Stress and Quality of Life of Parents of Children with POLR3-related Leukodystrophy

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Abstract

Leukodystrophies (LD) are a group of rare genetic disorders characterized by abnormal cerebral white matter whose main constituent is myelin, produced by oligodendrocytes. Disease-onset often occurs in childhood, and follows a progressive course, leading to increasing disability and premature death. Leukodystrophies can be classified by brain MRI characteristics as either non-hypomyelinating or hypomyelinating, according to whether there is abnormal myelin homeostasis or abnormal myelin deposition during development, respectively. RNA polymerase III-related leukodystrophy (POLR3-related leukodystrophy, POLR3-HLD or 4H) is a hypomyelinating leukodystrophy caused by biallelic pathogenic variants in genes that encode for RNA polymerase III subunits, including *POLR3A, POLR3B, POLR1C,* and *POLR3K*. Clinically, it is characterized by a combination of three cardinal features: **h**ypomyelination, **h**ypodontia and **h**ypogonadotropic **h**ypogonadism, hence the common abbreviation, 4H.

While studies of other chronic diseases with similar debilitating features have been shown to negatively impact the quality of life (QoL) of the affected children, as well as caregiver's stress, studies investigating parental stress and QoL of parents of patients with 4H are especially lacking, despite being a devastating disease that requires constant multidisciplinary care. As well, lower QoL and higher stress level outcomes are strongly associated with parental mental health issues which may impact the overall well-being of the parent and care of the child, hence re-affirming its importance.

We therefore chose to investigate the stress level and QoL of parents of patients with POLR3-related leukodystrophy in a cross-sectional study. Several questionnaires such as Demographics, Family Impact Module (FIM), Parenting Stress Index 4th Edition (PSI), Parental Stress Scale (PSS), Stress Index for Parents of Adolescents (SIPA), the Coping Health Inventory for Parents (CHIP), and the Injustice Experiences Questionnaire (IEQ) were administered to 27

mothers and 16 fathers, and patients' clinical assessments were collected to assess patients' characteristics and disease severity, along with parents' well-being, stress-impacting factors, perceptions of injustice, and coping mechanisms.

Parents of children with POLR3-related leukodystrophy had lower QoL compared to normative samples, and approximately 80% of parents' stress scores fell within normal stress level ranges. Mothers' perceived injustice scores ranged from average to high, and fathers' ranged from very low to very high. Correlations were found between and within mothers' and fathers' scores, such as QoL, stress level, and IEQ scores. Helpful coping mechanisms had a common theme of parents being directly involved in their child's life, and least helpful coping mechanisms were those that seemed to be irrelevant to their child's care. As well, some of the less helpful coping mechanisms became more helpful as stress increased. Relationships were found between mothers' stress scores, years since disease onset and certain life stress circumstances.

This is the first study that conducts a thorough examination of the overall well-being of parents with children suffering from POLR3-related leukodystrophy. The results show the importance of implementing services and social support to improve the quality of life of these parents.

Key words: leukodystrophy, POLR3-related leukodystrophy, 4H leukodystrophy, stress, parental stress, quality of life, experiences of injustice, coping mechanisms

Résumé

Les leucodystrophies (LD) sont un groupe de maladies génétiques rares caractérisées par des anomalies de la substance blanche cérébrale, laquelle est constituée majoritairement de myéline qui est produite par les oligodendrocytes. La maladie se déclare souvent dans l'enfance et suit une évolution progressive, entraînant souvent des handicaps croissants et un décès prématuré. Les leucodystrophies peuvent être classées comme non hypomyélinisantes ou hypomyélinisantes. Cela dépend soit respectivement d'une homéostasie anormale de la myéline ou d'un dépôt anormal de myéline au cours du développement, ainsi que des caractéristiques à l'IRM cérébrale. La leucodystrophie liée à l'ARN polymérase III (leucodystrophie liée à POLR3, POLR3-HLD ou 4H) est un trouble hypomyélinisant causé par des variants pathogènes bialléliques dans des gènes qui codent pour des sous-unités de l'ARN polymérase III, notamment *POLR3A*, *POLR3B*, *POLR1C* et *POLR3K*. Cliniquement, elle se caractérise par une combinaison de trois caractéristiques cardinales: **h**ypomyélinisation, **h**ypodontie et **h**ypogonadisme **h**ypogonadotrope, d'où l'abréviation courante, 4H.

Alors que des études portant sur d'autres maladies chroniques présentant des caractéristiques débilitantes similaires ont montré un impact négatif sur la qualité de vie (QdV) des enfants affectés, ainsi que sur le stress des soignants, les études portant sur le stress parental et la QdV des parents de patients atteints de 4H font particulièrement défaut, bien qu'il s'agisse d'une maladie dévastatrice qui nécessite une prise en charge constante et multidisciplinaire. De plus, une QdV plus faible et un niveau de stress plus élevé sont fortement associés aux problèmes de santé mentale des parents, ce qui peut avoir un impact sur le bien-être du parent et les soins de l'enfant, d'où son importance.

Nous avons donc choisi d'étudier la qualité de vie et le stress des parents de patients atteints de leucodystrophie liée à POLR3 dans une étude transversale. Plusieurs questionnaires tels que les données démographiques, le Parental Stress Index 4e édition (PSI), le Parental Stress Scale (PSS), le Stress Index for Parents of Adolescents (SIPA), le Injustice Experiences Questionnaire (IEQ), le Coping Health Inventory for Parents (CHIP) et le Family Impact Module (FIM) ont été administrés à 27 mères et 16 pères, et des évaluations cliniques des patients ont été recueillies de manière transversale pour évaluer le bien-être des parents, les facteurs influençant le stress, les perceptions d'injustice et les mécanismes d'adaptation, de même que les caractéristiques cliniques et la sévérité de la maladie des patients.

Les parents d'enfants atteints de leucodystrophie liée à POLR3 avaient une qualité de vie inférieure à celle des échantillons normatifs, et approximativement 80 % de scores de stress parental se situaient dans les limites de la normale. Les scores d'injustice perçue des mères allaient de moyen à élevé, et ceux des pères allaient de très faible à très élevé. Des corrélations ont été trouvées entre et au sein des scores des mères et des pères, comme la qualité de vie, les niveaux de stress, et les scores de l'IEQ. Les mécanismes d'adaptation utiles comprenaient un thème commun par lequel les parents sont directement impliqués dans la vie de leur enfant, et les moins utiles étaient ceux qui n'avaient rien à voir avec les soins de leur enfant. Aussi, certains des mécanismes d'adaptation moins utiles sont devenus plus utiles lorsque le stress augmentait. Des liens ont été établis entre les scores de stress des mères, le nombre d'années écoulées depuis l'apparition de la maladie et certaines circonstances de stress de la vie.

Il s'agit de la première étude qui a procédé à un examen approfondi du bien-être général des parents d'enfants souffrant de leucodystrophie liée à POLR3. Les résultats montrent

l'importance de mettre en place des services et un soutien social pour améliorer la qualité de vie de ces parents.

Mots clés: leucodystrophie, leucodystrophie liée à POLR3, leucodystrophie 4H, stress, stress parental, qualité de vie, expériences d'injustice, mécanismes d'adaptation

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Author Contributions

LL and GB contributed to the study design, and LL conducted the study and wrote the background literature review (Chapter 1). HT, SF and GB aided in the recruitment of participants. SF translated questionnaires and the abstract. LL collected the data and performed the statistical analyses, with help, ideas and expertise from XC (Chapter 2 and Chapter 3). LL wrote the discussion and conclusion sections, drafted the thesis and created the tables (Chapter 4 and Chapter 5). GB reviewed the thesis for intellectual content and supervised the entire study.

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List of Abbreviations

Molecular Biology and Genetics

POL III ---------- RNA Polymerase III

POLR3A ---------- Ribonucleic Acid Polymerase III Subunit A gene

POLR3B ---------- Ribonucleic Acid Polymerase III Subunit B gene

POLR1C---------- Ribonucleic Acid Polymerase I Subunit C gene

POLR3K---------- Ribonucleic Acid Polymerase III Subunit K gene

RNA ---------- Ribonucleic Acid

tRNA---------- Transfer Ribonucleic Acid

Questionnaires and Scales

CFCS ---------- Communication Function Classification System

CHIP ---------- Coping Health Inventory for Parents questionnaire

EDACS ---------- Eating and Drinking Ability Classification System

FIM ---------- Family Impact Module

GMFCS ---------- Gross Motor Function Classification System

IEQ ---------- Injustice Experiences Questionnaire

MACS ---------- Manual Ability Classification System

NeuroQOL ---------- Neuro Quality of Life questionnaire

PSI ---------- Parenting Stress Index 4th edition questionnaire

PSS ---------- Parental Stress Scale

SIPA ---------- Stress Index for Parents of Adolescents questionnaire

WHOQOL-100 ---------- World Health Organization Quality of Life – 100 questionnaire

Diseases

AIMP1 ------- Aminoacyl-tRNA Synthetase Complex-Interacting Multifunctional Protein 1 gene

AIMP2 ------- Aminoacyl-tRNA Synthetase Complex-Interacting Multifunctional Protein 2 gene

ADDH ---------- Ataxia, delayed dentition, and hypomyelination

COPD ---------- Chronic obstructive pulmonary disease

CTX---------- Cerebrotendinous xanthomatosis

GLIA ---------- Global Leukodystrophy InitiAtive

gLEs ---------- Genetically Determined Leukoencephalopathies

GM1 ---------- GM1 Gangliosidosis

GM2 ---------- GM2 Gangliosidosis

H-ABC ---------- Hypomyelination with Atrophy of the Basal Ganglia and Cerebellum

HCAHC ----- Hypomyelination with Cerebellar Atrophy and Hypoplasia of the Corpus Callosum

HCC ---------- Hypomyelination with Congenital Cataracts

IBD ---------- Inflammatory Bowel Disease

JC virus ---------- John Cunningham virus

LD ---------- Leukodystrophies

LO ---------- Leukodystrophy with Oligodontia

MLC ---------- Megalencephalic Leukoencephalopathy with Subcortical Cysts

MMC ---------- Myelomeningocele

PML ---------- Progressive Multifocal Leukoencephalopathy

PMD ---------- Pelizaeus-Merzbacher Disease

POLR3-HLD -------- Ribonucleic Acid Polymerase III-related Hypomyelinating Leukodystrophy

SASD ---------- Sialic Acid Storage Disease

TACH ---------- Tremor-Ataxia with Central Hypomyelination

4H ---------- Hypomyelination, Hypodontia and Hypogonadotropic Hypogonadism

Other

HRQoL ---------- Health-related Quality of Life

MRI ---------- Magnetic Resonance Imaging

QoL---------- Quality of Life

RI-MUHC ---------- McGill University Health Centre Research Institute

Introduction and Thesis Objectives

Rare diseases affect a small number of individuals (less than 200,000 cases reported)[1], thereby restricting their scientific research, including research on potential treatments, delaying diagnosis and interventions, limiting support, and increasing stigma surrounding the disease[1].

RNA Polymerase III (POLR3)-related leukodystrophy, also known as POLR3-HLD or 4H (hypomyelination, hypodontia, and hypogonadotropic hypogonadism) leukodystrophy, is a rare neurological disease (whose prevalence is around 1 in 7,663 births)[2] with a mostly pediatric age of onset. It is caused by biallelic pathogenic variants in genes that encode for subunits of RNA polymerase III[3]. It is characterized by hypomyelination on a brain MRI with a typical MRI pattern, and the presence of a variety of neurological and non-neurological features[3,4]. Unfortunately, there is no known cure for this neurodegenerative disease. Thus, supportive treatments are the only option for minimizing potential complications, which require the expertise and care of a multifaceted team of health care professionals[5].

Although POLR3-related leukodystrophy is a devastating disease, studies investigating the impact of this disease on patients and their caregivers' overall well-being are vastly lacking. Only a handful of studies have examined the effects of genetically determined leukoencephalopathies and leukodystrophies on individuals and their loved ones, including two studies published by our group, the MyeliNeuroGene Lab, in 2018 and 2020, respectively[6,7]. The first study looked at whether the presence and severity of specific clinical features of genetically determined leukoencephalopathies lead to lower health-related quality of life (HRQoL) for patients[6]. It found that children with genetically determined leukoencephalopathies had poorer health related quality of life, which correlated to the severity and presence of clinical features such as motor, emotional and social functioning[6]. The second, a pilot study, looked at whether

certain clinical and demographic features correlated with higher stress for parents of patients affected by genetically determined leukoencephalopathies[7]. The authors of this study found that parents with children with genetically determined leukoencephalopathies had higher stress percentile scores, and that behavior and physical functioning were most impactful on these scores[7]. Although these studies have determined lower health-related quality of life for patients, higher stress for parents, and certain clinical features that correlate with these levels, these studies looked at genetically determined leukoencephalopathies which included several types of diseases. While these diseases have similarities, they also have differences. Obtaining results that represent all genetically determined leukoencephalopathies together may not be a valid representation of specific diseases within the group. Here, we elected to study specifically POLR3-related leukodystrophy because the specific impact of POLR3-related leukodystrophy on families, notably parents, has not been studied before, particularly, understanding the impact of detrimental clinical features and life circumstances on parents' quality of life and their stress level. Poor overall quality of life and high parental stress can negatively impact a parent's and thus child's mental health, leading to anxiety, depression, and other health issues[8]. These factors could negatively affect parents' relationships with their children; their ability to respond and tend to their children's needs, and impair their child's behavior, growth, and emotional stability[8].

In this study, we sought to assess parents' quality of life, stress levels, and which modifiable factors (categorical and continuous) of POLR3-related leukodystrophy might impact their stress levels and quality of life. In line with this, we performed a cross-sectional study, including parents of patients who were followed at the Leukodystrophies and Neurometabolic Disorders Clinic at the McGill University Health Centre Research Institute (RI-MUHC) and international patients alike. We collected and analyzed parents' responses to five questionnaires

concerning demographics, stress, quality of life, experiences of injustice, and coping strategies, as well as their child's updated medical records.

We hypothesized that parents caring for children with POLR3-related leukodystrophy have lower quality of life and higher stress compared to parents of healthy children, and that the modifiable factors most impactful for determining both quality of life and stress scores would be behavioral issues[9], fatigue[10,11], and physical disability of the child[9,11,12]. To address these hypotheses, the aims of this project were as follows:

Aim 1: To determine whether parental stress and quality of life are affected in comparison to parents of healthy children.

Aim 2: To identify which modifiable factors (continuous or categorical) may negatively impact or influence parental stress and quality of life of parents of children with POLR3-related leukodystrophy.

