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Stress and Quality of Life of Parents of Children With POLR3-Related Leukodystrophy: A Cross-Sectional Pilot Study

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Abstract

Background: RNA polymerase III (POLR3)-related leukodystrophy is a rare, neurodegenerative disorder characterized by hypomyelination, hypodontia, and hypogonadotropic hypogonadism. Despite the challenges of caring for a child with POLR3-related leukodystrophy, few studies have examined parents' disease burden. We sought to investigate quality of life and stress levels amongst parents of children with POLR3-related leukodystrophy. **Methods:** 43 parents of 32 children completed questionnaires on demographics, stress, quality of life, coping mechanisms, and experience of injustice. Detailed clinical data was collected from all patients. **Results:** Mothers ($t[27] = -8.66$, $P < .001$) and fathers ($t[16] = -4.47$, $P < .001$) had lower quality of life scores compared to the normative population, yet 80% of parents' stress scores fell within the normal stress range. Parents' experience of injustice scores were high (>60). Correlations were found between and within parents' scores. Years since disease onset and certain life circumstances correlated to mothers' quality of life scores; however, no correlation was found between modifiable factors and fathers' quality of life scores. Helpful coping mechanisms included those that allowed parents to be involved in their child's life. **Conclusions:** This is the first study to assess stress and quality of life in this population. These results shed light on the importance of implementing services and social support to improve the well-being of parents.

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Leukodystrophies are a group of rare, hereditary disorders affecting the cerebral white matter of the brain. They primarily affect the pediatric population, running a progressively debilitating course leading to premature mortality. Altogether, they have a prevalence of 1:4733 live births.[1] Hypomyelinating leukodystrophies are a subset of leukodystrophies characterized by a lack of myelin production and deposition during development, and can be diagnosed based on brain MRI findings. RNA polymerase III-related leukodystrophy (POLR3-HLD; MIM: 607694, 614381, 616494) is an autosomal recessive hypomyelinating leukodystrophy caused by biallelic pathogenic variants in genes encoding subunits of RNA Polymerase III (Pol III); *POLR3A,*[2] *POLR3B,*[3] *POLR1C,*[4] *POLR3D,*[5] and *POLR3K.*[6] Pol III is an essential enzyme responsible for the synthesis of small noncoding RNAs, the majority of which are crucial for transcriptional control, RNA processing, ribosomal assembly, and protein translation.[7,8]

POLR3-related leukodystrophy, also known colloquially as 4H leukodystrophy because of its characteristic clinical features of hypomyelination, hypodontia, and hypogonadotropic hypogonadism, typically presents during childhood with delayed milestones and/or motor regression. Cerebellar features typically predominate, with progressive ataxia, dysmetria, and dysarthria, while pyramidal and extrapyramidal (ie, dystonia[9,10]) signs are usually less prominent. Cognitive involvement is common, but variable in severity, and may include learning and intellectual disabilities, behavioral abnormalities, and/or cognitive regression.[11,12] Endocrine manifestations (ie, delayed/arrested/absent puberty, or short stature[13]) and ocular anomalies (typically myopia) are often seen.[14] POLR3-related leukodystrophy is known to range in severity, spanning from milder forms with late-onset manifestations to more severe early presentations in infants with various defined phenotypes, depending on the specific combination of mutations.[6,11,12,15-19] Although disease manifestations can be variable, patients with biallelic variants in *POLR3A* have been associated with a more rapid disease progression compared to individuals with variants in *POLR3B.*[11] To date, no therapeutic interventions are available for POLR3-related leukodystrophy beyond symptom management.

Children with POLR3-related leukodystrophy require constant yet ever-evolving care because of the multisystemic and gradual progression of the disease. Consequently, as seen in other rare diseases, parents face increased parental responsibilities combined with the challenges of accessing specialized health care and the emotional burden of their child's disease progression.[20] Indeed, caring for a chronically ill child can have a substantial impact on a parent's stress levels and quality of life (QoL), placing these parents at an elevated risk for adverse mental health outcomes such as anxiety or depression.[21] This, in turn, can impact a parent's ability to effectively navigate and cope with their child's disease,[22-25] influencing their interactions and responsiveness toward their child, thereby affecting their child's growth and behavior.[26] Thus, identifying modifiable factors significantly influencing parental quality of life and stress are vital for improving outcomes for patients, their parents, and families. Caregiver susceptibility to increased stress and lower quality of life is determined by a variety of psychosocial, environmental, and personal factors. These include personal circumstances,[20] the availability of support systems,[27,28] the frequency of beneficial vs maladaptive coping mechanisms used,[29-31] and an individual's own appraisal of his or her situation, framed as perceived injustice.[23,32,33] Further, the nature of the child's disease, including disease severity and duration, degree of impairment, and the presence of specific clinical features such as physical impairments,[34-36] sleep,[35,37] and behavioral issues[34] have been demonstrated to influence parental stress levels and overall quality of life.

Despite POLR3-related leukodystrophy's progressive nature and the elevated risks associated with lower quality of life and higher stress, there is limited knowledge on the effects of this disease in this parent population. A pilot study of patients with leukodystrophies and genetically determined leukoencephalopathies reported poorer health-related quality of life[38] and higher parental stress levels compared to families with healthy children.[39] Furthermore, clinical variables such as the degree of functional impairment and behavior were associated with increased maternal stress levels, clinical characteristics commonly associated with POLR3-related leukodystrophy, suggesting POLR3-related leukodystrophy parents may be at risk of high stress.[39] In this study, we assessed parents' quality of life and stress levels and identified clinical, psychosocial, and personal factors that may impact these levels.

