.001$), either following a symptomatic diagnosis in a family member (65.4%) or after a younger relative was identified on newborn screening (NBS) (18.1%). Most symptomatic diagnoses (94.0%) were made in a male family member. Forty-six (36.2%) female individuals sought care for symptoms before diagnosis, and 22 of these patients were initially misdiagnosed, most commonly with multiple sclerosis or hereditary spastic paraplegia.

Barriers and Effect on QOL

Fifty-one (89.5%) of 57 interviewees reported encountering challenges to receiving sufficient medical care (Table 4). The most reported barrier was a lack of knowledge about ALD among health care providers (n = 40%, 70.2%). Fifty-three

Table 4 Challenges Faced by Female Individuals as Reported During Interviews (N = 57)

	n (%)
Barriers to medical care access	**51 (89.5)**
Lack of provider knowledge about ALD	40 (70.2)
Misbelief that female individuals do not develop symptoms	32 (56.1)
Shortage of specialists	32 (56.1)
Difficulty finding resources or information about ALD	27 (47.4)
Insurance not covering aspects of care	16 (28.1)
High expenses of traveling to appointments	15 (26.3)
Feeling the need to self-advocate to providers	14 (24.6)
Time commitment of traveling to appointments	10 (16.5)
ALD-related factors contributing to reduced QOL	**49 (86.0)**
Diagnosis in a family member	37 (64.9)
Physical symptoms	36 (63.2)
Effect of diagnosis on family	23 (40.4)
Management of disease	21 (36.8)
Mental symptoms	20 (35.1)
Social effect of explaining disease to others	14 (24.6)
Limitations with activities and/or traveling	11 (19.3)
Uncertainty or fear of the future	8 (14.0)
Guilt of passing the disease to children	5 (8.8)
Family planning	5 (8.8)
Inability to work	5 (8.8)
Activities of daily living affected	**25 (43.9)**
Using the toilet	15 (26.3)
Dressing/undressing	14 (24.6)
Bathing/showering	13 (22.8)
Transferring from bed/chair	11 (19.3)
Grooming	6 (10.5)
Eating	4 (7.0)

Abbreviations: ALD = adrenoleukodystrophy; QOL = quality of life.

(93.0%) had sought specialty care, including with a geneticist (66.7%), urologist (47.4%), orthopedic surgeon (35.1%), endocrinologist (31.6%), fertility specialist (29.8%), pain specialist (24.6%), physiatrist (24.6%), rheumatologist (15.8%), sleep specialist (12.3%), dietician (10.5%), podiatrist (8.8%), and/or gastroenterologist (7.0%).

Forty-nine (86.0%) interviewees reported that ALD reduced their QOL. Twenty-six (45.6%) reported a severe reduction, 12 (21.1%) a moderate reduction, and 11 (19.3%) a mild reduction. The factors contributing to a reduced QOL reported by participants are presented in Table 4.

Activities of daily living beyond walking were affected in 25 (43.9%). Fifteen (26.3%) reported that they had to make modifications to their home for accessibility.

Of the 30 interviewees who reported insomnia, 25 (83.3%) believed that ALD-related factors contributed to sleep disturbances, most commonly pain (n = 15), RLS (n = 15), urinary symptoms (n = 10), and anxiety (n = 6). Of the 41 interviewees who reported a history of anxiety or depression, 34 (82.9%) believe that their mental health symptoms were either caused by or exacerbated by their ALD diagnosis.

Discussion

This study highlights the disease burden in female individuals with ALD, with neurologic symptoms present in more than 90% of our female cohort. While pain and sensory symptoms were the earliest in onset, the symptoms of myelopathy increased with age and contributed to gait and bladder difficulties. Analgesics and antispasmodics were commonly used (60% and 37%, respectively), and more than a third of our female cohort required mobility devices. The rate of secondary complications was high, with 43% experiencing fractures from falls. In addition, female individuals experience mental health problems, fatigue, sleep disturbances, and sexual dysfunction. Despite high rates of depression and anxiety, few female individuals with ALD receive emotional support therapy.