By identifying whether poor quality of life and increased stress levels negatively influence parents, we can shed light on the significance of improving the well-being of parents, which will also benefit the care their children receive. We thus hope to raise awareness for the importance of parental well-being while caring for a child with a chronic disease. Furthermore, we aim to identify the specific modifiable factors that may impact parents, so that interventions can be developed to mitigate such factors, and both improve parental mental health and increase the support they receive.

Chapter 1: Background Literature Review

1.1 White Matter Disorders: Leukoencephalopathies

White matter disorders are those that affect the white matter of the brain, which is composed of blood vessels, glial cells (which are further composed of oligodendrocytes, microglia, and astrocytes in the central nervous system), and millions of bundles of neurons wrapped in myelin[13]. Oligodendrocytes are responsible for myelin sheath production[14]. These cells undergo a multifaceted system from proliferation through to maturation and myelination which lead to the creation of myelin sheaths that are also carefully maintained[15]. Microglia are in charge of brain development by acting as the brain's protective barrier[16]. Microglia act as the brain's macrophages which provide immune responses responsible for removing any substances that may harm the central nervous system, to help maintain healthy neuronal connections[16]. Astrocytes are the most abundant glial cell type and have many roles such as: synapses formation, maintaining the blood-brain barrier, regulating neurotransmitter uptake, and ensuring the proper functioning of other cells[17]. Myelin serves as a protective barrier and insulator for neurons, allowing for the propagation of electrical impulses from node to node through salutatory conduction[18]**.** It is also responsible for the protection of axons as well as for providing support for neurons to mature, regenerate, and survive[18]. Thus, myelin provides elements that are vital for efficient and effective neuronal signalling and connectivity within the central nervous system[19].

While white matter disorders are vast, the term "leukoencephalopathies" includes all disorders affecting the white matter of the central nervous system. Leukoencephalopathies include genetically determined leukoencephalopathies, leukodystrophies, as well as non-genetic diseases which may stem from trauma[20], malnutrition[20], inflammation[20], exposure to drugs or

toxins[20,21], infections[20] (i.e. progressive multifocal leukoencephalopathy or PML caused by the JC virus[22]) or neoplasms[20,23]. Genetically determined leukoencephalopathies (gLEs) are inherited cerebral white matter diseases, and include both leukodystrophies (where the primary disease process is thought to involve glial cells[24]) and diseases where the white matter involvement is thought to be secondary to another disease process (i.e., metabolic, vascular, etc.)[25]. Other examples of gLEs include neuronal diseases such as AIMP1 and AIMP2-related gLE[25–27], diseases that involve inborn metabolic errors such as GM1 and GM2- gangliosidosis[25], Menkes Syndrome[28], Allan-Herndon-Dudley Syndrome[29], and others.

Common signs and symptoms of leukoencephalopathies include motor dysfunction caused by, for example, pyramidal, extrapyramidal and/or cerebellar involvement, visual and hearing impairments, cognitive deficits, and in certain diseases, systemic manifestations[30,31].

1.2 Leukodystrophies

Further characterized from leukoencephalopathies are leukodystrophies (LDs). The most commonly accepted definition, even if imperfect (c.f. below), comes from the Global Leukodystrophy InitiAtive (GLIA) consortium consensus, whereby leukodystrophies are "a group of rare, inherited, genetic, progressive disorders primarily affecting the white matter (i.e. myelin) of the central nervous system, with or without peripheral nervous system involvement"[32]. Thus, leukodystrophies are hereditary disorders that have glial cell and myelin sheath (i.e. oligodendrocytes) anomalies, and the cells that are involved in the neuropathology of LDs are oligodendrocytes, astrocytes, and other non-neuronal cell types[25].

Leukodystrophies can be further classified as hypomyelinating (i.e., insufficient myelin deposition during development) and non hypomyelinating (i.e., altered myelin homeostasis), in which both have typical brain MRI characteristics[25]. Clinically, the majority of leukodystrophies

affect children and are progressive in nature, leading to disability and premature death, months to years following disease onset[3].

Considering that this classification system of leukodystrophies is imperfect, a novel classification system based on pathological changes was proposed by van der Knaap et al.[13]. It was realized that leukodystrophies are not only caused by mutated genes involved in myelin or oligodendrocyte development, but are also in axons, microglia, blood vessels and astrocytes[13]. Thus, van der Knaap et al. further classified leukodystrophies into five categories: myelin disorders (i.e., including primary defects in myelin and oligodendrocytes), microgliopathies, vascular pathology disorders, neuronal or axonopathies, and astrocytopathies[13]. Although this classification is more accurate on a pathophysiological level and more inclusive for genetic white matter disorders that were not included in the previous classification (i.e., vasculopathies), the classification of hypomyelinating vs. non-hypomyelinating disorders remains very helpful on a clinical basis because of the associated typical brain MRI patterns. For the remaining of this thesis, we will therefore use the hypomyelinating vs non-hypomyelinating classification.

1.3 Non-Hypomyelinating Leukodystrophies

Brain MRI patterns are key in determining whether a given disease is hypomyelinating or non-hypomyelinating. In non-hypomyelinating disorders, T1-weighted imaging would show white matter appearing darker than the surrounding grey matter (hypointense)[25], whereas T2-weighted imaging would show white matter appearing lighter than the surrounding grey matter (hyperintense)[26], compared to in a healthy brain where white matter is hyperintense on T1-weighted imaging and hypointense in T2-weighted imaging as compared to grey matter structures[32].

Non-hypomyelinating leukodystrophies are caused by altered or disrupted myelin homeostasis[25]. Non-hypomyelinating leukodystrophies have numerous causative-genes and varied methods of inheritance. Several examples of non-hypomyelinating leukodystrophies include Alexander disease[33], Krabbe's disease[34], Metachromatic Leukodystrophy[35], Mitochondrial Leukoencephalopathies[36], and Vanishing White Matter Disease[37], to name a few (see Table 1.1).

1.4 Hypomyelinating leukodystrophies

Hypomyelinating leukodystrophies are disorders characterized by a defect in myelin deposition during development, which leads to a permanent reduction of white matter in the central nervous system[25].

Common clinical signs and symptoms of hypomyelinating leukodystrophies are motor functioning issues such as spasticity and ataxia, and cognitive and developmental delays[38].

Magnetic resonance imaging is also key in diagnosing hypomyelinating leukodystrophies. Indeed, on brain MRI, T1-weighted imaging would show white matter appearing as either darker, similar, or somewhat lighter than the surrounding grey matter, whereas T2-weighted imaging would show white matter appearing marginally darker than the surrounding grey matter (but typically not as pronounced as in non-hypomyelinating disorders), compared to the appearance of healthy brains, as previously mentioned[39,40]. Further analysis of the MRI pattern can help with the diagnosis of the specific disease[39,40]. For example, disorders such as Hypomyelination with Atrophy of the Basal ganglia and Cerebellum (H-ABC)[41], POLR3-related leukodystrophy[3] and Salla's disease[42], can be associated with cerebellar atrophy.

Examples of hypomyelinating leukodystrophies include Pelizaeus-Merzbacher disease (PMD)[43], TUBB4A-related leukodystrophy[44], and POLR3-related leukodystrophy[3] (see Table 1.1).

Table 1.1 Short List of Non-Hypomyelinating and Hypomyelinating Diseases

Non-Hypomyelinating Diseases	**Affected Gene(s)**	**Phenotype MIM Disease Number (PMIM)**
Alexander disease[33]	*GFAP*	203450
Krabbe's disease[34]	*GALC*	245200
Aicardi-Goutières syndrome[45]	*ADAR*, *RNASEH2A*, *RNASEH2B*, *RNASEH2C*, *SAMHD1*, *TREX1*	610333, 225750, 610181
Metachromatic Leukodystrophy[35]	*ARSA*	250100
Mitochondrial Leukoencephalopathies[36]	*NDUFA1, NDUFV1, NDUFS2*	618225, 301020, 618228
Adrenoleukodystrophy[46]	*ABCD1*	300100
Vanishing White Matter disease[37]	*EIF2B1, EIF2B2, EIF2B3, EIF2B4, EIF2B5*	603896
Megalencephalic Leukoencephalopathy with subcortical Cysts (MLC)[47]	*HEPACAM, MLC1*	604004
Cerebrotendinous xanthomatosis (CTX)[48]	*CYP27A1*	213700
Canavan disease[49]	*ASPA*	271900
Hypomyelinating Diseases	**Affected Gene(s)**	**Phenotype MIM Disease Number (PMIM)**
Pelizaeus-Merzbacher disease (PMD)[43]	*PLP1*	312080
POLR3-related leukodystrophy[3]	*POLR3A, POLR3B, POLR1C, POLR3K*	614381, 607694, 616494
EPRS1-related disease[50]	*EPRS1*	617951
Sialic Acid Storage Disease (SASD)[51]	*SLC17A5*	604369
Hypomyelination with Congenital Cataracts (HCC)[52]	*FAM126A*	610532
Cockayne Syndrome[53]	*ERCC6, ERCC8*	133540, 216400
SOX10-related disease[54]	*SOX10*	609136

Hypomyelination with Atrophy of the Basal Ganglia and Cerebellum (H-ABC)[41]	*TUBB4A, UFM1*	612438

This table includes a brief (not complete) list of specific non-hypomyelinating and hypomyelinating diseases, the affected genes associated with each disease, and the Phenotype MIM (PMIM) disease numbers.

1.5 POLR3-related Leukodystrophy (4H Leukodystrophy)

Initially, there existed multiple diseases with similar phenotypic features that were considered separate, namely: Ataxia, delayed dentition, and hypomyelination (ADDH)[55], leukodystrophy with oligodontia (LO)[56], hypomyelination with cerebellar atrophy and hypoplasia of the corpus callosum (HCAHC)[57], hypomyelination, hypodontia, hypogonadotropic hypogonadism (4H)[58,59], and tremor-ataxia with central hypomyelination (TACH)[60,61]. However, with the identification of common causal genes, these diseases were later referred to as POLR3-related leukodystrophy, or 4H leukodystrophy, one of the most common hypomyelinating leukodystrophies known[62–64].

RNA Polymerase III (Pol III) is a 17-subunit complex responsible for transcribing small non-coding RNAs important for translation, including all tRNAs[65,66]. POLR3-related leukodystrophy is thus an autosomal recessive disorder caused by biallelic pathogenic variants in the genes that encode for Pol III subunits[3], including *POLR3A*[62], *POLR3B*[64], *POLR1C*[67] and *POLR3K*[68].

The cardinal features of POLR3-related leukodystrophy include hypomyelination, hypodontia and hypogonadotropic hypogonadism, creating its alternative name, 4H leukodystrophy[3]. It typically presents in early childhood[4], although early infantile[69] and later presentations[4,69,70] are also possible, depending on the mutation. It is characterized by both neurological and non-neurological features. Neurological features include cerebellar, pyramidal, extrapyramidal and cognitive manifestations[3,4,71–73], while non-neurological features include

dental (e.g., hypodontia, oligodontia, and others)[4,71,74], endocrine (most commonly hypogonadotropic hypogonadism and short stature)[4,71,75] and ocular (typically myopia) abnormalities[4,71].

Cerebellar features are the most frequent and hindering symptoms experienced by patients, which include motor limitations and regression that may lead to the use of a wheelchair[3,4]. In fact, while some patients remain independently mobile into adulthood, others may lose ambulation after 10 years and will require assistive mobility devices[4]. Cerebellar features, outside of gait ataxia[3,4] or balance difficulties[3,4], cause coordination difficulties (i.e., intention tremor[3,4], dysmetria[3,4], dysdiadochokinesis[3,4]), slurred speech (i.e., dysarthria)[3,4], and extraocular movement abnormalities such as progressive loss of ocular pursuits[3,4] and abnormal saccades[3,4]. There are also pyramidal and extrapyramidal features that are caused by altered corticospinal tracts and basal ganglia circuits, respectively[3]. Pyramidal involvement leads to spasticity[3], which by definition, is increased tone that is velocity dependent[66]. The most common extrapyramidal feature seen in patients is dystonia[72,73], defined as involuntary muscle contractions of agonist and antagonist muscles causing abnormal postures or slow, repetitive movements[77]. Other features include swallowing difficulties or dysphagia which may lead to tube feeding; sialorrhea, fatigue, cognitive delay and/or regression, and in some cases, behavioral issues[3,4,71].

Non-neurological clinical features include dental abnormalities, such as hypodontia (absence of 1-5 primary or permanent teeth), oligodontia (absence of 6 or more primary or permanent teeth), and abnormally placed or shaped teeth, or delayed tooth eruption from the gums[3,74]. There are also endocrine abnormalities, such as hypogonadotropic hypogonadism, which presents itself as delayed or halted puberty, or the absence of early pubertal changes, as

well as short stature (in around 50% of individuals) with or without growth hormone deficiency[3,4,75]. Some patients also reported having thyroid abnormalities[75]. Lastly, there are ocular abnormalities, including myopia[3,4], which typically progresses rapidly, and is the most common non-neurological clinical feature present in patients[3,4]. Less common ocular abnormalities include optic atrophy[3,4] and cataracts[3,4].

The MRI pattern of POLR3-related leukodystrophy include characteristics of hypomyelination (mentioned above), as well as typical relative preservation of myelination of the globus pallidus, anterolateral nucleus of the thalamus, optic radiations, dentate nucleus, as well as, in some cases, the corticospinal tracts at the level of the posterior limb of the internal capsule, along with potential cerebellar atrophy and the thinning of the corpus callosum usually found in older patients[4,39,78–80]. The MRI pattern of patients with an early infantile and severe form of the disease showcase abnormalities of the basal ganglia and overall inadequate myelin deposition[81,82], whereas the MRI pattern of patients with a later onset and milder forms of the disease show either normal myelination (i.e., in cases presenting with spastic paraparesis or spastic ataxia)[83,84], normal myelination with basal ganglia involvement (i.e., in cases with a mild striatal form of the disease)[81], or hypomyelination with more myelin present compared to the typical presentation of hypomyelination[3,40].

POLR3B mutations are the most prevalent (49% incidence)[3,4], followed by *POLR3A* mutations (41% incidence)[3,4], and *POLR1C* mutations (5% incidence)[3,4]. The prevalence of genetic mutations varies within patient populations, and therefore if single gene sequencing is chosen as a diagnostic process, a certain order of single-gene sequencing should be performed[3]. The *POLR3B* gene should be sequenced first to test for a mutation if the patient is a descendant of European ancestry[3], whereas the *POLR3A* gene should be sequenced first to test for a

mutation if the patient is a descendant of French-Canadian populations[3]. However, it is important to note that with the development of next generation sequencing, most patients are currently investigated with gene panels which would include all 4 disease-causing genes, along with others[3]. It is also important to note that although *POLR3A*-related leukodystrophy is more common within the French-Canadian population[3,4], this is likely due to the founder effect, where a population stems from a small group of individuals, leading to reduced genetic variation and a potential increase in the occurrence of allele patterns responsible for rare disorders like POLR3-related leukodystrophy[85].