Patients and Methods

Participants

The study sample consisted of parents of children with POLR3-related leukodystrophy recruited from the Leukodystrophy and Neurometabolic Diseases Clinic at the Montreal Children's Hospital, or who were referred from international collaborators between September 2021 and December 2022. Inclusion criteria included parents of patients with a confirmed POLR3-related leukodystrophy molecular diagnosis, parents that were either considered primary or secondary caregivers, and parents who lived with their affected child(ren). Exclusion criteria included parents who were not literate in English or French. This study was approved by the Research Ethics Board of the McGill University Health Centre Research Institute (11-105-PED, 2019-4972). All participants were informed about the research study, and written informed consent was obtained. All data was collected, recorded, and assessed in a standardized fashion by researchers at the Montreal Children's Hospital.

Questionnaires

Several questionnaires and their instructions were shared in-person or sent electronically to all parents, and were available in English or French. These questionnaires included a demographics questionnaire; the PedsQL Family Impact Module,[40] which measures the impact of pediatric chronic health conditions on parents' quality of life; the Parenting Stress Index 4th Edition (PSI),[41] the Stress Index for Parents of Adolescents (SIPA),[42] or the Parental Stress Scale (PSS),[43] which assess the stress levels through one's parenting role and relationship with children, adolescents, or adult children, respectively; the Coping Health Inventory for Parents (CHIP),[44] which focuses on parents' methods for coping with the responsibilities of a child with a chronic medical condition, and the Injustice Experiences Questionnaire (IEQ),[45] which determines the causes and consequences of injustice appraisals in situations of those with physical and mental health conditions (Table 1). These questionnaires were chosen based on their strong validity, reliability, and consistent use in other studies with populations with similar chronic illnesses.[38,46-51]

Clinical History

Updated medical records of clinical visits within 1 to 6 months prior to the questionnaires' administration were reviewed. Recorded clinical information included age of onset, years since diagnosis, relevant clinical features such as spasticity, tremor, dystonia, ataxia, dysmetria, dysarthria, sialorrhea, dysphagia, anarthria, delayed cognitive development, behavioral issues, fatigue, gait abnormality, wheelchair use, feeding tube dependency, the number of features present, and scores for severity scales of gross motor, fine motor, eating and swallowing, and speech (ie, Gross Motor Function Classification System,[52] Manual Ability Classification System,[53] Eating and Drinking Ability Classification System,[54] and Communication Function Classification System[55]) (Table 2).

Statistical Analysis

Statistical analyses were performed using SPSS, version 26.0. Parental stress and quality of life scores were the primary outcomes. Unpaired *t* tests were conducted to compare mothers' and fathers' stress percentile scores, and one-sample 2-tailed *t* tests were conducted to compare mothers' and fathers' raw stress, PedsQL Family Impact Module (and specific domains) and Parental Stress Scale scores with their respective normative population samples. The total mean score of each coping mechanism was also considered. Stress percentile scores and Injustice Experiences Questionnaire scores were considered on their respective ranges. Pearson correlation coefficients were used to study the relationship between continuous variables, different coping mechanisms, and other parental questionnaire scores along with mothers' and fathers' stress percentile and PedsQL Family Impact Module scores. Chi square analyses were performed to compare mothers' stress percentile scores with children's clinical features and certain parental life circumstances. Alpha was set to .05.

Table 1. List of Questionnaires.[a]

Measurement	Questionnaire	Applicable age range
Demographic information	• Demographic Questionnaire	All ages
Stress	• Parenting Stress Index 4th Edition (PSI)	<12 y
	• Stress Index for Parents of Adolescents (SIPA)	12-18 y
	• Parental Stress Scale (PSS)	>18 y
Quality of life	• Family Impact Module (FIM)	All ages
Coping mechanisms	• Coping Health Index for Parents (CHIP)	All ages
Experiences of injustice	• The Injustice Experiences Questionnaire (IEQ)	All ages

[a]This table includes a list of questionnaires used in this study, what each questionnaire measures, and the age groups for each questionnaire.

Results

Population Characteristics

A total of 43 caregivers (26 biological mothers, 1 foster mother, and 16 fathers, including 3 families with 2 affected children) participated in the study. The characteristics of the parent population are summarized in Table 3. Most parents reported being in a marital or common law relationship (33 of 43; 77%). The education level was statistically equivalent between genders, with most parents reporting postsecondary-level education (35 of 43; 81%). Employment status differed between parents, with more fathers reporting employment (14 of 16; 88%) compared to mothers (15 of 27; 56%); however, more than half of the total cohort was employed (29 of 43; 63%). All mothers presented as the primary caregiver.