Of interest, in the retrospective chart review, we found evidence of cerebellar ataxia and dystonia in 35% and 14% of female patients, respectively. These manifestations were not found to correlate with brain lesions on MRI, but we cannot exclude that subtle tract-specific abnormalities would be detected by advanced neuroimaging. A recent article has revealed that ABCD1 protein is highly expressed within deep gray nuclei such as the basal forebrain,[30] potentially pointing to an etiology of cerebellar ataxia and dystonia. In female heterozygotes, tract-specific dysfunction and poor connectivity in the presence of residual ABCD1 protein may be contributing to symptoms. However, these findings warrant further investigation and should be explored in future studies.

Brain imaging rarely explained the symptom burden because the cALD phenotype is extremely rare in the female patient population. Only 6 known cases of female patients with adult-onset cALD have been reported in the literature, with disease onset age ranging from 28 to 55 years.[31-35] One female patient in our cohort had active cALD with contrast enhancement primarily originating in the cerebellum and corticospinal tracts. This individual had a highly skewed X-inactivation pattern and VLCFA levels in the male ALD range.

Most female patients had degenerative changes in the vertebra, which are expected with age, and have been reported in healthy individuals as young as 20 years old.[36,37] However, it is likely that female individuals with ALD who already experience myelopathic symptoms are more susceptible to symptoms related to normal age-related vertebral changes, especially if these degenerative changes result in, for example, symptomatic neural foraminal stenosis or vertebral compression-related back pain.

In telephone interviews, 86% of participants volunteered that ALD reduces their QOL. Quality of life in female individuals is affected by many aspects beyond physical symptoms and disease management. The most reported contributing factor was diagnosis in a family member, typically a male child. This is consistent with previous findings that having a child with ALD has a larger effect on mental health than one's own disability.[9] Parents of children with cALD have a high risk of depression, with mothers being most affected.[38] Caring for an affected child and guilt associated with genetic inheritance may hinder female individuals from establishing care with a neurologist and addressing their own symptoms.[39]

Our findings highlight disparities in medical care received by female patients with ALD. While neurologic symptoms present approximately a decade later, the onset of symptoms is less likely to prompt the diagnosis of ALD in female compared with male patients. Delays in diagnosis and access to specialists make preventive guidance and lifestyle modifications less likely. It also prevents female individuals from making informed decisions regarding family planning and alternative reproductive options.[15]

Close to 90% of female participants in our prospective cohort reported encountering barriers to receiving medical care due to lack of provider awareness, scarcity of specialists and resources, and the financial and time commitments of medical appointments. Although these are common challenges faced in rare disease populations,[40] more than half of our cohort reported encountering the misconception that heterozygotes are rarely affected. Such barriers may further deter female individuals from seeking medical care. Nearly one-third of symptomatic female individuals with ALD do not present for regular medical check-ups.[9]

The introduction of ALD NBS in 2013 has contributed to earlier diagnosis in female individuals due to disease detection in female infants and screening of older family members.[41] Nearly one-fifth of our female cohort was diagnosed because of NBS in a younger relative. As NBS programs continue to be implemented across the United States, there will be an increasing number of female individuals with ALD identified, stressing the urgency of determining appropriate treatments, and establishing disease-specific standard of care guidelines for this patient population. Recent guidelines for longitudinal management of adults with ALD recommend a multidisciplinary approach which incorporates neurologic symptom management, psychosocial support, genetic counseling, and connecting patients with support networks and resources.[39]

One limitation of our study is that a large proportion of data relies on self-reported information, increasing the risk for recall bias. There is also a potential for selection bias because our retrospective cohort included patients seen in a specialty outpatient clinic and our prospective cohort was recruited through a patient advocacy group. Therefore, it is possible that our results overestimate disease burden and require future studies to become generalizable.

We conclude that symptoms related to myelopathy and neuropathy are prevalent in female individuals with ALD and contribute to mental health problems, injuries, and complications requiring treatment. Female individuals with ALD

disproportionately experience barriers to health care access such as diagnostic delays and lack of treatment options. There is an overwhelming need to improve QOL, raise disease awareness, and develop standard of care guidelines for this patient population.