Genotype-phenotype correlations have been reported in POLR3-related leukodystrophy or POLR3-related disorders. Indeed, some phenotypic generalities (c.f. below) can be predicted from the mutated genes, although this needs to be done with caution since this is not always a definitive relationship. Also, some specific variants are known to be associated with a defined phenotype, an earlier or later onset of disease as well as a severe or milder disease severity and progression. It is more difficult to draw conclusions because there are hundreds of mutations[62,80] published, with numerous private mutations, and most patients are compound heterozygotes. However, for several specific mutations, there is a clear genotype-phenotype correlation.

Biallelic pathogenic variants in *POLR3A* are typically characterized by a more severe phenotype, i.e., a later onset and more rapid progression of the disease, and a shorter lifespan[4]. Most specifically, patients with a *POLR3A* mutation generally present with earlier loss of ambulation[3,4], and commonly have abnormal puberty[75] and severe dystonia[73].

Mutations in *POLR3A* have been found to cause several other conditions such as Wiedemann Rautenstrauch syndrome (a form of neonatal progeroid syndrome)[86,87], which is characterized by an individual's pre- and post-natal growth delay and subcutaneous lipoatrophy,

among other manifestations[88,89]. Other variants in *POLR3A* are the cause for striatal[81,82] and later onset forms of the disease involving spastic paraparesis and spastic ataxia[84].

Biallelic pathogenic variants in *POLR3B* are typically characterized by a less severe phenotype, i.e., with a slower progression of the disease. However, patients with pathogenic variants in this gene will typically present earlier than patients with variants in *POLR3A*[4].

Drawing conclusions on the severity or disease progression associated with biallelic pathogenic variants in *POLR1C* is more difficult due to the rarity and the smaller number of patients reported with this genotype[71]. However, a characteristic found in some of these patients was craniofacial characteristics indicative of Treacher Collins Syndrome[71].

The understanding of the phenotypic spectrum of biallelic pathogenic variants in *POLR3K* is quite narrow due to only two patients being published with this genotype[68]. However, it was observed that both these patients had an earlier onset of the disease, shorter lifespan, and significant clinical symptoms such as digestive and motor manifestations[68].

1.6 Quality of Life

Quality of life (QoL) is defined by the World Health Organization as an "individual's perception of their position in life in the context of the culture and value systems in which they live, and in relation to their goals, expectations, standards and concerns"[90]. Essentially, quality of life is the standard of health, comfort, and happiness in life experienced by an individual[90].

Quality of life can be measured using several different scales and questionnaires, such as the Quality-of-Life Scale[91], the Health-Related Quality of Life Questionnaire[92], or the World Health Organization Quality of Life Instrument[90], to name a few. These questionnaires contain thorough, comprehensive items that measure aspects of an individual's physical and mental

health, social/family/partner relationships, positive and negative feelings of one's self, personal development, levels of independence, home/work environment, etc.

Since individuals who experience chronic diseases may or may not have a viable cure or treatment, it is imperative to have a way to evaluate how their well-being is maintained throughout their disease progression[91]. An example of this is the health-related quality of life (HRQoL) measure, created to examine the health of an individual in relation to how it may affect their QoL[92].

HRQoL of patients with a variety of non-neurological and neurological diseases have been well documented. Indeed, patients with chronic diseases such as Crohn's disease[93], type II diabetes[94], chronic obstructive lung disease[94], coronary artery disease[94], osteoarthritis[94], cancer[94], multiple sclerosis[95], inflammatory brain diseases[96] and Krabbe's disease[97,98] were found to have statistically significantly impaired HRQoL compared to healthy individuals. It was also found that the HRQoL of these patients was directly related to the number of clinical features present, the duration, instability, and severity of the disease, the ability to participate in daily life activities, as well as the functional status at the specific phase of their disease[93–98]. Specifically, features that greatly impacted HRQoL of patients with chronic illnesses were physical impairments[9,11,12], fatigue[10,11], and cognitive and behavioural dysfunction[9]. These significant risk factors lead to impaired functioning across all subdomains of health-related quality of life (i.e., physical, emotional, and social domains)[10,96], leading to poorer quality of life for these patients. Indeed, the study conducted by our lab in 2018 demonstrated that clinical features such as motor, emotional, and social functioning were all related to poorer HRQoL in patients with leukodystrophies and genetically determined leukoencephalopathies as a group[6]. For parents of patients with rare diseases, psychosocial factors such as coping and social support, and their

child's disease characteristics, were shown to have a significant effect on parental HRQoL, showcasing the importance of consideration for these facets along with managing their child's disease[1,99]. Patients with chronic diseases with low HRQoL were also more prone to developing mental health issues, such as anxiety and depression[8,100]. These issues may affect their willingness to participate within society as they struggle to both cope with their disease and improve their mental health.

As previously mentioned, it is important to note that HRQoL only measures factors that are a part of an individual's physical and mental health, whereas *overall* quality of life is an all-inclusive concept incorporating all factors that impact an individual's life (emotional, social, psychological, etc.). While previous research mostly focused on the HRQoL of patients and their families, there lacks significant evidence for the overall quality of life of parents and caregivers caring for individuals with rare diseases, and more specifically, POLR3-related leukodystrophy, despite its devastating nature.

Table 1.2 Summary of Quality of Life Scores for Different Diseases, and Impactful Features:

Disease	Quality of Life Scores	Impactful Features
Crohn's Disease[93]	Decreased - worse in active state	Number of clinical features
Inflammatory bowel disease (IBD)[101]	Decreased- worse in active state	Lower recurrence, disease duration, symptom activity
Type II Diabetes[94]	Decreased	Duration of clinical features, comorbidity
Asthma, Chronic obstructive pulmonary disease (COPD) [102]	Decreased	Age, economic status
Coronary artery disease[103]	Decreased	Depressive symptoms, distressed personality type
Stroke[104]	Decreased	Post-stroke disability
Rare Diseases[99] (i.e., Motor Neuron Disease[105], Progressive Supranuclear Palsy[106])	Decreased - 82% considered health status to be poor	Pain, fatigue, physical limitations, duration and severity of clinical features
Myelomeningocele (MMC), Spina Bifida[107]	Decreased	Number of clinical features, psychosocial and environmental factors
Multiple Sclerosis[95]	Decreased	Higher severity, number of clinical features, cognitive impairments
Inflammatory Brain Disease[96]	Decreased	Seizures and cognitive and/or behavioral dysfunction
Microcephaly, Guillain-Barré Syndrome[10]	Decreased	Physical impairments, fatigue

This table includes a summary of specific diseases, the quality of life scores of individuals with the disease compared to healthy individuals, and the features that mostly impacted these scores.

1.7 Stress

According to the Mental Health Foundation, stress is defined as "the feeling of being overwhelmed or unable to cope with physical, mental or emotional tension or pressure. It is often triggered when we experience something new, unexpected or that threatens our sense of self"[108]. Essentially, stress is the inability to cope with physical, mental, emotional, or novel situations[108].

Stress can be measured using several existing questionnaires that examine different features of stress. Some examples include: the Perceived Stress Score[109], which measures how diverse circumstances affect one's stress level, the General Health Questionnaire[110], which specifically measures one's psyche and ability to carry out healthy life functions, and the Holmes-Rahe Stress Scale[111], which measures the number of stressful events one has recently encountered.

While stress is a relevant factor for patients with chronic diseases, parental stress is often overlooked, yet just as important. Research on parental stress found that parents of children with chronic illnesses such as cancer[112], cystic fibrosis[112], congenital heart conditions[113], or other rare diseases[114] reported statistically significantly greater general parenting stress than parents of healthy children. The same was found for parents of children with neurodevelopmental disorders[115], cerebral palsy[116,117], and other chronic physical/motor conditions[12,117]. A study conducted by our lab in 2020 also showed that parents of children affected by leukodystrophies and genetically determined leukoencephalopathies had higher stress level percentile scores compared to a normative sample[7].

In these studies, parental stress levels were found to be associated to specific features of the child's disease, such as physical impairments[9,11,12], sleep[10,11], and behavioral issues[9], to broader factors related to illness severity, disease duration, number of symptoms, and the child's

age[12,114,115]. As well, parental stress was impacted by parents' situations. Greater responsibility for their child's treatment management, marital quality, and levels of perceived support were all characteristics that determined a parent's stress level, and these levels were shown to have further increased due to the lack of competence, social isolation and high emotional demands when caring for a child with a rare disease[9,114].

Other studies have shown that high parental stress can precede negative consequences such as parental anxiety and depression, which can lead to maladaptive parenting practices and relationships, further affecting a parent's ability to cope with a child's disease[118]. Mental health issues may also affect the interactions and responsiveness of the parent towards the child, disregarding their needs, and thus affecting their child's growth and behavior[8]. Interventions targeting both the child's as well as the parents' stressors were shown to help improve parents' overall well-being and stress level. These factors would then help parents to continue to provide the supportive care required for their children, and lead happier lives[119].

While it is evident that parental stress increases when caring for children with severe medical conditions, there lacks significant evidence for the impact of stress on parents with children with POLR3-related leukodystrophy specifically, despite its progressive and difficult nature.

Table 1.3 Summary of Stress Scores for Different Diseases, and Impactful Features:

Disease	Stress Scores	Impactful Features
Cancer, Cystic Fibrosis[112]	Increased	Number of clinical features, greater parental responsibility for treatment management
Chronic Physical Conditions (i.e., cerebral palsy, spina bifida)[9,12]	Increased – small-moderate levels in parent-child relationship, moderate-high levels in HRQoL	Illness severity, duration, child age, marital status, behavioral problems, etc.
Rare disabilities[114]	Increased	Lack of competence, social isolation & high emotional demands
Congenital heart conditions[113]	Increased – in mothers higher than in fathers	Number of clinical features, parental health, SES
Neurodevelopmental disorders[115]	Increased	Child's emotional and behavioral problems

This table includes a summary of specific diseases, the stress scores of individuals with the disease compared to healthy individuals, and the features that mostly impacted these scores.

1.8 Coping Mechanisms

Contrary to defense mechanisms, which are involuntary adaptive responses, coping is a voluntary action, behavior or thought aimed at dealing with a stressful circumstance or stressor that is either external or internal[120].

Coping mechanisms (or strategies) are an array of attributes that one can use to deal with a stressor[120]. Coping mechanisms can be categorized into four main groups, such as: meaning-focused[121,122], where individuals focus on drawing the meaning from the circumstance, and use cognitive strategies to deal with that situation; problem-focused[121,122], where individuals use mechanisms that actively address and deal with the main issues causing their stress; social coping[121,122], where individuals rely on others for support throughout their distress; and emotion-focused[121,122], where individuals try to recognize and lessen negative emotions brought on by

stressors (cognitive behavioral therapy is a widely used and well-known psychological technique that utilizes this coping mechanism)[121,122].

There also exists another group, known as maladaptive coping mechanisms, which are strategies or behaviors aimed at reducing stress in an unhealthy manner[123]. Some examples of these include escapism/avoidance of a stressful situation, substance abuse, self-harm, binge/emotional eating, and emotional suppression[123]. It has been found in several studies that while maladaptive coping mechanisms are an immediate solution to a stressful situation, they are associated to poorer physical and mental health outcomes, lower quality of life, and are found to increase the original stress desired to be reduced in the first place[124,125]. On the other hand, positive (or adaptive) coping mechanisms specifically focused on finding support and having a positive outlook on life have been shown to lead to reduced stress, the development of fewer chronic health issues, and improved quality of life[123–125].

Coping strategies also have clinical significance, both in healthcare and at-home care settings. In healthcare settings, teaching patients and acknowledging patients' coping strategies are vital towards building and maintaining a healthy, trustworthy patient-physician relationship[120]. It gives healthcare providers insight into patients' levels of distress, and whether patients' coping strategies are useful in reducing their stress[120]. Unfortunately, associations have been made between maladaptive coping strategies and both physical and mental health disorders, such as anxiety, depression, and heart disease, posing a further risk to patient's health if these coping mechanisms are not immediately addressed[123,126,127].

In at-home care, coping mechanisms can be beneficial for parents and caregivers caring for individuals with chronic health conditions. These individuals have the task of caring for their loved ones, along with balancing responsibilities of their family, work, and day-to-day duties,

which make up the added stressors of their daily lives. Parents responsible for a child's end-of-life care deal specifically with continuous uncertainty, feelings of denial and anxiety of losing a child, and constant changes in decisions in their child's care[128]. Due to their child's ever-evolving situations, coping mechanisms that provide instant reinforcement are mostly used[128]. Unfortunately, these involve negative coping mechanisms such as avoidance and emotional suppression which can affect parental mental health in the long-run[8,128]. However, for on-going care, such as for children with cancer or physical disabilities, coping mechanisms that were maintained long-term, such as building a support system and being emotionally focused, were found to be the most helpful and widely used[120,129,130].

While it is imperative to understand why and which kinds of coping mechanisms are used by parents caring for children with chronic illnesses, this has not yet been studied in the parent population of children with POLR3-related leukodystrophy, despite it being a demanding disease for both the child and parent.

1.9 Perceived and Experiences of Injustice

The term perceived injustice is the concept by which an individual believes they have been treated unfairly by someone, and are suffering because of this poor treatment[131]. Perceived injustice is also considered as the negative appraisal of oneself (blame), unfairness, severity and irreparability of loss within a situation due to the situation at hand[131,132]. Experiences of injustice indicate one's experiences of being subjected to the perceived injustice[131].

Experiences of injustice and perceived injustice can occur in any situation: socioeconomic status, race and ethnicity, religion, gender, as well as conflicts within one's self[133]. Mental or physical health issues, especially if these health conditions are less well-

understood or not easily visible to others, may evoke stigmatization, furthering the feelings of unfairness for those suffering[133].

There have been several studies that have determined that populations suffering with chronic pain (after musculoskeletal injury or whiplash) do perceive their situations to be unjust, and that a high level of perceived injustice are positively correlated with various poor health outcomes, advanced deterioration of symptoms of chronic pain, and increased recovery times[134–136]. Similar results were found for those suffering from traumatic brain injuries[131], as well as cervical cancer patients[137], where perceived injustice predicted the development of anxiety and depressive symptoms. However, studies showed that if individuals with chronic health conditions perceived their situations as fair, along with having a combination of adaptive coping strategies such as having a positive attitude towards their situation, these became significant predictors of patients' life satisfaction and led to improved well-being for these individuals[138].