32 patients (16 males and 16 females) ranging from 2 to 40 years old with POLR3-related leukodystrophy were included in the study. Characteristics of the patient population are summarized in Table 4. Most patients in the cohort were aged 12 years old or younger (12 of 32; 38%), compared to patients aged 12-18 years (10 of 32; 31%) or >18 years (10 of 32; 31%). The majority of children had biallelic pathogenic variants in *POLR3A* (14 of 32; 44%) and *POLR3B* (16 of 32; 50%), with only a minority with biallelic variants in *POLR1C* (2 of 32;

Table 2. List of Severity Scales.[a]

Outcome assessment	Populations for which the assessment has been validated	Age range
Gross Motor Function Classification System (GMFCS)	CP[52], MLD[56], AGS[57,58]	2-18 y
Manual Ability Classification System (MACS)	CP[53], AGS[59]	4-18 y
Eating and Drinking Classification System (EDACS)	CP[54]	3-18 y
Communication Function Classification System (CFCS)	CP[55], AGS[58]	2-18 y

Abbreviations: AGS, Aicardi-Goutières Syndrome; CP, Cerebral Palsy; MLD, Metachromatic leukodystrophy.
[a]This table includes a list of severity scale assessments, the populations for which the assessment has been validated for, and the age ranges for each assessment.

Table 3. Parent Characteristics.[a]

Demographics	Mother/ father, n	Mother/ father, %
Married	17/14	65/88
Common law	1/1	4/6
Single	7/1	27/6
Divorced	1/0	6/–
Unemployed	9/1	35/6
Retired	2/2	8/13
Employed	15/14	56/88
Postsecondary education	23/12	88/75
High school education	3/4	12/25
Household income less than $50 000	1/1	4/7
Household income between $50 000-100 000	12/7	46/44
Household income >$100 000	13/8	50/50
Parental life stress circumstances	**Mother/ father, n**	**Mother/ father, %**
Marital reconciliation	1/2	4/13
Marriage	0/0	–
Separation	0/0	–
Pregnancy	1/0	4/–
Other relative moved into household	1/0	4/–
Income increased substantially (20 or more)	2/2	8/13
Went deeply into debt	3/1	12/7
Moved to new location	0/0	–
Promotion at work	2/2	8/13
Income decreased substantially	1/2	4/13
Alcohol or drug problem	0/2	–/13
Death of close family friend	2/3	8/19
Began new job	1/3	4/19
Child entered new school	3/2	12/13
Trouble with superiors at work	0/2	–/13
Child having trouble with teachers at school	1/1	4/7
Legal problems	0/0	–
Lost job	0/0	–
Death of immediate family member	1/0	4/–
Demands or illness of aging parent	3/1	12/7
Serious injury or medical problem	1/1	4/7
Continuing or chronic medical condition	3/1	12/7

[a]This table summarizes parental demographics including relationship status, education, household income, as well as life circumstances.

Table 4. Patient Characteristics.

Patients	N = 32	Percentage
Sex		
Males	16	50%
Females	16	50%
Child age group (range)		
<12 years old	12	38%
12-18 years old	10	31%
+18 years old	10	31%
Genotype		
POLR3A	14	44%
POLR3B	16	50%
POLR1C	2	6%
Age at disease Onset		
<1 year old	6	19%
1-5 years old	20	63%
5-10 years old	2	6%
10 + years old	2	6%
Unknown	2	6%
Number of Years Since Disease Diagnosis		
0-5 years	11	34%
5-10 years	7	22%
10-15 years	3	9%
15 + years	6	19%
Unknown	5	16%
Clinical Features Present		
Abnormal Gait	21	66%
Delayed Cognitive Development	19	59%
Fatigue	3	9%
Gross Motor Function Issues	7	22%
Fine Motor Function Issues	4	13%
Spasticity	14	44%
Tremor	18	56%
Dystonia	10	31%
Ataxia	20	63%
Dysmetria	7	22%
Dysarthria	12	38%
Sialorrhea	7	22%
Dysphagia	11	34%
Wheelchair Use	19	59%
Feeding Tube	9	28%
Anarthria	6	19%
Behavioral Issues	5	16%
Scales	**N = 30**	**Median (IQR)**
GMFCS	26	4 (1,5)
MACS	15	4 (1,5)
EDACS	21	4 (1,5)
CFCS	20	3 (1,5)

Abbreviations: CFCS, Communication Function Classification System; EDACS, Eating and Drinking Ability Classification System; GMFCS, Gross Motor Function Classification System; MACS, Manual Ability Classification System.
[a]This table summarizes the characteristics of patients who participated in this study, such as sex, age group, mutated genes, age of clinical feature onset, number of years since diagnosis, present clinical features of the children, and number of completed scores per child as well as median scores of each severity scale.

6%). Age of disease onset primarily occurred between 1 and 5 years (20 of 32; 63%). At the time of questionnaire completion, the time elapsed since diagnosis varied from 0 to 5 years (11 of 32; 34%), 5 to 10 years (7 of 32; 22%), 10 to 15 years (3 of 32; 9%), and >15 years (6 of 32; 19%). The most prevalent clinical features reported were abnormal gait (21 of 32; 66%), ataxia (20 of 32; 63%), delayed cognitive development (19 of 32; 59%), and wheelchair use (19 of 32; 59%). Classification median scores for Gross Motor Function Classification

System, Eating and Drinking Ability Classification System, and Manual Ability Classification System were 4, indicating severe functional impairment.