Acknowledgment

The authors thank the patients who participated in this study for their time and dedication. The authors also thank ALD Connect for their assistance with patient recruitment.

Author Contributions

N.R. Grant: 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. Y. Li: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. L. De La Rosa Abreu: major role in the acquisition of data. C. Becker: major role in the acquisition of data; study concept or design. B.D. Wishart: drafting/revision of the manuscript for content, including medical writing for content; study concept or design. A. Nagy: drafting/revision of the manuscript for content, including medical writing for content. F.S. Eichler: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data. R. Sadjadi: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data.

Study Funding

This work was supported by the Hammer Family Fund for ALD Research and Therapies for Women, the Arrivederci ALD Foundation, and the Global Leukodystrophy Initiative Clinical Trials Network, NIH-NINDS U54NS11505.

Disclosure

N.R. Grant, L. De La Rosa Abreu, Y. Li, and C. Becker report no disclosures relevant to the manuscript. B.D. Wishart was supported by a National Institute of Child Health and Human Development grant (5R00HD093814), Patient-Centered Outcomes Research Institute Engagement award (Contract# EACB-35316), the Dr. Linda Michaud Pediatric Rehabilitation Research Fund, Hunter's Hope, and the Mucolipidosis Type IV Foundation. A. Nagy reports no disclosures relevant to the manuscript. F.S. Eichler is the founder and chair of ALD Connect, is the chair of European Leukodystrophy Association, medical advisor to Remember the Girls, is an executive committee member of Global Leukodystrophy Initiative, is founder of Swanbio Therapeutics, and received honoraria for presenting at NIH Rare Disease Day. R. Sadjadi reports no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

Publication History

Received by *Neurology* October 15, 2024. Accepted in final form December 11, 2024. Submitted and externally peer reviewed. The handling editors were Assistant Editor Marcello Moccia, MD, PhD and Deputy Editor Bradford Worrall, MD, MSc, FAAN.