While research has been done to determine the effects of perceived injustice and experiences of injustice within certain populations, there lacks evidence for how perceived injustice impacts the caregiving population who care for others with chronic illnesses like POLR3-related leukodystrophy, despite their situations being comparably serious to those suffering from an illness.

Chapter 2: Methods

Participants, Ethics Statement, and Data Collection

Parents and their children with POLR3-related leukodystrophy were recruited from the Leukodystrophy and Neurometabolic Diseases Clinic at the Montreal Children's Hospital and abroad. Inclusion criteria included 1) parents of patients with a confirmed POLR3-related leukodystrophy molecular diagnosis, 2) parents that were either considered primary or secondary caregivers, 3) the ability to communicate in English or French, and 4) lived with their affected child(ren). This study was approved by the Research Ethics Board of the McGill University Health Center Research Institute (11-105-PED, 2019-4972). All patients and their caregivers were informed about the research study and written informed consent was obtained. All their information was kept confidential and strictly used for this study.

Study Design

Several questionnaires were used for this study, including a Demographics Questionnaire, Parenting Stress Index 4th Edition, Stress Index for Parents of Adolescents, Parental Stress Scale (where the appropriate stress questionnaire was distributed to parents based on their child's current age), Family Impact Module, Injustice Experiences Questionnaire, and Coping Health Inventory for Parents (see Table 2.1). These questionnaires were physically given or sent out electronically to parents, and were available in English or French. Instructions for each questionnaire were included, however parents were encouraged to contact the research team if any questions arose, or if they preferred to complete it along with a researcher.

Demographics Questionnaire

The demographics questionnaire was created by our lab and included questions on ethnicity, marital status, education, household income, number of children in the household, days

their child has been absent from school, days the child has visited the emergency room, as well as which resources were used by the family.

PedsQL Family Impact Module (FIM):

The PedsQL Family Impact Module (FIM) measures the impact of pediatric chronic health conditions on parents' quality of life, looking at 8 different domains: physical, emotional, social, and cognitive functioning, communication, worry, daily activities, and family relationships (totalling 36 items)[139]. Parents are asked to complete the 10-minute questionnaire by rating each item from 1: strongly disagree to 5: strongly agree. The rating of each item is added to produce a total score. The scores are then reverse-scored and linearly transformed to a 0–100 scale, where higher scores indicate a more positive impact on parents' overall quality of life, and lower scores indicate a more negative impact on parents' overall quality of life[139]. The FIM was found to be valid and reliable, with an internal consistency reliability alpha for the Total Scale Score being 0.97[139]. Importantly, the FIM has been used in various other studies with populations of parents of children with chronic illnesses[6,140,141–145].

One encountered challenge was identifying a comparator population. Thus, a published population similar in demographics to our sample, and who used the same questionnaire for their study, was chosen as the normative sample[146].

Parenting Stress Index 4th Edition (PSI)

The Parenting Stress Index 4th Edition (PSI) is a 20-minute 120-item questionnaire that focuses on evaluating the stress level of parents with children aged 0-12 years old[147]. The questionnaire consists of 3 domains (Child, Parent, Life Stress) that make up the Total Stress score. Within these 3 domains, there are several subscales that measure various aspects of each domain. For the Child domain, these include: distractibility/hyperactivity, adaptability, reinforces

parent, demandingness, mood, and acceptability. For the Parent domain, there are: competence, isolation, attachment, health, role restriction, depression, and spouse/parenting partner relationship[147]. There is also a Situational/Demographic Life Stress scale which measures certain parental characteristics and situational circumstances that may influence stress score outcomes[147]. Parents are asked to rate each item from 1: strongly disagree to 5: strongly agree, which are summed to produce a Total Stress raw score that is then converted into a percentile based on the age of the child, indicating a parent's score relative to the normative sample. This percentile score will then be considered on a range, whether within the normal stress range (between the 16th to 84th percentile), high stress range (85th to 89th percentile) or clinically significant stress range (above the 90th percentile)[147]. Defensive scoring, in which a total score below 24 on certain items, is also taken into account as this could suggest that the parent may have underscored their level of stress, and therefore the results would not be representative of their true stress level. According to the developers of the PSI, coefficient alpha reliability was high; 0.78 to 0.88 for the Child Domain and 0.75 to 0.87 for the Parent Domain[147]. Reliability coefficients were also high at 0.96 for the two domains and Total Stress scale, indicating high internal consistency[147]. This questionnaire has also been validated for French-Canadian[148] and American populations[149] which makes up the majority of our research sample.

Stress Index for Parents of Adolescents (SIPA)

The Stress Index for Parents of Adolescents (SIPA) is a 20-minute derivative of the PSI that focuses on identifying which factors of an adolescent's or parent's life (behavioral and emotional) causes the highest stress level of parents with adolescents aged 11-19 years old[150]. It is a 112-item questionnaire that is divided into 3 domains: Adolescent domain, Parent domain, Situational/Demographic Life Stress scale. Each domain is made up of subscales. For the

Adolescent domain, there are: moodiness/emotional lability, social isolation/withdrawal, delinquency/antisocial, and failure to achieve or persevere[150]. For the Parent domain, these include: life restrictions, relationship with a spouse/partner, social alienation, and incompetence/guilt[150]. Similar to the PSI, there is also a Situational/Demographic Life Stress scale which measures certain parental characteristics and situational circumstances that may influence stress score outcomes[150]. Each item's scores are added to make up a Total Stress score. Duration, scoring, percentile ranges, reliability and validity are all very similar to the PSI[150], making it an acceptable choice.

One reason why these two stress questionnaires were selected for this study was because the normative sample is 'embedded' within the stress percentile score. The PSI and SIPA percentile scores indicate where parents of patients' scores fall on the range relative to a percentage of the normative sample (which was determined by the developers of the questionnaires). Therefore, a comparison of our population to a normative sample is possible.

Parental Stress Scale (PSS)

The Parenting Stress Scale (PSS) assesses the parenting role and relationship with individuals of any age, including adult children (18+ years old)[151]. It is a 10-minute questionnaire composed of 18 items that examine both the positive (i.e., overall self-development) and negative (i.e., demandingness of the situation) aspects of parenting[151]. Additionally, it encompasses other factors that may contribute to stress, such as emotional and social support, family/work stressors, and satisfaction as a parent. Parents are asked to rate each item from 1: strongly disagree to 5: strongly agree, and the rating of each item is summed and inversely scored to produce a final score. Scores rank as either low stress (between 10-30), moderate stress

(between 31-60), or high stress (between 61-90)[151]. Internal consistency across various samples, construct validity, and test-re-test reliability were all found to be strong[151].

This questionnaire was chosen specifically for two reasons. Primarily, it is the only questionnaire found to measure parental stress of adult children that shows strong reliability and validity[151]. Secondly, it is a good equivalent to the PSI and SIPA questionnaires because its questions are comparable to the PSI and SIPA. For example, in the PSS it states: "It is difficult to balance different responsibilities because of my child(ren)"[151], whereas in the PSI/SIPA it states: "I feel trapped by my responsibilities as a parent"[150]. This reinstates the reliability of the different questionnaires depending on the different age groups.

As with the FIM questionnaire, an encountered limitation was identifying a comparator population. Since the results of a normative sample[152] used to measure the psychometric properties of this questionnaire were published and available to researchers, this was elected to be our normative sample.

Coping Health Inventory for Parents (CHIP):

The Coping Health Inventory for Parents **(**CHIP) questionnaire measures parents' responses to managing the responsibilities of a child with a chronic medical condition[153]. It is a 15-minute questionnaire composed of 3 subdomains: "1. maintaining family integration, cooperation, and an optimistic definition of the situation, 2. maintaining social support, self-esteem, and psychological stability, and 3. understanding the medical situation through communication with other parents and consultation with medical staff"[153]. The 45 items are scored on a 4-point Likert scale, where 0 indicates not used, 1 indicates not helpful, 2 indicates helpful, and 3 indicates extremely helpful[153]. For our purposes, the responses of this questionnaire were considered both quantitatively and qualitatively, delving into which specific

coping mechanisms were used by parents, and which were found to be the most helpful. With this information, we could determine factors that may affect the true relationship between our outcomes' variables, as well as reveal what parents do to cope with their circumstances.

The CHIP questionnaire was chosen for its diverse options of coping mechanisms, including both positive and negative mechanisms. Furthermore, this questionnaire has been used by various other research studies with parents of children with chronic health conditions[154–157], reinstating its validity and reliability (where alpha reliabilities for the 3 subscales are 0.79, 0.79, and 0.71, respectively)[154].

Injustice Experiences Questionnaire (IEQ)

As a part of determining quality of life, the 5-minute Injustice Experiences Questionnaire (IEQ) was used[158]. The IEQ was developed to determine the causes and consequences of injustice appraisals in situations of those with physical and mental health conditions (i.e., how parents perceive their situations)[158]. It consists of two factors: severity/irreparability of loss and blame/unfairness, with a total of 12 items[158]. It is scored on a 5-point scale, where 0 indicates never, and 4 indicates all the time[158]. The IEQ total score is calculated by summing all 12-item responses, and scores above 34 are considered very high levels of perceived injustice[158].

While the IEQ has been shown to be internally reliable, these results are based on research samples with musculoskeletal injury and pain, the population that the questionnaire was designed to measure[158]. As such, our population sample could not be compared to a normative sample, posing a limitation. To overcome this, this questionnaire was assessed through its raw scores and where these scores ranked on a range.

Table 2.1 List of Questionnaires

What is Measured?	Questionnaire	Age Range of Child
Demographic Information	• Demographic Questionnaire	All Ages
Stress	• Parenting Stress Index 4th Edition (PSI)	<12 y.o
	• Stress Index for Parents of Adolescents (SIPA)	12-18 y.o
	• Parental Stress Scale (PSS)	>18 y.o
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

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

Paper and electronic updated medical records of the closest clinical visits (1-6 months) to the questionnaires' administration were also collected. Patients for which the time between the clinical note and the questionnaires were more spaced out (>2 months), were included only if they had a relatively stable disease course between the visit before and the visit after questionnaire completion. A stable disease was determined by considering the most recent medical record and comparing it to that of the previous one. If within the medical note it was mentioned that the patient was stable, or if in both notes the patient's symptoms were identical, we considered the disease to be stable. Of note, there were no patients excluded due to disease course instability. These steps were taken to ensure that the clinical information provided was the most up to date to when the questionnaires were completed, to see what clinical features patients presented with, allowing for optimal correlation of results. Recorded clinical features and information included: age of onset, years since diagnosis, genotype and phenotype, fatigue, gait, delayed cognitive development, spasticity, tremor, dystonia, ataxia, dysmetria, dysarthria,

sialorrhea, dysphagia, wheelchair use, feeding tube, anarthria, behavioral issues, and the number of features present in each patient. As well, these updated medical records were used to score several diagnostic tests, such as the Gross Motor Function Classification System (GMFCS)[159], the Manual Ability Classification System (MACS)[160], the Eating and Drinking Ability Classification System (EDACS)[161], and the Communication Function Classification System (CFCS)[162], to determine the level of disability of the child[163] (See Table 2.2).

Table 2.2: Functional Scales

Functional Scale	Level 1	Level 2	Level 3	Level 4	Level 5
GMFCS[159]	Walks without limitation	Walks with some limitations	Uses assistive mobility devices irregularly	Uses assistive mobility devices regularly	No independent mobility
MACS[160]	Handles objects independently	Independent but with reduced quality	Often requires external help	Can only perform certain actions	Can only perform basic actions
EDACS[161]	Eats and drinks independently, safely, and efficiently	Eats and drinks independently and safely, but with reduced quality	Limitations to safety and efficiency, with some risk of choking	Significant limitations to safety, high risk of choking	Unable to eat or drink without feeding tube
CFCS[162]	Sends and receives info with unfamiliar individuals	Sends and receives info with reduced quality	Sends and receives info with familiar individuals	Has difficulty sending and receiving info with familiar individuals	Rarely sends or receives info with familiar individuals

Abbreviations: GMFCS: Gross Motor Function Classification System; MACS: Manual Ability Classification System; EDACS: Eating and Drinking Ability Classification System; CFCS: Communication Function Classification System. The higher the level, the greater the disability of the individual.

Statistical Analysis

All statistical analyses were done using SPSS Statistics Ver.26.0, along with PRISM Ver.9.4.1 which was used to produce the figures and tables. For Aim 1, 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, FIM and PSS scores with their respective normative population samples. Stress percentile scores are already compared to a

normative sample. Since IEQ scores did not have a normative sample to be compared to, these scores were analyzed qualitatively. Pearson correlation coefficients and *p*-values were used to study the relationship between mothers' stress percentile scores and the CHIP questionnaire domain scores. In regards to Aim 2, chi square analyses were performed to compare mothers' stress percentile scores and children's categorical features. Correlations between continuous variables and different coping mechanisms with mothers' and fathers' stress percentile and FIM scores were performed, and Pearson correlation coefficients and *p*-values were noted.

The total mean score of each coping mechanism was also measured to determine which coping mechanisms were considered the most and least helpful to parents. Alpha was set to 0.05.

Chapter 3: Results

A total of 43 caregivers; 26 biological mothers, 1 foster mother, and 16 fathers, and 3 families with two affected children participated in the study. Amongst the cohort, 26 out of 43 caregivers completed *all* questionnaires, yet all 43 parents completed at least 3 questionnaires.

Demographic information of the parent cohort is presented in Table 3.1. In brief, 17/27 of mothers (65%) and 14/16 of fathers (88%) were married, and 2/43 of parents (5%) were in a common law relationship, compared to single parents (7/27 of mothers (27%) and 1/16 of fathers (6%)) or divorced parents (only 1/27 of mothers (6%)). The majority of parents had post-secondary level education (23/27 of mothers (88%) and 12/16 of fathers (75%)) and were employed (12/17 of fathers (88%) compared to 15/27 of mothers (58%)), yet there was a diverse range of household incomes (21/43 parents (49%) had a household income of >100 000$).