PedsQL Family Impact Module Dimension Scores (Quality of Life Measurement)

The average total PedsQL Family Impact Module score (which included domains such as physical, emotional, social and cognitive functioning, communication, worry, daily activities, family relationships, parent health-related quality of life, and family functioning) for mothers was 48.36 ± 16.40, and 52.56 ± 20.72 for fathers. Lower scores on the PedsQL Family Impact Module indicate poorer quality of life or greater negative family impact.[60] These average scores were statistically significantly lower compared to the average total PedsQL Family Impact Module score of a normative population (75.70 ± 14.50) found in the literature.[59] The selection of this population was based on demographic similarities with our cohort. Therefore, mothers ($t[27] = -8.66$, $P < .001$) and fathers ($t[16] = -4.47$, $P < .001$) had statistically significantly lower quality of life scores compared to the normative population (Table 5). Analysis of each domain included within the PedsQL Family Impact Module questionnaire revealed that both mothers and fathers had significantly high mean scores in the family relationship domain ($M_{(mother)} = 62.41$, $M_{(father)} = 60.67$), indicating that this domain positively affects their quality of life. Conversely, both parents had significantly low mean scores in the worry domain ($M_{(mother)} = 34.71$, $M_{(father)} = 38.70$), indicating that this domain negatively impacts their quality of life.

Parenting Stress Index / Stress Index for Parents of Adolescents / Parental Stress Scale Dimension Scores (Stress Measurement)

When assessing stress levels, both mothers' (221.10 ± 59.60) and fathers' (228.20 ± 61.70) average total raw Parenting Stress Index 4th Edition / Stress Index for Parents of Adolescents scores were comparable to the normative samples.[41] These raw scores were then transformed into a percentile score. 70% of mothers and 73% of fathers had a score above the 50th percentile, where the percentile represents a score that is equal to or greater than the percentage of a standardized and representative normative sample. Percentile scores that fall between the 16th and 84th percentiles are considered within the normal range, scores between the 85th and 89th percentiles are considered high, and scores at the 90th percentile and above are within the clinically significant range.[41] Consequently, a majority of caregivers reported stress levels within the normal range (74% of mothers, 81% of fathers), with a subset falling within the high stress level range (15% of mothers, 9% of fathers), and a smaller subset within the clinically significant stress level range (7% of mothers, 9% of fathers). For parents of adult children, both mothers ($t[7] = -15.38$, $P < .001$) and fathers ($t[5] = -6.05$, $P = .002$) exhibited statistically significantly lower Parental Stress Scale scores compared to the normative sample[61] as outlined in Table 5.

Predictors of Stress and Quality of life: Injustice Experiences Questionnaire and Coping Health Inventory for Parents Dimension Scores

Parents reported variable outcomes on the Injustice Experiences Questionnaire, with the average parental score falling within or on the cusp of the average range (14-22). Specifically, mothers mostly fell within the average (14-22) to very high (>34) ranges, whereas fathers' scores ranged from very low (<5) to very high (>34). For the Coping Health Inventory for Parents questionnaire scores, coping mechanisms found to be the most helpful included investing oneself in their children ($M = 2.80 \pm 0.40$), doing activities with one's children ($M = 2.63 \pm 0.88$), and doing activities together as a family ($M = 2.60 \pm 0.49$). Conversely, the least helpful coping mechanisms included allowing oneself to get angry ($M = 1.43 \pm 0.49$), getting other members of the family to help with chores and tasks at home ($M = 1.33 \pm 0.85$), and believing that one's child(ren) will get better ($M = 1.48 \pm 1.15$).

There is no significant difference between the scores of mothers and fathers both within couples or across families in regards to the Parenting Stress Index 4th Edition / Stress Index for Parents of Adolescents, Parental Stress Scale, PedsQL Family Impact Module, Injustice Experiences Questionnaire, or Coping Health Inventory for Parents questionnaires. All results are outlined in Table 5.

Relationship Between Sociodemographic and Psychosocial Factors, Stress and Quality of Life

To explore the intricate multivariate relationship between stress, quality of life, and the sociodemographic and psychosocial profiles investigated, Pearson correlations were conducted for each category. Mothers' PedsQL Family Impact Module scores were found to correlate with their Injustice Experiences Questionnaire scores ($r = -0.52$, $P = .01$), Parenting Stress Index scores ($r = -0.56$, $P = .02$), as well as fathers' PedsQL Family Impact Module scores ($r = 0.74$, $P = .002$) and Injustice Experiences Questionnaire scores ($r = -0.71$, $P = .01$). These findings indicate that there is a correlation between mothers' quality of life and both parental experiences of injustice, stress levels, and fathers' quality of life. Similarly, fathers' PedsQL Family Impact Module scores were found to negatively correlate with their Injustice Experiences Questionnaire scores ($r = -0.84$, $P < .001$) and mothers' Injustice Experiences Questionnaire scores ($r = -0.80$, $P < .001$), indicating a correlation between fathers' quality of life and both parental experiences of injustice.

Moreover, mothers' and fathers' Parenting Stress Index percentile scores were positively correlated ($r = 0.89$, $P < .001$), indicating mutual influence between parental stress levels.