References

1. Moser HW, Moser AB, Naidu S, Bergin A. Clinical aspects of adrenoleukodystrophy and adrenomyeloneuropathy. *Dev Neurosci*. 1991;13(4-5):254-261. doi:10.1159/000112170
2. Engelen M, Kemp S, de Visser M, et al. X-linked adrenoleukodystrophy (X-ALD): clinical presentation and guidelines for diagnosis, follow-up and management. *Orphanet J Rare Dis*. 2012;7(1):51. doi:10.1186/1750-1172-7-51
3. Dubey P, Raymond GV, Moser AB, Kharkar S, Bezman L, Moser HW. Adrenal insufficiency in asymptomatic adrenoleukodystrophy patients identified by very long-chain fatty acid screening. *J Pediatr*. 2005;146(4):528-532. doi:10.1016/j.jpeds.2004.10.067
4. Engelen M, Barbier M, Dijkstra IM, et al. X-linked adrenoleukodystrophy in women: a cross-sectional cohort study. *Brain*. 2014;137(3):693-706. doi:10.1093/brain/awt361
5. 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(1):6. doi:10.1186/1750-1172-9-6
6. Schirinzi T, Vasco G, Aiello C, et al. Natural history of a cohort of *ABCD* variant female carriers. *Eur J Neurol*. 2019;26(2):326-332. doi:10.1111/ene.13816
7. Bachiocco V, Cappa M, Petroni A, et al. Pain study in X-linked adrenoleukodystrophy in males and females. *Pain Ther*. 2021;10(1):505-523. doi:10.1007/s40122-021-00245-0
8. Corre CS, Grant N, Sadjadi R, et al. Beyond gait and balance: urinary and bowel dysfunction in X-linked adrenoleukodystrophy. *Orphanet J Rare Dis*. 2021;16(1):14. doi:10.1186/s13023-020-01596-1
9. Schäfer L, Roicke H, Bergner CC, Köhler W. Self-reported quality of life in symptomatic and asymptomatic women with X-linked adrenoleukodystrophy. *Brain Behav*. 2023;13(3):e2878. doi:10.1002/brb3.2878
10. Horn MA, Nilsen KB, Jørum E, Mellgren SI, Tallaksen CM. Small nerve fiber involvement is frequent in X-linked adrenoleukodystrophy. *Neurology*. 2014;82(19):1678-1683. doi:10.1212/WNL.0000000000000415
11. Van den Veyver IB. Skewed X inactivation in X-linked disorders. *Semin Reprod Med*. 2001;19(02):183-192. doi:10.1055/s-2001-15398
12. Maier EM, Kammerer S, Muntau AC, Wichers M, Braun A, Roscher AA. Symptoms in carriers of adrenoleukodystrophy relate to skewed X inactivation. *Ann Neurol*. 2002;52(5):683-688. doi:10.1002/ana.10376
13. Watkiss E, Webb T, Bundey S. Is skewed X inactivation responsible for symptoms in female carriers for adrenoleucodystrophy? *J Med Genet*. 1993;30(8):651-654. doi:10.1136/jmg.30.8.651
14. Salsano E, Tabano S, Sirchia SM, et al. Preferential expression of mutant ABCD1 allele is common in adrenoleukodystrophy female carriers but unrelated to clinical symptoms. *Orphanet J Rare Dis*. 2012;7(1):10. doi:10.1186/1750-1172-7-10
15. Choi J, Kane T, Propst L, Spencer S, Kostialik J, Arjunan A. Not just carriers: experiences of X-linked female heterozygotes. *J Assist Reprod Genet*. 2021;38(10):2757-2767. doi:10.1007/s10815-021-02270-6
16. Dooley JM, Wright BA. Adrenoleukodystrophy mimicking multiple sclerosis. *Can J Neurol Sci*. 1985;12(1):73-74. doi:10.1017/s0317167100046631
17. Holmberg BH, Hägg E, Duchek M, Hagenfeldt L. Screening of patients with hereditary spastic paraparesis and Addison's disease for adrenoleukodystrophy/adrenomyeloneuropathy. *Acta Neurol Scand*. 1992;85(2):147-149. doi:10.1111/j.1600-0404.1992.tb04015.x
18. van Geel BM, Assies J, Haverkort EB, et al. Delay in diagnosis of X-linked adrenoleukodystrophy. *Clin Neurol Neurosurg*. 1993;95(2):115-120. doi:10.1016/0303-8467(93)90004-z
19. Stöckier S, Millner M, Molzer B, Ebner F, Körner E, Moser HW. Multiple sclerosis-like syndrome in a woman heterozygous for adrenoleukodystrophy. *Eur Neurol*. 1993;33(5):390-392. doi:10.1159/000116978
20. Shaw-Smith CJ, Lewis SJ, Reid E. X-linked adrenoleukodystrophy presenting as autosomal dominant pure hereditary spastic paraparesis. *J Neurol Neurosurg Psychiatry*. 2004;75(5):686-688. doi:10.1136/jnnp.2003.022970
21. Wilkins A, Ingram G, Brown A, et al. Very long chain fatty acid levels in patients diagnosed with multiple sclerosis. *Mult Scler*. 2009;15(12):1525-1527. doi:10.1177/1352458509351731
22. Costello DJ, Eichler AF, Eichler FS. Leukodystrophies: classification, diagnosis, and treatment. *Neurologist*. 2009;15(6):319-328. doi:10.1097/NRL.0b013e3181b287c8
23. Zhan ZX, Liao XX, Du J, et al. Exome sequencing released a case of X-linked adrenoleukodystrophy mimicking recessive hereditary spastic paraplegia. *Eur J Med Genet*. 2013;56(7):375-378. doi:10.1016/j.ejmg.2013.04.008
24. Berger J, Pujol A, Aubourg P, Forss-Petter S. Current and future pharmacological treatment strategies in X-linked adrenoleukodystrophy. *Brain Pathol*. 2010;20(4):845-856. doi:10.1111/j.1750-3639.2010.00393.x
25. Volmrich AM, Cuénant LM, Forghani I, Hsieh SL, Shapiro LT. ABCD1 gene mutations: mechanisms and management of adrenomyeloneuropathy. *Appl Clin Genet*. 2022;15:111-123. doi:10.2147/TACG.S359479
26. 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. doi:10.1186/s13023-019-1008-6