In total, 32 children (16 males and 16 females) with POLR3-related leukodystrophy were included in the study from the consent of their parents. Ages ranged from 2-40 years old. Most patients were aged younger than 12 years old (12/32, 38%) compared to patients aged 12-18

years old (10/32, 31%) or aged above 18 years old (10/32, 31%). The majority of children had biallelic pathogenic variants in the *POLR3B* gene (16/32, 50%) or *POLR3A* gene (14/32, 44%), more so than the *POLR1C* gene (2/32, 6%). Age of disease onset was mostly between the ages of 1-5 years old (20/32, 63%), and younger than 1 year old (6/32, 19%). The majority of children's years since disease diagnosis were between 0-10 years old (18/32, 56%), while 10-15 years since disease diagnosis was the least prevalent (3/32, 9%). Present clinical features that were most prevalent were abnormal gait (21/32, 66%), delayed cognitive development (19/32, 59%), tremor (18/32, 56%), ataxia (20/32, 63%), and wheelchair use (19/32, 59%). Fatigue (3/32, 9%), fine motor function issues (4/32, 13%) and behavioral issues (5/32, 16%) were the least prevalent. Classification scores for gross motor, fine motor, communication and swallowing were completed with medical records, whenever possible. The median scores were 4 (indicating severe difficulty in ability) for all scores except CFCS. More detailed information can be found in Table 3.2.

Table 3.1 Parent Characteristics

Demographics	**N (Mother) / N (Father)**	**% (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	58% / 88%
Post-Secondary 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 above 100 000$	13/8*	50% / 50%*
Parental Life Stress Circumstances	**N (Mother) / N (Father)**	**% (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/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%

This table summarizes parental demographics including relationship status, education, and household income, as well as parental life stress circumstances experienced by the parent cohort.

Table 3.2 Patients' 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 of Clinical Feature 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)

This table summarizes the number of children who participated in the study, sex, age group, mutated genes, age of clinical feature onset, number of years since disease diagnosis and present clinical features of the children, and number of completed scores as well as the median score of each severity scale. Functional scale abbreviations: GMFCS: Gross Motor Function Classification System; MACS: Manual Ability Classification System; EDACS: Eating and Drinking Ability Classification System; CFCS: Communication Function Classification System.

The means, standard deviations, *t*- and *p*- values, and effect sizes of the parents' scores on the FIM, PSI/SIPA, PSS, IEQ, and CHIP questionnaires are displayed in Table 3.3.

The FIM questionnaire was used to measure parental QoL. The average FIM score for mothers was 48.36 ± 16.40, and 52.56 ± 20.72 for fathers which were statistically significantly lower compared to the normative population (75.70 ± 14.50)[164], indicating a statistically significantly lower quality of life for mothers (t(27)=-8.66, $p<0.001$) and fathers (t(16)=-4.47, $p<0.001$). The PSI/SIPA questionnaires were used to measure parental stress of patients aged 0-18 years old. The average PSI/SIPA raw score for mothers was 235.11 ± 63.39, and 242.45 ± 64.09 for fathers, which was comparable to the normative samples ($M_{mothers}$=221.10 ± 59.60; $M_{fathers}$=228.20 ± 61.70, $p>0.05$)[147]. When transformed into a percentile according to the patient's age, it was shown that 74% of mothers (20/27) and 81% of fathers (9/11) fell within the normal stress level range (<84%), 15% of mothers (4/27) and 9% of fathers (1/11) fell within the

high stress level range (85%-90%), and 7% of mothers (2/27) and 9% of fathers (1/11) fell within the clinically significant stress level range (>90%). PSS was used to measure the parental stress of adult patients (18+ years old). The average PSS score for mothers was 10.33 ± 2.80, and 12.80 ± 5.54 for fathers, which indicates a low stress level. Interestingly, the PSS score was also largely and statistically significantly lower than the normative sample (27.78 ± 6.28)[152] for both mothers ($t(7)=-15.38$, $p<0.001$) and fathers ($t(5)=-6.05$, $p=0.002$).

For the IEQ score, which measures experiences of injustice, mothers' average score was 23.44 ± 7.83, and fathers' average score was 22.82 ± 11.52. Mothers mostly fell within the average (14-22) to very high (<34) range, whereas fathers' scores ranged from very low (<5) to very high (<34).

For the CHIP questionnaire domain scores, mothers' averaged 34.96 ± 11.81, and fathers' averaged 31.06 ± 12.43 for domain 1, which is maintaining family integration, cooperation, and an optimistic definition of the situation. Mothers' average score for domain 2, which is maintaining social support, self-esteem, and psychological stability, was 35.14 ± 9.93, and fathers' average score was 36.19 ± 9.42. Mothers' average score for domain 3, which is understanding the medical situation through communication with other parents and consultation with medical staff, was 14.96 ± 5.60, and fathers' average score was 14.00 ± 5.99. Qualitatively, the coping mechanisms that were found to be the most helpful (with an average score of closest to 3), were the following: 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 ($M=2.60 \pm 0.49$). On the other hand, the coping mechanisms that were found to be the least helpful (with an average score closest to 1), were the following: allowing myself 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 ± 0.85), and believing that my child(ren) will get better (M=1.48 ± 1.15).

No difference was found between mothers' and fathers' scores for the PSI/SIPA, PSS, FIM, IEQ, or CHIP questionnaires.

Table 3.3 Descriptive Statistics for Questionnaire Scores

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	0.11	0.22
Fathers	242.45±64.09	228.20 ± 61.70	228.2	0.13	0.27
PSI/SIPA (%ile)					
Mothers	60.65 ± 27.17	N/A. See PSI/ SIPA sections in 'Methods'.	-	-	-
Fathers	62.27 ± 26.91	"	-	-	-
PSS					
Mothers	10.33 ± 2.80	27.78 ± 6.28	-15.38	**<0.001***	-5.81
Fathers	12.80 ± 5.54	27.78 ± 6.28	-6.05	**0.002***	-2.70
FIM					
Mothers	48.36± 16.40,	75.70 ± 14.50	-8.66	**<0.001***	-1.67
Fathers	52.56 ± 20.72	75.70 ± 14.50	-4.47	**<0.001***	-1.12
IEQ (raw scores)					
Mothers	23.44 ± 7.83	N/A. See IEQ section in 'Methods'.	-	-	-
Fathers	22.82 ± 11.52	"	-	-	-
CHIP					
Mothers (Domain 1)	34.96 ± 11.81	N/A. See CHIP section in 'Methods'.	-	-	-
Fathers (Domain 1)	31.06 ± 12.43	"	-	-	-
Mothers (Domain 2)	35.14 ± 9.93	"	-	-	-
Fathers (Domain 2)	36.19 ± 9.42	"	-	-	-
Mothers (Domain 3)	14.96 ± 5.60	"	-	-	-
Fathers (Domain 3)	14.00 ± 5.99	"	-	-	-
Helpful vs. Unhelpful Coping Mechanisms					
Investing myself in my children	2.80 ± 0.40	-	-	-	-
Doing things with my children	2.63 ± 0.88	-	-	-	-
Doing things together as a family (involving all members of the family)	2.60 ± 0.49	-	-	-	-
Allowing myself to get angry	1.43 ± 0.49	-	-	-	-
Getting other members of the family to help with chores and tasks at home	1.33 ± 0.85	-	-	-	-
Believing that my child(ren) will get better	1.48 ± 1.15	-	-	-	-

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, FIM scores, and PSS scores, and the effect sizes were represented by Cohen's d. Legend: *: statistically significant (p<0.05).

Pearson correlations were used to assess the correlations between mothers' and fathers' FIM and PSI/SIPA scores with PSI/SIPA, PSS, FIM, IEQ, and CHIP questionnaire scores, patients' continuous variables, and coping mechanisms, as listed in Table 3.4. Mothers' FIM scores were only found to correlate with mothers' IEQ scores (r=-0.52, p=0.01), mothers' PSI stress percentile scores (r=-0.56, p=0.02), as well as fathers' FIM scores (r=0.74, p=0.002) and IEQ scores (r=-0.71, p=0.01). This data suggests that mother's poorer quality of life correlated with both mothers' and fathers' feelings of unfairness and higher stress. Mothers' IEQ scores were not found to be correlated with mothers' PSI stress percentile scores or PSS stress scores. Fathers' FIM scores were only found to negatively correlate with fathers' IEQ scores (r=-0.84, p<0.001), and mothers' IEQ scores (r=-0.80, p<0.001). This data suggests that fathers' poorer quality of life correlated with both mothers' and fathers' feelings of unfairness. Fathers' IEQ scores were not found to be correlated with fathers' PSI stress percentile scores or PSS stress scores. Mothers and fathers' stress percentile scores were positively correlated (r=0.89, p<0.001), indicating that mothers' and fathers' stress level tend to influence one another.

There were no correlations found between mothers' PSI stress percentile scores and age of disease onset, current age, number of years since disease diagnosis, number of affected or unaffected siblings, number of symptoms, and number of life stress circumstances (p>0.05). Only mothers' quality of life scores were positively correlated with years since disease diagnosis (r=0.49, p=0.02), meaning that as their child's disease progressed, mother's quality of life improved.

There were no statistically significant correlations found between the CHIP questionnaire individual domain scores and mothers' and fathers' PSI and FIM scores. However, there were

statistically significant correlations found between mothers' PSI scores and the scores for the following coping mechanisms: doing things with family relatives (r=0.80, *p*=0.02), trying to maintain family stability (r=0.51, *p*=0.02), involvement in social activities with friends (r=0.79, *p*=0.02), time spent alone (r=-0.55, *p*=0.02), and purchasing gifts for oneself and/or other family members (r=-0.62, *p*=0.01). This indicates that mothers' stress scores increased when using coping strategies that they determined either helpful or unhelpful.

Table 3.4 Summary of Pearson Correlations of Continuous Factors for PSI/SIPA and FIM Scores

Pearson Correlation	Mothers' PSI/SIPA Stress Percentile	Mothers' FIM Score	Fathers' PSI/SIPA Stress Percentile	Fathers' FIM Score
Questionnaire Scores				
Mothers' PSI/SIPA Score	-	**r=-0.56, *p*=0.02***	**r=0.89, *p*<0.001***	r=-0.64, *p*=0.05
Fathers' PSI/SIPA Score	**r=0.89, *p*<0.001***	r=-0.38, *p*=0.28	-	r=-0.60, *p*=0.09
Mothers' FIM Score	**r=-0.56, *p*=0.02***	-	r=-0.38, *p*=0.28	**r=0.74, *p*=0.002***
Fathers' FIM Score	r=-0.64, *p*=0.05	**r=0.74, *p*=0.002***	r=-0.60, *p*=0.09	-
Mothers' IEQ Score	r=0.21, *p*=0.41	**r=-0.52, *p*=0.01***	r=0.27, *p*=0.44	**r=-0.80, *p*<0.001***
Fathers' IEQ Score	r=0.16, *p*=0.65	**r=-0.71, *p*=0.01***	r=0.42, *p*=0.22	**r=-0.84, *p*<0.001***
Mothers' PSS Score	-	r=0.25, *p*=0.59	-	r=-0.18, *p*=0.77
Fathers' PSS Score	-	r=0.37, *p*=0.54	-	r=-0.05, *p*=0.94
Mothers' CHIP domain 1 scores	r=-0.18, *p*=0.48	r=0.30, *p*=0.16	r=-0.19, *p*=0.60	r=-0.19, *p*=0.60
Fathers' CHIP domain 1 scores	r=-0.14, *p*=0.71	r=0.03, *p*=0.91	r=-0.13, *p*=0.74	r=-0.13, *p*=0.74
Mothers' CHIP domain 2 scores	r=-0.36, *p*=0.13	r=0.31, *p*=0.15	r=-0.26, *p*=0.46	r=-0.05, *p*=0.94
Fathers' CHIP domain 2 scores	r=-0.17, *p*=0.66	r=-0.30, *p*=0.32	r=-0.25, *p*=0.51	r=-0.25, *p*=0.51
Mothers' CHIP domain 3 scores	r=-0.17, *p*=0.50	r=0.17, *p*=0.45	r=-0.26, *p*=0.46	r=-0.26, *p*=0.46
Fathers' CHIP domain 3 scores	r=-0.33, *p*=0.38	r=-0.15, *p*=0.61	r=-0.25, *p*=0.51	r=-0.25, *p*=0.51
Continuous Variables				
Age of Feature Onset	r=0.18, *p*=0.45	r=-0.270, *p*=0.17	-	-
Years since Disease Diagnosis	r=-0.17, *p*=0.49	**r=0.49, *p*=0.02***	-	-
Current age	r=-0.08, *p*=0.75	r=0.28, *p*=0.18	-	-
Number of Siblings	r=-0.05, *p*=0.84	r=0.06, *p*=0.78	-	-
Number of Features	r=0.16, *p*=0.51	r=0.25, *p*=0.20	-	-
Number of Life Stress Circumstances	r=0.09, *p*=0.72	r=-0.17, *p*=0.50	-	-
Coping Mechanisms				
Doing things with family relatives	**r=0.80, *p*=0.02***	r=-0.09, *p*=0.79	-	-
Trying to maintain family stability	**r=0.51, *p*=0.02***	r=-0.34, *p*=0.25	-	-
Involvement in social activities with friends	**r=0.79, *p*=0.02***	r=0.18, *p*=0.58	-	-

Getting away by myself	**r=-0.55, *p*=0.02***	r=0.05, *p*=0.88	-	-
Purchasing gifts for oneself and/or other family members	**r=-0.62, *p*=0.01***	r=-0.53, *p*=0.08	-	-

Pearson correlations were performed (presented by *r*) for mothers' and fathers' PSI/SIPA and FIM scores, clinical features, GMFCS, MACS, EDACS, and CFCS severity scores, and coping mechanisms (all other coping mechanisms not listed did not reach statistical significance). Legend: *: statistically significant ($p<0.05$). Legend: - : the correlation could not be performed due to similarities in the variables, or not enough data was available to render a correlational analysis.

As shown in Table 3.5, the chi-square analysis did not show any statistically significant relationship between PSI stress percentile scores of mothers and fathers and categorical variables (i.e., child's clinical features, severity scores, or parent demographics). However, it did show statistically significant relationships between PSI stress percentile scores of mothers and certain parents' life stress circumstances such as: debt (for mothers) (X^2 (1, n=15) = 12.94, p=0.01), substantial income decrease (for fathers) (X^2 (1, n=8) = 14.44, p=0.04), taking care of an ill parent (for fathers) (X^2 (1, n=17) =11.91, p<0.01), suffering from an injury or chronic health condition (for fathers) (X^2 (1, n=17) =11.91, p=0.01), and having a child enter a new school (for mothers) (X^2 (1, n=15) = 16.35, p=0.01). There was no statistically significant relationship between fathers' PSI stress percentile scores and any categorical variable (most likely due to the small sample size).