Table 5. Descriptive Statistics for Questionnaire Scores.[a]

Questionnaire scores	Mean ± standard deviation	Normative sample	*t* value	*P* value	Effect size (*d*)
PSI/SIPA (raw scores)					
Mothers	235.11±63.39	221.10 ± 59.60	221.10	.11	0.22
Fathers	242.45±64.09	228.20 ± 61.70	228.2	.13	0.27
PSI/SIPA (%ile)					
Mothers	60.65 ± 27.17	N/A	–	–	–
Fathers	62.27 ± 26.91	"	–	–	–
PSS					
Mothers	10.33 ± 2.80	27.78 ± 6.28	−15.38	<.001*	−5.81
Fathers	12.80 ± 5.54	27.78 ± 6.28	−6.05	.002*	−2.70
FIM					
Mothers	48.36± 16.40,	75.70 ± 14.50	−8.66	<.001*	−1.67
Fathers	52.56 ± 20.72	75.70 ± 14.50	−4.47	<.001*	−1.12
IEQ					
Mothers	23.44 ± 7.83	N/A	–	–	–
Fathers	22.82 ± 11.52	N/A	–	–	–
CHIP					
Mothers (domain 1)	34.96 ± 11.81	N/A	–	–	–
Fathers (domain 1)	31.06 ± 12.43	N/A	–	–	–
Mothers (domain 2)	35.14 ± 9.93	N/A	–	–	–
Fathers (domain 2)	36.19 ± 9.42	N/A	–	–	–
Mothers (domain 3)	14.96 ± 5.60	N/A	–	–	–
Fathers (domain 3)	14.00 ± 5.99	N/A	–	–	–
Helpful vs unhelpful coping mechanisms					
Investing myself in my children	2.80 ± 0.40	N/A	–	–	–
Doing things with my children	2.63 ± 0.88	N/A	–	–	–
Doing things together as a family (involving all members of the family)	2.60 ± 0.49	N/A	–	–	–
Allowing myself to get angry	1.43 ± 0.49	N/A	–	–	–
Getting other members of the family to help with chores and tasks at home	1.33 ± 0.85	N/A	–	–	–
Believing that my child(ren) will get better	1.48 ± 1.15	N/A	–	–	–

Abbreviations: CHIP, Coping Health Inventory for Parents; FIM, PedsQL Family Impact Module; IEQ, Injustice Experiences Questionnaire; PSI/SIPA, Parenting Stress Index / Stress Index for Parents of Adolescents; PSS, Parental Stress Scale

[a]The means and standard deviations were obtained for the questionnaire scores of mothers and fathers, as well as the normative sample (when applicable). One-sample *t* tests were performed on the PSI/SIPA raw scores, PSS scores, and FIM scores, and the effect sizes were represented by Cohen *d*.

*Statistically significant ($P < .05$).

Statistically significant correlations were also found between mothers' Parenting Stress Index scores and Coping Health Inventory for Parents scores for the following coping mechanisms: doing things with family relatives ($r = 0.80$, $P = .02$), trying to maintain family stability ($r = 0.51$, $P = .02$), involvement in social activities with friends ($r = 0.79$, $P = .02$), time spent alone ($r = –0.55$, $P = .02$), and purchasing gifts for oneself and/or other family members ($r = –0.62$, $P = .01$), determining that mothers' stress levels can be influenced by the type of coping mechanism practiced. Additionally, statistically significant correlations were found between mothers' PedsQL Family Impact Module scores and Coping Health Inventory for Parents scores for the following coping mechanisms: talking with the doctor about my concerns about my child(ren) with the medical condition ($r = 0.45$, $P < .05$), talking over personal feelings and concerns with a spouse ($r = 0.46$, $P < .05$), doing things with my children ($r = 0.45$, $P < .05$), and telling myself that I have many things I should be thankful for ($r = 0.44$, $P < .05$).

When exploring correlations with clinical features and medical history, a positive correlation was found between mothers' quality of life scores and years since disease diagnosis ($r = 0.49$, $P = .02$). Complete results are listed in Table 6.

A χ^2 analysis showed statistically significant relationships between Parenting Stress Index stress percentile scores of mothers and certain parental life circumstances such as debt (for mothers), $\chi^2(1, n = 15) = 12.94$, $P = .01$; substantial income decrease (for fathers), $\chi^2(1, n = 8) = 14.44$, $P = .04$; taking care of an ill parent (for fathers), $\chi^2(1, n = 17) = 11.91$, $P < .01$; suffering from an injury or chronic health condition (for fathers), $\chi^2(1, n = 17) = 11.91$, $P = .01$; and having a child enter a new school (for mothers), $\chi^2(1, n = 15) = 16.35$, $P = .01$. There is no statistically significant relationship found for fathers' Parenting Stress Index stress percentile scores. Multivariate analysis between parental scores and severity scores could not be performed because of the small sample size. Complete results are shown in Table 7.