27. 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. doi:10.1001/jamanetworkopen.2019.20356
28. Rattay TW, Rautenberg M, Söhn AS, et al. Defining diagnostic cutoffs in neurological patients for serum very long chain fatty acids (VLCFA) in genetically confirmed X-Adrenoleukodystrophy. *Sci Rep*. 2020;10(1):15093. doi:10.1038/s41598-020-71248-8
29. Allen RC, Zoghbi HY, Moseley AB, Rosenblatt HM, Belmont JW. Methylation of HpaII and HhaI sites near the polymorphic CAG repeat in the human androgen-receptor gene correlates with X chromosome inactivation. *Am J Hum Genet*. 1992;51(6):1229-1239.
30. Gong Y, Laheji F, Berenson A, et al. Role of basal forebrain neurons in adrenomyeloneuropathy in mice and humans. *Ann Neurol*. 2024;95(3):442-458. doi:10.1002/ana.26849
31. Pilz P, Schiener P. Kombination von Morbus Addison und Morbus Schilder bei einer 43 jährigen Frau [Combination of Addison's and Schilder's disease in a woman aged 43 years (author's transl)]. *Acta Neuropathol*. 1973;26(4):357-360. doi:10.1007/BF00688083
32. Simpson RH, Rodda J, Reinecke CJ. Adrenoleukodystrophy in a mother and son. *J Neurol Neurosurg Psychiatry*. 1987;50(9):1165-1172. doi:10.1136/jnnp.50.9.1165
33. Schlote W, Molzer B, Peiffer J, et al. Adrenoleukodystrophy in an adult female. A clinical, morphological and neurochemical study. *J Neurol*. 1987;235:1-9. doi:10.1007/BF00314189
34. Jung HH, Wimplinger I, Jung S, Landau K, Gal A, Heppner FL. Phenotypes of female adrenoleukodystrophy. *Neurology*. 2007;68(12):960-961. doi:10.1212/01.wnl.0000257129.51273.73
35. Chen X, Chen Z, Huang D, Liu X, Gui Q, Yu S. Adult cerebral adrenoleukodystrophy and Addison's disease in a female carrier. *Gene*. 2014;544(2):248-251. doi:10.1016/j.gene.2014.04.056
36. Machino M, Ito K, Ando K, et al. Normative magnetic resonance imaging data of age-related degenerative changes in cervical disc morphology. *World Neurosurg*. 2021;152:e502-e511. doi:10.1016/j.wneu.2021.05.123
37. Wocial K, A Feldman B, Mruk B, Sklinda K, Walecki J, Waśko M. Imaging features of the aging spine. *Pol J Radiol*. 2021;86:e380-e386. doi:10.5114/pjr.2021.107728
38. Kuratsubo I, Suzuki Y, Shimozawa N, Kondo N. Parents of childhood X-linked adrenoleukodystrophy: high risk for depression and neurosis. *Brain Dev*. 2008;30(7):477-482. doi:10.1016/j.braindev.2007.12.012
39. Kornbluh AB, Baldwin A, Fatemi A, et al. Practical approach to longitudinal neurologic care of adults with X-linked adrenoleukodystrophy and adrenomyeloneuropathy. *Neurol Genet*. 2024;10(5):e200192. doi:10.1212/NXG.0000000000200192
40. Kole A, Faurisson F. Rare diseases social epidemiology: analysis of inequalities. *Adv Exp Med Biol*. 2010;686:223-250. doi:10.1007/978-90-481-9485-8_14
41. Prinzi J, Pasquali M, Hobert JA, et al. Diagnosing X-linked adrenoleukodystrophy after implementation of newborn screening: a reference laboratory perspective. *Int J Neonatal Screen*. 2023;9(4):64. doi:10.3390/ijns9040064