Table 3.5 Summary of Chi Square Analysis Results for Categorical Variables

	Mothers' Stress Percentile Score		
Categorical Variables	**Chi Squared Value**	***p*-value**	**Cramer's V**
Abnormal Gait	17.00	0.32	1.00
Delayed Cognitive Development	56.25	0.29	0.97
Fatigue	13.00	0.37	1.00
Spasticity	60.00	0.18	1.00
Tremor	15.51	0.42	0.93
Dystonia	17.00	0.26	1.00
Ataxia	14.22	0.43	0.92
Dysmetria	14.81	0.39	0.93
Dysarthria	15.11	0.44	0.92
Sialorrhea	15.11	0.44	0.92
Dysphagia	16.95	0.39	0.94

Wheelchair Use	15.24	0.51	0.90
Feeding Tube	14.37	0.57	0.87
Anarthria	20.00	0.27	1.00
Behavioral Issues	14.37	0.57	0.87
GMFCS	59.22	0.36	0.93
EDACS	55.00	0.36	0.96
MACS	34.13	0.41	0.94
CFCS	58.40	0.25	0.96
Marital Status	13.56	0.48	0.48
Education	23.43	0.61	0.61
Employment Status	13.40	0.38	0.38
Household Income	25.63	0.36	0.36
Mothers' Debt	12.94	**0.01***	0.89
Fathers' Substantial Income Decrease	14.44	**0.04***	0.80
Fathers taking care of an ill parent	11.91	**0.003***	0.84
Fathers suffering from an injury or chronic health condition	11.91	**0.01***	0.84
Mothers having a child enter a new school	16.35	**0.01***	0.75

Chi square analysis was used for each factor. Cramer's V represents the strength of the relationship between variables. Categorical variables such as the child's clinical features or severity scores and parents' demographics were not found to contribute to mothers' stress percentile scores *(p*>0.05). 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 due to 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*>0.05). Legend: *: statistically significant (*p*<0.05).

Chapter 4: Discussion

POLR3-related leukodystrophy is a devastating rare neurological disease, in which patients may experience several debilitating clinical features. While this disease has a grave impact on those affected, there is little known about the impact of the disease on those who care for these patients. To our knowledge, it is the first study to examine the impact of this disease on parental quality of life, stress levels, experiences of injustice, and coping mechanisms used.

Rationale for the Selection of Questionnaires

The choice of questionnaires played an important role in obtaining concise and reliable results. For example, there were several other quality of life questionnaires of interest for our

study's purpose, such as the NeuroQOL[165] and the WHOQOL-100[166] questionnaires. The NeuroQOL is a 17-domain questionnaire designed to measure quality of life for individuals with neurological diseases[165]. While the population is in line with ours, we deemed several questions as distressing for parents which could impact their ability to respond truthfully, potentially causing defensive responses and skewing obtained results. As an example, distressing questions included: "I feel like I have no reason for living [due to my situation]", or, "Some people acted as though it was my fault my child has this illness". The WHOQOL-100 is a 100-item questionnaire that investigates numerous factors that may impact an individual's quality of life[166]. This questionnaire was not chosen due to the time demands it would impose on parents, therefore potentially limiting the participation or response rates from parents. It also contained items that went beyond the scope of our research study, such as questions about an individual's physical environment (i.e., traffic, pollution, and climate), as well as the physical safety and sexual activity of the individual. For these reasons, we elected to use the Family Impact Module (FIM), a widely use questionnaire. The FIM questionnaire has an appropriate amount of items that could be answered in a relatively short time frame, covering a variety of aspects of quality of life, such as relationships, health and wellness, and cognitive and social functioning[139], and the questions are not formulated in a way that would be distressing nor suggestive towards an answer.

Regarding assessing parental stress, besides the Parenting Stress Index 4th Edition questionnaire, several other stress questionnaires were also available, such as the Parenting Daily Hassles Scales[167] and the Caregiver Strain Questionnaire[168]. The Parenting Daily Hassles Scales focuses on the-day-to-day issues and difficulties encountered as a caregiver; however it does not assess external stress factors such as support systems or life stress circumstances[167]. The

Caregiver Strain Questionnaire does examine a variety of potential stressors a caregiver might face; however the questionnaire was specifically designed for neurotypical children and not children with disabilities[168]. Therefore, we elected to use the Parenting Stress Index 4th Edition (PSI) (and the Stress Index for Parents of Adolescents (SIPA)), which is a relatively concise and thorough questionnaire that assesses the role of a parent, the parent-child relationship, the difficulties and stressors of parenting (both objective and subjective), child(ren)'s behavior, and external life stress situations[147]. Of note, this questionnaire has good reliability[147] and validity[147] and has been cited many times, including being used in the young patient population with chronic illnesses[112,169–172].

To observe parents' coping strategies, it was important to use a questionnaire that specifically included different types of coping mechanisms (both adaptive and maladaptive). There were other questionnaires to choose from, such as the Coping Scale[173], Coping Questionnaire[174], and Coping Strategies Questionnaire[175], however, these questionnaires had been created for a specific population, such as individuals with chronic pain and anxious youth, which differ from our cohort. As well, these questionnaires did not offer actual coping mechanisms, but instead asked what parents did when they faced a problem (i.e., "When dealing with a problem, I try to see the humor in it"), which was less useful for our research purposes. Therefore, the CHIP questionnaire was chosen because, as previously mentioned, it had been used in several other research studies with parents of children with chronic health conditions[154–157], reinstating its validity and reliability[154].

Lastly, to measure whether parents perceive their situations as unjust, the IEQ[158] was the best choice as it is the only known questionnaire to fully and thoroughly measure experiences of injustice.

Parents of Patients with POLR3-Related-Leukodystrophy have Normal Stress Level Results as Measured by the Stress Questionnaires

The PSI stress percentile scores of parents with children with POLR3-related leukodystrophy were compared to the normative sample (represented by percentiles). The percentile scores represent a score that is equal to or greater than the normative sample. For example, if a parent scored a 52%, this indicates that their score would be equal to or greater than 52% of the normative sample. If considered individually, the majority of parents' scores were higher than 50% of the normative sample. This indicates that our parent population had higher stress scores compared to 50% of the normative sample, and thus, represents what has been found in past literature in similar chronic diseases[116,117,176–178]. However, if one were to only look at the scores relative to the normative sample, then this would also mean that any parent who completes this questionnaire will obtain a value that will always be higher than a percentage of the normative sample, regardless of whether or not their child has a chronic disease such as POLR3-related leukodystrophy in this case. For example, if a mother with a healthy child completes the questionnaire, and receives an 80%, then her score would also represent a score that would be equal to or greater than 80% of the normative sample, even though her child does not have a chronic illness. Therefore, we must also consider where these parents' individual scores rank within the range of normal, high, and clinically significant stress levels. When doing so, we notice that around 80% of our parent population had stress percentile scores within the normal stress level range, contrasting our hypothesis and results found in past literature[116,117,176–178].

There are multiple factors that could have influenced the normal stress level results of parents. One hypothesis takes into account how we define/consider stress. It is possible that stress is emphasized as being this inability to cope with physical, psychological, or emotional

pressure, yet may not necessarily take into account the actual situation at hand. Therefore, we should also consider stress to be relative to whether there is shock or novelty, uncertainty, or instability of a circumstance. For example, shock or novelty is less significant in parents who have known about their child(ren)'s diagnosis or who's child has been living with the disease for some time, compared to parents for whom the diagnosis was very recently disclosed. In fact, in this cohort, the average years passed since disease diagnosis was approximately 11 years, and the median was 8 years at the time of questionnaire completion, which indicates that many of the patients were further into their disease course when the questionnaires were completed. This may contribute to the reduced stress level experienced by parents since, as mentioned previously, parents were aware of their child's diagnosis for some time, and thus, probably had time to adjust and adapt to their child's disease and its implications. As well, in most patients, POLR3-related leukodystrophy has a certain stability of progression and clinical features, which makes it more straightforward when expecting and caring for the next steps of the child's disease, also contributing to the previous ideas of stability and certainty in relation to stress level. Lastly, there is less uncertainty for parents and a sense of control and preparedness when caring and providing for their sick child(ren) when they have had time to adjust to the diagnosis.

Additionally, factors such as access to a leukodystrophy center of excellence and availability of resources may explain why our population sample has a normal level of stress compared to populations with other chronic health conditions. Our population is being followed by specialized leukodystrophy centers that employ various medical health professionals with advanced knowledge on leukodystrophy care and research. Other populations may not have such centers that specialize in caring for leukodystrophies or may not have widespread knowledge on how to do so. As well, along with being followed at these specialized leukodystrophy centers,

parents could also be introduced to certain resources (i.e., finding adaptable equipment for their child, finding financial support, etc.) which could help make it easier to care for their child. However, this could also lead to a potential limitation, as our patients have both specialized leukodystrophy care and access to resources, while others living in locations where these resources do not exist were not recruited to this study, and this may have skewed our results.

Rationale for the Qualitative Results: A Parent's Perspective on Their Situations

From our findings, it is evident that parents may not be as stressed as initially hypothesized. While the focus was on obtaining and analyzing quantitative results, it is important to note that most participating parents provided information on how they and their children live with the disease on a daily basis. Some mothers sent our team photos of their children's drawings, enjoying fun activities and new experiences with classmates, or simply smiling with family and friends. Another mother sent us a video of her son bicycle riding without training wheels, stating that: "Although we are aware that this capability can be lost in the future, we were really happy for this step forward in his growth". Another couple explicitly mentioned: "[the] overall level of stress for both of us is very low. [My son] has lived longer than we ever could have hoped for, and he is very happy with his current situation… We are simply grateful for every day and will need to plan for the day that he will probably outlive us". The fact that these parents sent us these photographs, videos and messages through their own willingness may illustrate that capturing the little happy moments of their children, and showing us how they feel, also encourages these parents to see their children in a new light; enjoying life to the fullest despite their condition. This may in turn alter parents' perceptions of their situations for the better.

Secondly, these examples may imitate a phenomenon known as emotional contagion, where there is an influential predisposition to both feel and express emotions similar to those around you[179]. From our team's clinical experience, children with POLR3-related leukodystrophy are known to be happy children. Therefore, their emotions and feelings of happiness may in turn be 'spread' to parents who regularly care for their child, positively changing parents' perspectives on their circumstances and potentially reducing their stress level.

Thirdly, there may exist disconnect between objectively upsetting situations and stress, where this would depend on the changing of expectations. An example of this is shown through a mother's letter to us describing her situation. Here is an excerpt from her letter: "[He] was first diagnosed with a leukodystrophy at age 14. We were told there is not treatment, no cure and we should expect him to die young. Making peace with that information took some time and we finally decided to live day by day and to keep [him] happy. All of our efforts were to make sure he had fun every day. Now, as he turns 40 years old in September, he is still laughing, telling jokes and is content…". This portion of the letter showcases that this mother expected her son to live a short life (which thus represents the upsetting situation). If she did not accept this news, and thus built unrealistic expectations to cope (i.e., that he would live a long life), in the event that the worst did occur, then this upsetting situation would not surprisingly be associated with, and strongly affect, her stress level and overall well-being. However, we see that this mother shifted her expectations to focus on making sure her son was content and cared for, for however long she would have with him. Since her son has lived past anyone's expectations, this mother may have been able to appreciate this positive outcome and thus change her perspective on the entire situation, potentially allowing her to disassociate the objectively upsetting situation from the stress she may have experienced, and reduce her stress level altogether.

Of course, it is also possible that parents who are less stressed, and who do not experience many stressful life circumstances as shown by the PSI/SIPA Life Stress scores, are more likely to spend time completing these questionnaires. This is a potential limitation of this study, and therefore, due to this preliminary research, a qualitative study which incorporates many parent accounts should be performed to complement these research findings.

Low Parental Quality of Life Scores May Not Be Associated with Parental Stress Scores

For quality of life results, our parent population scored lower than the normative sample, with large effect sizes indicating that these findings have practical significance. These results are found in the literature for other chronic diseases[93–96,99,101] and are in line with our hypothesis. One of the most fundamental responsibilities of a parent is taking care of their child. If they frequently witness their child suffering with a chronic disease, this can have a grave impact on their life, leading to lower quality of life scores. However, if we recognize stress and quality of life as interlinked, then lower quality of life scores should be associated with higher stress scores, as our hypothesis suggests, when in fact, the opposite result was found. We hypothesize that these stress and quality of life results may be explained by how we measure each concept. The parental stress level measured by the PSI/SIPA/PSS questionnaires relate to the parents' experiences from their child's experiences (i.e., "My child cries and fusses", "It takes a long time and it is very hard for my child to get used to new things"), once again, taking into consideration the shock or novelty, uncertainty, or instability of their child's circumstance, whereas the FIM questionnaire relates directly to the parents' thoughts and feelings of themselves (i.e., "I feel helpless or hopeless", "I feel isolated from others"), where individuals may potentially perceive their lives to be more difficult when thinking introspectively. Therefore, they may be more

inclined to score lower on the FIM questionnaire when responding to these questions, thus lowering their quality of life scores altogether.

Lower Quality of Life Scores May Lead to Higher Experiences of Injustice Scores

Along with finding that parents of children with POLR3-related leukodystrophy have lower quality of life scores compared to the normative sample, these parents were also shown to have high experiences of injustice raw scores. Similar results were found for experiences of injustice in individuals with chronic pain[180]. As previously mentioned, the injustice experiences questionnaire was used to measure whether parents perceived their situations to be unfair[158]. Experiences of injustice are included in examining a person's overall quality of life, as quality of life is defined as an individual's perception of their position in life in certain contexts, along with their physical and emotional well-being in that moment[90]. These parents are dealing with anomalous situations; having to take care of a child with a rare chronic disease on top of other parental responsibilities. The more they think or are reminded of their situations and the situation of their child, as well as how they perceive their lives to be, may determine how well they live overall, where the higher perceived blame, irreparability, and repetitive thought may result in greater experiences of injustice and thus poorer quality of life[181].

Correlational Results Found Between and Within Mothers' and Fathers' Questionnaire Scores, Life Stress Situations, Debt, and Years Since Disease Diagnosis

There were a few correlations found between mothers' and fathers' scores, such as between mothers' and fathers' quality of life scores, mothers' quality of life scores and fathers' experiences of injustice scores, fathers' quality of life scores and mothers' experiences of injustice scores, and mothers' and fathers' stress scores. It is possible that the correlations seen between mothers and fathers are due to the fact that the majority of our population are married or

in a common-law relationship, and live in the same household. Therefore, one parent's stress level, quality of life, and experiences of injustice are likely to influence the other parent, ultimately leading to similar scores between the different questionnaires.

Additionally, negative correlations were found within mothers' and fathers' scores, such as between mothers' quality of life and experiences of injustice scores, mothers' quality of life and stress scores, and fathers' quality of life and experiences of injustice, which is consistent with our hypotheses and what has been published in the chronic disease literature[182,183].