Table 6. Pearson Correlation for Mothers' and Fathers' Stress and Quality of Life Scores. [a]

	Mothers' PSI/SIPA stress percentile	Mothers' FIM score	Fathers' PSI/SIPA stress percentile	Fathers' FIM score
Questionnaires				
PSI/SIPA				
Mothers	–	$r = -0.56$, $P = .02$*	$r = 0.89$, $P < .001$*	$r = -0.64$, $P = .05$
Fathers	$r = 0.89$, $P < .001$*	$r = -0.38$, $P = .28$	–	$r = -0.60$, $P = .09$
FIM				
Mothers	$r = -0.56$, $P = .02$*	–	$r = -0.38$, $P = .28$	$r = 0.74$, $P = .002$*
Fathers	$r = -0.64$, $P = .05$	$r = 0.74$, $P = .002$*	$r = -0.60$, $P = .09$	–
IEQ				
Mothers	$r = 0.21$, $P = .41$	$r = -0.52$, $P = .01$*	$r = 0.27$, $P = .44$	$r = -0.80$, $P < .001$*
Fathers	$r = 0.16$, $P = .65$	$r = -0.71$, $P = .01$*	$r = 0.42$, $P = .22$	$r = -0.84$, $P < .001$*
PSS				
Mothers	–	$r = 0.25$, $P = .59$	–	$r = -0.18$, $P = .77$
Fathers	–	$r = 0.37$, $P = .54$	–	$r = -0.05$, $P = .94$
CHIP [b]				
Mothers' domain 1	$r = -0.18$, $P = .48$	$r = 0.30$, $P = .16$	$r = -0.19$, $P = .60$	$r = -0.19$, $P = .60$
Fathers' domain 1	$r = -0.14$, $P = .71$	$r = 0.03$, $P = .91$	$r = -0.13$, $P = .74$	$r = -0.13$, $P = .74$
Mothers' domain 2	$r = -0.36$, $P = .13$	$r = 0.31$, $P = .15$	$r = -0.26$, $P = .46$	$r = -0.05$, $P = .94$
Fathers' domain 2	$r = -0.17$, $P = .66$	$r = -0.30$, $P = .32$	$r = -0.25$, $P = .51$	$r = -0.25$, $P = .51$
Mothers' domain 3	$r = -0.17$, $P = .50$	$r = 0.17$, $P = .45$	$r = -0.26$, $P = .46$	$r = -0.26$, $P = .46$
Fathers' domain 3	$r = -0.33$, $P = .38$	$r = -0.15$, $P = .61$	$r = -0.25$, $P = .51$	$r = -0.25$, $P = .51$
Continuous variables				
Age of feature onset	$r = 0.18$, $P = .45$	$r = -0.270$, $P = .17$	–	–
Years since diagnosis	$r = -0.17$, $P = .49$	$r = 0.49$, $P = .02$*	–	–
Current age	$r = -0.08$, $P = .75$	$r = 0.28$, $P = .18$	–	–
Number of siblings	$r = -0.05$, $P = .84$	$r = 0.06$, $P = .78$	–	–
Number of features	$r = 0.16$, $P = .51$	$r = 0.25$, $P = .20$	–	–
Number of life stress circumstances	$r = 0.09$, $P = .72$	$r = -0.17$, $P = .50$	–	–
Coping mechanisms				
Doing things with family relatives	$r = 0.80$, $P = .02$*	$r = -0.09$, $P = .79$	–	–
Trying to maintain family stability	$r = 0.51$, $P = .02$*	$r = -0.34$, $P = .25$	–	–
Involvement in social activities with friends	$r = 0.79$, $P = .02$*	$r = 0.18$, $P = .58$	–	–
Getting away by myself	$r = -0.55$, $P = .02$*	$r = 0.05$, $P = .88$	–	–
Purchasing gifts for oneself and/or other family members	$r = -0.62$, $P = .01$*	$r = -0.53$, $P = .08$	–	–
Talking with the doctor about my concerns about my child(ren) with the medical condition	$r = -1.35$, $P = .58$	$r = 0.45$, $P < .05$		
Talking over personal feelings and concerns with spouse	$r = -0.07$, $P = .76$	$r = 0.46$, $P < .05$		
Doing things with my children	$r = -0.32$, $P = .19$	$r = 0.45$, $P < .05$		
Telling myself that I have many things I should be thankful for	$r = 1.43$, $P = .55$	$r = 0.44$, $P < .05$		

Abbreviations: CHIP, Coping Inventory for Parents; FIM, PedsQL Family Impact Module; IEQ, Injustice Experiences Questionnaire; PSI/SIPA, Parental Stress Index/Stress Index for Parents of Adolescents; PSS, Parental Stress Scale.

[a]Pearson correlations were performed (results presented by *r*) for mothers' and fathers' PSI/SIPA and FIM scores, clinical features, and coping mechanisms (all other coping mechanisms not listed did not reach statistical significance). Dashes indicate that the correlation could not be performed because of similarities in the variables, or not enough data was available to render a correlational analysis.

[b]CHIP domain 1 indicates "maintaining family integration, cooperation, and an optimistic definition of the situation."[44] CHIP domain 2 indicates "maintaining social support, self-esteem, and psychological stability."[44] CHIP domain 3 indicates "understanding the medical situation through communication with other parents and consultation with medical staff."[44]

*Statistically significant ($P < .05$).

Table 7. Summary of χ^2 Analysis Results for Categorical Variables.[a]

Mothers' stress percentile score			
Categorical variables	χ^2 value	*P* value	Cramer *V*
Abnormal gait	17.00	.32	1.00
Delayed cognitive development	56.25	.29	0.97
Fatigue	13.00	.37	1.00
Spasticity	60.00	.18	1.00
Tremor	15.51	.42	0.93
Dystonia	17.00	.26	1.00
Ataxia	14.22	.43	0.92
Dysmetria	14.81	.39	0.93
Dysarthria	15.11	.44	0.92
Sialorrhea	15.11	.44	0.92
Dysphagia	16.95	.39	0.94
Wheelchair use	15.24	.51	0.90
Feeding tube	14.37	.57	0.87
Anarthria	20.00	.27	1.00
Behavioral issues	14.37	.57	0.87
GMFCS	59.22	.36	0.93
EDACS	55.00	.36	0.96
MACS	34.13	.41	0.94
CFCS	58.40	.25	0.96
Marital status	13.56	.48	0.48
Education	23.43	.61	0.61
Employment status	13.40	.38	0.38
Household income	25.63	.36	0.36
Mothers' debt	12.94	.01*	0.89
Fathers' substantial income decrease	14.44	.04*	0.80
Fathers taking care of an ill parent	11.91	.003*	0.84
Fathers suffering from an injury or chronic health condition	11.91	.01*	0.84
Mothers having a child enter a new school	16.35	.01*	0.75

Abbreviations: CFCS, Communication Function Classification System; EDACS, Eating and Drinking Ability Classification System; GMFCS, Gross Motor Function Classification System; MACS, Manual Ability Classification System.
[a]χ^2 analysis was conducted for each categorical variable. Cramer *V* represents the strength of the relationship between variables. Categorical variables such as the child's clinical features and parents' demographics were not found to contribute to mothers' stress percentile scores ($P > .05$). Some parental life stress situations were found to contribute to mothers' stress percentile scores. Relationships between the variables listed and fathers' stress percentile scores were omitted because of missing data, and other parental life stress situations were omitted to keep the table succinct; however, all situational life factors that were excluded were not found to contribute to mothers' stress percentile scores ($P > .05$). Analysis between fathers' scores and severity scores could not be performed because of the small sample size.
*Statistically significant ($P < .05$).

Discussion

Caring for children with POLR3-related leukodystrophy poses multifaceted challenges because of their child's ever-evolving symptoms and the progressive nature of their disease. Our study investigated the impact of caregiving on self-reported stress and quality of life, as well as their inter-relationships and determinants, among parents of children with POLR3-related leukodystrophy. Overall, our cohort exhibited stress levels within the normal range, but lower quality of life compared with the normative samples, highlighting the importance of considering and supporting caregiver well-being in POLR3-related leukodystrophy disease management.

Interestingly, approximately 80% of our cohort exhibited stress percentile scores within the normal range, contrasting results found in previous studies.[62-66] Stress is a subjective experience that can only be measured in relation to previous experiences, and usually fluctuates over time. Often, feelings of heightened stress will coincide with moments of shock from the novelty of the situation, uncertainty, or circumstantial instability. In our cohort, the average time elapsed since diagnosis with POLR3-related leukodystrophy was 11 years, indicating parents had sufficient time to adapt to their child's condition and care plan, potentially contributing to extended periods of stability and thereby lowering stress levels to normal ranges. This study would need to be expanded to more recently diagnosed individuals to explore this explanation. Additionally, factors such as access to a Leukodystrophy Center of Excellence and availability of resources may be a reason for contributing to normal stress scores, as our cohort is being followed at specialized leukodystrophy centers with knowledge in leukodystrophy care and research that also offer resources (ie, receiving adaptable equipment for their child or financial support). These factors may alleviate some of the challenges of caring for a child with this disease. Notably, parental stress did not correlate with the child's clinical features or disease progression, potentially because of the minimal behavioral issues observed in our cohort and the generally happy nature of children (mentioned by parents) affected by this disease. However, a larger study with patients with greater symptom heterogeneity may be needed to validate this finding. Although life stressors did not correlate significantly with parental stress level, parents with clinically significant stress levels were also more likely to have experienced increased debt or financial issues,[67,68] personal medical issues,[69] and/or starting a new job, all of which are factors known to impact stress. This suggests that although parents may be well-adjusted to their life circumstances and caregiving responsibilities, they may be more sensitized to stressful life events, explaining the coincidence of these factors in the clinically stressed group.

Despite the relatively normal stress levels among our cohort, parents of children with POLR3-related leukodystrophy had significantly lower quality of life than the normative sample, primarily in domains relating to feelings of worry. Parents reported significant distress associated with the child's illness and treatments, how others perceived their child's illness, the future of their child, and the impact of the illness on the family unit. Feelings of worry and apprehension are common among parents of children with chronic diseases,[70,71] potentially because of the paucity of information regarding long-term prognosis as well as the lack of supportive interventions offered. Constant worrying by the parent for their ill child can place these parents at high risk for developing mood-related disorders, most commonly, anxiety and depression.[70,72] Despite the overall low quality of life, family relationships remained unaffected, suggesting that a strong family unit can promote

parental well-being. Cohesive familial functioning is associated with high levels of family support and resilience which are protective factors for both stress and quality of life.[73]