For the categorical modifiable variables, a strong positive relationship was found between increased mothers' stress levels and increased fathers' stress levels due to life stress situations such as taking care of an ill parent and suffering from an injury or chronic health condition. The majority of mothers in our cohort considered themselves to be the primary caregiver, indicating that they take on a greater role in caring for their child. However, caring for a child who requires significant medical attention can create added pressure on the mother if she is the main person dealing with the situation. So, when a father is tending to other needs such as taking care of an ill parent or dealing with his own personal health issues (which can increase his stress levels), the mother must take on more of the responsibilities within the family, thus potentially increasing the mothers' stress level. We can also see how life stress circumstances influence each other. It has been shown that, along with mental health, the physical health of an individual can contribute to one's financial issues, and vice versa[184]. Therefore, having a chronic health condition and/or taking care of an ill parent may in turn affect one's ability or availability to work, thus affecting their income, and therefore potentially contributing to higher stress. This stress can in turn worsen the physical and mental health of the parent, as well as the ability of that parent to take care of their ill parent (for example), continuing on this vicious cycle, and

therefore contributing to the increase in stress of the mother (where a positive correlation between mothers' and fathers' stress level was found). All in all, if outside factors are found to influence the parental stress level, it may be useful to consider these when allocating resources for these families.

While there was no relationship found between fathers' stress and life stress circumstances likely due to our small sample size, there did exist a relationship between mothers' stress and debt. There have been several studies that have documented the correlation between debt or financial issues with stress in America[185,186], and many of our participants are American, where healthcare and health insurance is becoming increasingly expensive[187,188]. Interestingly enough, 11% (3/27) of families are Canadian (7% (2/27) being from and residing in Quebec), whereas 74% (20/27) of patients are from the US, and 15% (4/27) are international (from other European, South American, and Northern African countries). To our surprise, families where parents were highly stressed were families that resided both in Quebec and abroad, but not in the United States of America. These results do not corroborate what has been seen in other studies[185,186,189,190] and it remains unclear why this is the case. It is important to note that because of the small sample size (as mentioned previously), strong conclusions cannot be drawn.

Other than these results, we did not find other statistically significant relationships between any other clinical features and stress level, such as behavioral issues, fatigue, and physical disability of the child, which was originally hypothesized. Nevertheless, it is possible that this (and the rest of our study's insignificant results) is due to our small sample size, in which case a study with a larger population sample would need to be conducted. As well, this was a cross-sectional study, meaning that only one time point was considered for examination.

This would be an issue as parental stress and quality of life can change over time as their child's disease progresses. Therefore, in order to have a more accurate and thorough analysis, a prospective study would need to be conducted for the future direction of this project.

For continuous variables, only a positive correlation between mothers' quality of life scores and years since diagnosis was found. These results can be expected since, as previously mentioned, most of our mothers in our parent population were primary caregivers, and revealed they attended their child's medical appointments the majority of the time. Therefore, as the disease progresses, mothers potentially have more time to cope with, understand, and adapt to the care plan for their child's disease, thus improving their own overall well-being.

All in all, from an observational perspective, the modifiable factors that directly affected the parent-child relationship and family functioning seemed to impact parental mental health the most.

With a larger sample size, we may have found that on top of financial burdens, family dynamics (i.e., marital status, number of siblings, coping strategies that involve the family) are also most likely going to greatly influence parental mental health.

Without a stable home environment, and with persistent financial issues, parents will struggle to care for their family, and specifically, their ill child. Therefore, having interventions such as having a support system (whether friends, family, psychologists, social workers) that can help in creating a strong familial relationship, engaging in fun activities that will include the ill child regardless of their limitations, and governmental financial support are all great ways to alleviate some of the parents' worries and thus improve their mental health.

Rationale for Considering Parents' Helpful and Unhelpful Coping Mechanisms from the CHIP Questionnaire, and Its Issues

Based on the mean scores of specific coping mechanisms used by parents, coping mechanisms found to be the most helpful for parents seemed to be those that directly involved them with their children/in their children's lives (such as spending time and doing activities with their children). This is the case, as parents may feel a sense of control and connection when tending to their children who may require more care than the average child. By focusing their time and energy on helping their child and seeing a direct improvement through their actions may allow them to feel as though they can better cope with their situation and the situation of their child. Conversely, coping mechanisms such as the parent getting angry because of the situation, believing their child will be healed, or getting other members of the family to help around the house were found to be the least helpful for parents. This may be due to the fact that these coping mechanisms do not help the parent with the child's life directly, and thus may not improve the well-being of their child nor themselves in the long run.

While the above analysis of coping mechanisms may be true, there are also potential issues. Primarily, these outcomes may be a result of a parent's defensive responding, which could not be determined for this questionnaire. Parents may not want to reveal what is truly unhelpful to them, or exaggerate what is helpful, to make them feel better in caring for their child. For example, if parents report that going for a walk alone is a helpful coping strategy for their stress, they may feel guilty about not spending this time with their child(ren). To avoid feeling guilty or being judged because of these observations, parents may be more inclined to rate this coping mechanism as unhelpful, creating a bias in the results. Secondly, when looking at the average scores of each coping mechanism individually, it is possible that coping mechanisms were found to be either more or less helpful in relation to helping with the child's situation.

However, feeling as though a coping mechanism is more or less helpful does not indicate whether it has a direct effect on factors like stress and quality of life.

On the other hand, the correlational analysis between mothers' stress and certain coping mechanisms provided some interesting results. Coping mechanisms such as 'getting away by myself' or 'purchasing gifts for myself' were negatively correlated with mothers' stress scores, indicating that these coping strategies decreased in helpfulness as stress increased. However, the correlational analysis showed that positive correlations were found between mothers' stress and coping mechanisms such as 'going to social gatherings with friends' or 'doing things with other family relatives outside of their immediate family', meaning that these coping mechanisms were found to be more helpful as mothers' stress increased, which goes against our hypothesis of why certain coping mechanisms were either helpful or unhelpful.

A few reasons for these correlational results may be that: parents may use certain coping strategies to help them deal with their child's illness, but it is that same illness or the act of taking care of their child that may in turn be that stressor for them. Therefore, disassociating from that situation and doing something completely different, such as spending time with others or attending social events, may allow them to relieve some stress, and thus find those coping mechanisms helpful during their moments of increased stress. As well, in line with the statement above, for day-to-day stressors, superficial, 'unhelpful' coping mechanisms may be more helpful in shifting parents' attention away from the immediate situation, as a short-term coping strategy. However, we hypothesize that it is only when more stressful situations present themselves (meaning situations that can affect the parent or their child(ren) long-term), such as deciding whether or not their child needs a feeding tube, that the unhelpful coping mechanisms will remain unhelpful. While there are many ways to interpret the above results, it is important to

note that these results only suggest a correlation, not causation as to whether these coping mechanisms are found to be more helpful when a parent is stressed, or whether a parent's stress will dictate if they find this coping mechanism to be helpful. A deeper investigation on stress and coping mechanisms would be required to address this.

Limitations

One limitation of this study was the small population size, i.e., 32 patients from 26 families, with 43 parents total answering questionnaires. To date, 152 international patients with POLR3-related leukodystrophy are known to our study team. Excluding patients for whom we did not have contact information, who were deceased, or who were adult patients that did not require a caregiver, 50 patients remained, amounting to approximately 64 parents, as some parents were single. While no parent directly refused to participate in the study, there were 21 parents who did not respond back confirming their completion of the questionnaires, or whether they were interested in participating in our research. This left us with only 43 parents who were responsive and agreed to participate. In the field of rare diseases, these numbers are acceptable, but having a larger sample size may have allowed us to draw stronger conclusions.

Another limitation relates to the burden of completing the questionnaires. Only 26 out of 43 parents completed *all* questionnaires required, with some families having both parents fill them, others with one parent filling all questionnaires, and others where only a fraction of the required questionnaires were filled. This contributed to the small sample size and posed challenges for statistical analysis, namely correlational analysis where many results were insignificant. Selection bias could have also come into play, potentially affecting the internal and external validity of the results. While unfortunately unavoidable, to try to overcome this issue, newly recruited parents were asked to participate, and reminders were sent to the other parents

along with an offer of completing the questionnaires together with a researcher through a virtual meeting.

Another challenge encountered for this study was the statistical analysis (chi-square analysis) between the FIM and PSS scores of parents and the categorical modifiable factors. Parents' stress percentiles have designated ranges that determine whether these scores are normal, high, or clinically significant. However, the FIM and PSS scores can only be considered *higher* or *lower* than a sample population such as a normative sample. Therefore, we could not perform the chi-square analysis to conclude whether certain FIM or PSS scores were directly associated with certain categorical factors. However, all parents were shown to have lower FIM and PSS scores compared to their normative samples, potentially indicating that all categorical factors could be considered to correlate to these results, which would need to be further investigated.

Lastly, the design of the study may have been a limitation, both considering that it is a cross-sectional study and that a sole quantitative approach was undertaken. Regarding the cross-sectional nature of the study, studying a population at one single time point makes it hard to determine how the population evolves as their situation progresses. In this case, parental stress and poor quality of life in our population is hypothesized to be at its peak at the time of diagnosis, and at the end-of-life, where stress and quality of life will fluctuate in between depending on the patient's health status and parents' and family's life situation. Therefore, a prospective study that follows a larger population would be required to properly assess both parental stress and quality of life, as well as determine which modifiable factors influence parental stress and quality of life. Regarding the sole quantitative approach, we have learned, through this study and from parents' feedback about their situations, that a combined quantitative

and qualitative approach may be ideal. Quantitatively, the results of this study suggested that the overall majority of parents with children with POLR3-related leukodystrophy have a normal stress level, yet also have poorer quality of life compared to normative samples. We identified some contributing factors to this but could not obtain granular information as to why parents answered the way they did. While a few parents sent us explanations which 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.

Chapter 5: Conclusion

While there have been several studies examining parental stress and patients' quality of life with diverse diseases, parents' overall well-being relative to their child's POLR3-related leukodystrophy diagnosis has never been studied. In this study, we conducted a thorough examination of the impact of a child's disease on parents' overall well-being, including various factors such as stress, quality of life, experiences of injustice, and coping mechanisms used by these parents. The aims of this study, such as determining whether parental stress and quality of life of this particular parent cohort are affected in comparison to parents of healthy children, as well as which modifiable factors (continuous or categorical) negatively impacted or influenced parental stress and quality of life, were met through the obtained results, where the obtained results also added to the gaps in literature. Parents of children with POLR3-related leukodystrophy had lower QoL scores compared to normative samples, and ~80% of these parents had normal stress level scores. For the IEQ questionnaire, fathers' perceived injustice scores ranged from very low to very high, where mothers' scores ranged from average to high. There were correlations found between and within mothers' and fathers' scores, such as QoL, stress level, and IEQ scores. Helpful coping mechanisms (i.e., 'investing myself in my children',

'doing things with my children', 'doing activities together as a family') seemed to be related to situations where parents were directly involved in their child's life, and least helpful (i.e., 'believing that my child(ren) will get better', 'getting other members of the family to help with tasks at home', 'allowing myself to get angry') were those that seemed to be irrelevant to their child's care. For certain less helpful coping mechanisms in certain situations, they were found to be more helpful as stress increased. Lastly, relationships were found between mothers' stress scores, years since disease onset and certain life stress circumstances such as debt. The obtained results contribute to the understanding of where focus should be directed in healthcare. In terms of healthcare research, developing future treatments for these children's diseases rely heavily on conducting clinical trials, in which identifying patient outcomes are essential. In terms of providing healthcare services, these should be considered useful to both patients and their caregivers, especially when caring for individuals with rare diseases that are less well-understood and carry stigma[1]. Our results suggest that implementing psychological and social support throughout patients' disease progression, as well as offering access to activities or programs to integrate families with children with disabilities, may improve quality of life of these parents. Also, since outside factors such as life stress situations directly correlate with parents' stress and quality of life, this information can be useful to consider when allocating resources for these families, whether financially or other.

This is the first pilot study looking at the well-being of parents and caregivers of patients with POLR3-related leukodystrophy. We have identified factors leading to reduced quality of life of patients and caregivers. It is possible that due to our sample size and cross-sectional nature of the study, other factors are also contributing and therefore, a larger prospective study to follow a parent's stress level and quality of life throughout their child's disease would be an interesting

future path and beneficial to further our understanding of how a child's disease can impact those who care for and live with them.

References

1. Bogart K, Hemmesch A, Barnes E, et al. Healthcare access, satisfaction, and health-related quality of life among children and adults with rare diseases. *Orphanet J Rare Dis*. 2022;17(1):196. doi:10.1186/s13023-022-02343-4

2. Bonkowsky JL, Nelson C, Kingston JL, Filloux FM, Mundorff MB, Srivastava R. The burden of inherited leukodystrophies in children. *Neurology*. 2010;75(8):718-725. doi:10.1212/WNL.0b013e3181eee46b

3. Bernard G, Vanderver A. POLR3-Related Leukodystrophy. In: Adam MP, Mirzaa GM, Pagon RA, et al., eds. *GeneReviews*®. University of Washington, Seattle; 1993. Accessed May 25, 2023. http://www.ncbi.nlm.nih.gov/books/NBK99167/

4. Wolf NI, Vanderver A, van Spaendonk RML, et al. Clinical spectrum of 4H leukodystrophy caused by POLR3A and POLR3B mutations. *Neurology*. 2014;83(21):1898-1905. doi:10.1212/WNL.0000000000001002

5. Helman G, Van Haren K, Bonkowsky JL, et al. Disease specific therapies in leukodystrophies and leukoencephalopathies. *Mol Genet Metab*. 2015;114(4):527-536. doi:10.1016/j.ymgme.2015.01.014

6. Mirchi A, Pelletier F, Tran LT, et al. Health-Related Quality of Life for Patients With Genetically Determined Leukoencephalopathy. *Pediatr Neurol*. 2018;84:21-26. doi:10.1016/j.pediatrneurol.2018.03.015

7. Dermer E, Spahr A, Tran LT, et al. Stress in Parents of Children With Genetically Determined Leukoencephalopathies: A Pilot Study. *J Child Neurol*. 2020;35(13):901-907. doi:10.1177/0883073820938645

8. Hattangadi N, Cost KT, Birken CS, et al. Parenting stress during infancy is a risk factor for mental health problems in 3-year-old children. *BMC Public Health*. 2020;20(1):1726. doi:10.1186/s12889-020-09861-5

9. Pinquart M, Shen Y. Behavior problems in children and adolescents with chronic physical illness: a meta-analysis. *J Pediatr Psychol*. 2011;36(9):1003-1016. doi:10.1093/jpepsy/jsr042

10. Miranda RN, Ximenes R, Gebretekle GB, Bielecki JM, Sander B, RADAM-LAC Research Team. Health-Related Quality of Life in Neurological Disorders Most Commonly Associated With Zika-Virus Infection: A Systematic Review. *Value Health J Int Soc Pharmacoeconomics Outcomes Res*. 2020;23(7):969-976. doi:10.1016/j.jval.2020.03.004