Although no specific disease characteristics were associated with quality of life scores, time elapsed since diagnosis was an important predictor of increased quality of life in mothers. Diagnosis is a challenging and stressful time for a caregiver, as one must process new and potentially upsetting information and adapt to novel care plans. Moreover, although POLR3-related leukodystrophy is a neurodegenerative disorder, progression can be relatively slow, contributing to perceived stability and adaptation to the situation, ultimately improving quality of life. This correlation was not found in fathers, however, which may reflect the mothers' role as the primary caregiver. Certain psychosocial factors were found to influence quality of life in POLR3-related leukodystrophy parents. Although parents reported diverse feelings of injustice or unfairness of their situations, parents who perceived more injustice within their situations also reported lower quality of life. Greater perceived experiences of injustice are associated with feelings of blame for, irreparability of, and repetitive thought about their child's situation, perpetuating the cycle of injustice and leading to feelings of isolation and loss.[45] Furthermore, the use of specific adaptive coping mechanisms was found to predict higher maternal quality of life. Coping strategies involving speaking or discussing one's thoughts, feelings, and decisions with others regarding their child were associated with improved quality of life. This is not surprising as talk therapies and promoting emotional expression is a known and effective therapeutic strategy to improving one's well-being.[74] Although not predictive of increased quality of life, other helpful coping mechanisms for parents included those centered around involvement in their children's lives, such as spending time and completing activities together. Conversely, the least helpful coping mechanisms involved feelings of anger, hope that the child will improve, and asking other family members to help around the house—coping mechanisms that did not have a direct effect on the child's condition.

An overall limitation of this study was the relatively small population size. Although these numbers are acceptable given the rarity of POLR3-related leukodystrophy, having a larger sample size may allow for more significance in the results and the ability to draw stronger conclusions. One recommendation for future studies would be to use a longitudinal mixed-methods quantitative and qualitative approach to capture the evolution of this population over time. Parental stress and poor quality of life in our population are hypothesized to be at its peak at the time of diagnosis and at the end of life, with fluctuations throughout life as a patient's health status and parents' and family's life situation changes, which can also affect obtained results. We identified some contributing factors to this but could not obtain granular information as to why parents answered as they did. Although a few parents sent us explanations that complemented their results, a formal qualitative research approach would allow us to understand the entirety of parents' situations and may further help us draw conclusions from these results. Lastly, the fact that questionnaires were only available in English and French may have excluded participants who speak other languages, potentially overlooking individuals at higher risk of stress and low quality of life. However, families from several countries within North America, Europe, and Africa were included to address this limitation, allowing for the best possible chance of both diversifying and generalizing the sample.

Conclusion

Our study indicates that parents of children with POLR3-related leukodystrophy are at risk of low quality of life, but not necessarily high stress levels. Time elapsed since diagnosis, feelings of perceived injustice, and the use of adaptive coping mechanisms were found to significantly predict quality of life in this population. We highlight the importance of early quality of life interventions for newly diagnosed families, which may include psychological,[75] educational,[76] or community/social group-based support,[76,77] access to services pertaining to their child's health,[76] or financial resources[78] when necessary, which have been shown to improve quality of life outcomes for families coping with an array of chronic diseases. These findings pinpoint specific areas requiring support, including implementing effective communication strategies for caregivers and devising approaches to alleviate a caregiver's worries about their child's health and prognosis. Additionally, our results importantly show that although quality of life and stress may be interrelated, they are not the same entity and therefore must both be taken into account when assessing overall parental well-being. A larger longitudinal study on parental stress levels and quality of life throughout their child's disease would be an interesting future path and beneficial to further our understanding of how POLR3-related leukodystrophy can impact caregivers.

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Author Contributions

LL and GB contributed to the study design, and LL conducted the study and wrote the first draft of the manuscript. AC contributed to drafting the manuscript. HT, SF, AL, and FE aided in the recruitment of participants. SF translated questionnaires. LL and XC performed the statistical analyses. GB supervised the entire study. All authors reviewed the manuscript for intellectual content and approved the final version.

Declaration of Conflicting Interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: EB has been a consultant for Orchard Therapeutics, and Advisory Board for Novartis, PTC, Biogen, Pfizer, Roche. SK is a site investigator for the Ionis Alexander disease clinical trial (2022-present) and BioMarin long-term extension study for CLN2 patients treated with Brineura (2022-present). She was also a consultant for Veristat

regarding MLD (2022) and is on the board of directors for the United Leukodystrophy Foundation. ER is a consultant for Taysha Gene Therapies (2023-present) and Acadia (2023-present). She is the PI on the REVEAL trail for Rett syndrome by Taysha Gene Therapies (2022-present). She is/was a subinvestigator on a therapeutic trial by BioMarin (2021-present), Glaxo Smith Kline (2015-2016), Pfizer (2017-2018), and Acadia (2020-2021). AV receives funding from Ionis, Sana, Illumina, Orphan Disease Center, Homology, Affinia, Sanofi, Orchard therapeutics, Takeda, Biogen, Boehringer Ingelhiem, Eli Lilly, Synaptix Bio, and PMD Foundation without any personal compensation. GB is/was a consultant for Orchard Therapeutics (2023), Passage Bio Inc (2020-2022), and Ionis (2019). She is/was a site investigator for the Alexander's disease trial of Ionis (2021-present), Metachromatic leukodystrophy of Shire/Takeda (2020-2021), Krabbe (2021-2023), and GM1 gene therapy trials (2021-present) of Passage Bio, GM1 natural history study from the University of Pennsylvania sponsored by Passage Bio (2021-present) and Adrenoleukodystrophy/Hematopoietic stem cell transplantation natural history study of Bluebird Bio (2019), and a site subinvestigator for the MPS II gene therapy trial of Regenxbio (2021-present) and the MPS II clinical trial of Denali (2022-present). She has received unrestricted educational grants from Takeda (2021-2022). All other authors did not have any potential conflicts of interest with respect to the research or publication of this article.

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