11. Dymecka J, Gerymski R, Tataruch R, Bidzan M. Fatigue, Physical Disability and Self-Efficacy as Predictors of the Acceptance of Illness and Health-Related Quality of Life in Patients with Multiple Sclerosis. *Int J Environ Res Public Health*. 2021;18(24):13237. doi:10.3390/ijerph182413237

12. Pinquart M. Parenting stress in caregivers of children with chronic physical condition—A meta-analysis. *Stress Health*. 2018;34(2):197-207. doi:10.1002/smi.2780

13. van der Knaap MS, Bugiani M. Leukodystrophies: a proposed classification system based on pathological changes and pathogenetic mechanisms. *Acta Neuropathol (Berl)*. 2017;134(3):351-382. doi:10.1007/s00401-017-1739-1

14. Kuhn S, Gritti L, Crooks D, Dombrowski Y. Oligodendrocytes in Development, Myelin Generation and Beyond. *Cells*. 2019;8(11):1424. doi:10.3390/cells8111424

15. Bradl M, Lassmann H. Oligodendrocytes: biology and pathology. *Acta Neuropathol (Berl)*. 2010;119(1):37-53. doi:10.1007/s00401-009-0601-5

16. Colonna M, Butovsky O. Microglia Function in the Central Nervous System During Health and Neurodegeneration. *Annu Rev Immunol*. 2017;35:441-468. doi:10.1146/annurev-immunol-051116-052358

17. Wei DC, Morrison EH. Histology, Astrocytes. In: *StatPearls*. StatPearls Publishing; 2023. Accessed May 25, 2023. http://www.ncbi.nlm.nih.gov/books/NBK545142/

18. Susuki K. Myelin. A Specialized Membrane for Cell Communication. *Nature Education*. 2010;3(9):59.

19. Paz Soldán MM, Pirko I. Biogenesis and significance of central nervous system myelin. *Semin Neurol*. 2012;32(1):9-14. doi:10.1055/s-0032-1306381

20. Magnetic Resonance of Myelination and Myelin Disorders, 3rd ed. *AJNR Am J Neuroradiol*. 2006;27(4):947-948.

21. Filley CM, Kleinschmidt-DeMasters BK. Toxic leukoencephalopathy. *N Engl J Med*. 2001;345(6):425-432. doi:10.1056/NEJM200108093450606

22. Cortese I, Reich DS, Nath A. Progressive multifocal leukoencephalopathy and the spectrum of JC virus-related disease. *Nat Rev Neurol*. 2021;17(1):37-51. doi:10.1038/s41582-020-00427-y

23. Daroff R, Aminoff M. *Encyclopedia of the Neurological Sciences - 2nd Edition*. 2nd ed. Academic Press https://shop.elsevier.com/books/encyclopedia-of-the-neurological-sciences/daroff/978-0-12-385157-4

24. Garcia LM, Hacker JL, Sase S, Adang L, Almad A. Glial cells in the driver seat of leukodystrophy pathogenesis. *Neurobiol Dis*. 2020;146:105087. doi:10.1016/j.nbd.2020.105087

25. Vanderver A, Prust M, Tonduti D, et al. Case definition and classification of leukodystrophies and leukoencephalopathies. *Mol Genet Metab*. 2015;114(4):494-500. doi:10.1016/j.ymgme.2015.01.006

26. Feinstein M, Markus B, Noyman I, et al. Pelizaeus-Merzbacher-like Disease Caused by AIMP1/p43 Homozygous Mutation. *Am J Hum Genet*. 2010;87(6):820-828. doi:10.1016/j.ajhg.2010.10.016

27. Homozygosity for a nonsense variant in AIMP2 is associated with a progressive neurodevelopmental disorder with microcephaly, seizures, and spastic quadriparesis - PubMed. Accessed May 25, 2023. https://pubmed.ncbi.nlm.nih.gov/29215095/

28. Tümer Z, Møller LB. Menkes disease. *Eur J Hum Genet EJHG*. 2010;18(5):511-518. doi:10.1038/ejhg.2009.187

29. Schwartz CE, May MM, Carpenter NJ, et al. Allan-Herndon-Dudley syndrome and the monocarboxylate transporter 8 (MCT8) gene. *Am J Hum Genet*. 2005;77(1):41-53. doi:10.1086/431313

30. Leukoencephalopathy with vanishing white matter: MedlinePlus Genetics. Accessed May 25, 2023. https://medlineplus.gov/genetics/condition/leukoencephalopathy-with-vanishing-white-matter/

31. Van Der Knaap MS, Pronk JC, Scheper GC. Vanishing white matter disease. *Lancet Neurol*. 2006;5(5):413-423. doi:10.1016/S1474-4422(06)70440-9

32. Ashrafi MR, Tavasoli AR. Childhood leukodystrophies: A literature review of updates on new definitions, classification, diagnostic approach and management. *Brain Dev*. 2017;39(5):369-385. doi:10.1016/j.braindev.2017.01.001

33. Messing A, Brenner M, Feany MB, Nedergaard M, Goldman JE. Alexander disease. *J Neurosci Off J Soc Neurosci*. 2012;32(15):5017-5023. doi:10.1523/JNEUROSCI.5384-11.2012

34. Pavuluri P, Vadakedath S, Gundu R, Uppulety S, Kandi V. Krabbe Disease: Report of a Rare Lipid Storage and Neurodegenerative Disorder. *Cureus*. 9(1):e949. doi:10.7759/cureus.949

35. Shaimardanova AA, Chulpanova DS, Solovyeva VV, et al. Metachromatic Leukodystrophy: Diagnosis, Modeling, and Treatment Approaches. *Front Med*. 2020;7:576221. doi:10.3389/fmed.2020.576221

36. Management of mitochondrial leukoencephalopathy-related atax... : Medicine: Case Reports and Study Protocols. Accessed May 25, 2023. https://journals.lww.com/md-cases/Fulltext/2021/06000/Management_of_mitochondrial.6.aspx

37. La Piana R, Vanderver A, van der Knaap M, et al. Adult-Onset Vanishing White Matter Disease Due to a Novel EIF2B3 Mutation. *Arch Neurol*. 2012;69(6):765-768. doi:10.1001/archneurol.2011.1942

38. Charzewska A, Wierzba J, Iżycka-Świeszewska E, et al. Hypomyelinating leukodystrophies - a molecular insight into the white matter pathology. *Clin Genet*. 2016;90(4):293-304. doi:10.1111/cge.12811

39. Steenweg ME, Vanderver A, Blaser S, et al. Magnetic resonance imaging pattern recognition in hypomyelinating disorders. *Brain J Neurol*. 2010;133(10):2971-2982. doi:10.1093/brain/awq257

40. Schiffmann R, van der Knaap MS. Invited article: an MRI-based approach to the diagnosis of white matter disorders. *Neurology*. 2009;72(8):750-759. doi:10.1212/01.wnl.0000343049.00540.c8

41. Hamilton EM, Polder E, Vanderver A, et al. Hypomyelination with atrophy of the basal ganglia and cerebellum: further delineation of the phenotype and genotype–phenotype correlation. *Brain*. 2014;137(7):1921-1930. doi:10.1093/brain/awu110

42. Aula P. "Salla Disease": A New Lysosomal Storage Disorder. *Arch Neurol*. 1979;36(2):88. doi:10.1001/archneur.1979.00500380058006

43. Osório MJ, Goldman SA. Neurogenetics of Pelizaeus-Merzbacher disease. *Handb Clin Neurol*. 2018;148:701-722. doi:10.1016/B978-0-444-64076-5.00045-4

44. Nahhas N, Conant A, Hamilton E, et al. TUBB4A-Related Leukodystrophy. In: Adam MP, Mirzaa GM, Pagon RA, et al., eds. *GeneReviews®*. University of Washington, Seattle; 1993. Accessed May 25, 2023. http://www.ncbi.nlm.nih.gov/books/NBK395611/

45. Crow YJ. Aicardi-Goutières Syndrome. In: Adam MP, Mirzaa GM, Pagon RA, et al., eds. *GeneReviews®*. University of Washington, Seattle; 1993. Accessed June 8, 2023. http://www.ncbi.nlm.nih.gov/books/NBK1475/

46. van der Knaap MS, Valk J, de Neeling N, Nauta JJP. Pattern recognition in magnetic resonance imaging of white matter disorders inchildren and young adults. *Neuroradiology*. 1991;33(6):478-493. doi:10.1007/BF00588038

47. van der Knaap MS, Abbink TE, Min R. Megalencephalic Leukoencephalopathy with Subcortical Cysts. In: Adam MP, Mirzaa GM, Pagon RA, et al., eds. *GeneReviews®*. University of Washington, Seattle; 1993. Accessed June 8, 2023. http://www.ncbi.nlm.nih.gov/books/NBK1535/

48. Federico A, Gallus GN. Cerebrotendinous Xanthomatosis. In: Adam MP, Mirzaa GM, Pagon RA, et al., eds. *GeneReviews®*. University of Washington, Seattle; 1993. Accessed June 8, 2023. http://www.ncbi.nlm.nih.gov/books/NBK1409/

49. Matalon R, Delgado L, Michals-Matalon K. Canavan Disease. In: Adam MP, Mirzaa GM, Pagon RA, et al., eds. *GeneReviews®*. University of Washington, Seattle; 1993. Accessed June 8, 2023. http://www.ncbi.nlm.nih.gov/books/NBK1234/

50. Mendes MI, Gutierrez Salazar M, Guerrero K, et al. Bi-allelic Mutations in EPRS, Encoding the Glutamyl-Prolyl-Aminoacyl-tRNA Synthetase, Cause a Hypomyelinating Leukodystrophy. *Am J Hum Genet*. 2018;102(4):676-684. doi:10.1016/j.ajhg.2018.02.011

51. Verheijen FW, Verbeek E, Aula N, et al. A new gene, encoding an anion transporter, is mutated in sialic acid storage diseases. *Nat Genet*. 1999;23(4):462-465. doi:10.1038/70585

52. Wolf NI, Biancheri R, Zara F, et al. Hypomyelination and Congenital Cataract. In: Adam MP, Mirzaa GM, Pagon RA, et al., eds. *GeneReviews®*. University of Washington, Seattle; 1993. Accessed June 8, 2023. http://www.ncbi.nlm.nih.gov/books/NBK2587/

53. Hafsi W, Badri T. Cockayne Syndrome. In: *StatPearls*. StatPearls Publishing; 2023. Accessed June 8, 2023. http://www.ncbi.nlm.nih.gov/books/NBK525998/

54. Inoue K, Shilo K, Boerkoel CF, et al. Congenital hypomyelinating neuropathy, central dysmyelination, and Waardenburg–Hirschsprung disease: Phenotypes linked by SOX10 mutation. *Ann Neurol*. 2002;52(6):836-842. doi:10.1002/ana.10404

55. Wolf NI, Harting I, Innes AM, et al. Ataxia, delayed dentition and hypomyelination: a novel leukoencephalopathy. *Neuropediatrics*. 2007;38(2):64-70. doi:10.1055/s-2007-985137

56. Atrouni S, Darazé A, Tamraz J, Cassia A, Caillaud C, Mégarbané A. Leukodystrophy associated with oligodontia in a large inbred family: fortuitous association or new entity? *Am J Med Genet A*. 2003;118A(1):76-81. doi:10.1002/ajmg.a.10019

57. Sasaki M, Takanashi J ichi, Tada H, Sakuma H, Furushima W, Sato N. Diffuse cerebral hypomyelination with cerebellar atrophy and hypoplasia of the corpus callosum. *Brain Dev*. 2009;31(8):582-587. doi:10.1016/j.braindev.2008.09.003

58. Wolf NI, Harting I, Boltshauser E, et al. Leukoencephalopathy with ataxia, hypodontia, and hypomyelination. *Neurology*. 2005;64(8):1461-1464. doi:10.1212/01.WNL.0000158615.56071.E3

59. Timmons M, Tsokos M, Asab MA, et al. Peripheral and central hypomyelination with hypogonadotropic hypogonadism and hypodontia. *Neurology*. 2006;67(11):2066-2069. doi:10.1212/01.wnl.0000247666.28904.35

60. Bernard G, Thiffault I, Tetreault M, et al. Tremor-ataxia with central hypomyelination (TACH) leukodystrophy maps to chromosome 10q22.3-10q23.31. *Neurogenetics*. 2010;11(4):457-464. doi:10.1007/s10048-010-0251-8

61. Tétreault M, Putorti ML, Thiffault I, et al. TACH leukodystrophy: locus refinement to chromosome 10q22.3-23.1. *Can J Neurol Sci J Can Sci Neurol*. 2012;39(1):122-123. doi:10.1017/s0317167100022174

62. Bernard G, Chouery E, Putorti ML, et al. Mutations of POLR3A encoding a catalytic subunit of RNA polymerase Pol III cause a recessive hypomyelinating leukodystrophy. *Am J Hum Genet*. 2011;89(3):415-423. doi:10.1016/j.ajhg.2011.07.014

63. Saitsu H, Osaka H, Sasaki M, et al. Mutations in POLR3A and POLR3B Encoding RNA Polymerase III Subunits Cause an Autosomal-Recessive Hypomyelinating Leukoencephalopathy. *Am J Hum Genet*. 2011;89(5):644-651. doi:10.1016/j.ajhg.2011.10.003

64. Tétreault M, Choquet K, Orcesi S, et al. Recessive Mutations in POLR3B, Encoding the Second Largest Subunit of Pol III, Cause a Rare Hypomyelinating Leukodystrophy. *Am J Hum Genet*. 2011;89(5):652-655. doi:10.1016/j.ajhg.2011.10.006

65. Borchert GM, Lanier W, Davidson BL. RNA polymerase III transcribes human microRNAs. *Nat Struct Mol Biol*. 2006;13(12):1097-1101. doi:10.1038/nsmb1167

66. Werner M, Thuriaux P, Soutourina J. Structure-function analysis of RNA polymerases I and III. *Curr Opin Struct Biol*. 2009;19(6):740-745. doi:10.1016/j.sbi.2009.10.005

67. Thiffault I, Wolf NI, Forget D, et al. Recessive mutations in POLR1C cause a leukodystrophy by impairing biogenesis of RNA polymerase III. *Nat Commun*. 2015;6:7623. doi:10.1038/ncomms8623

68. Dorboz I, Dumay-Odelot H, Boussaid K, et al. Mutation in POLR3K causes hypomyelinating leukodystrophy and abnormal ribosomal RNA regulation. *Neurol Genet*. 2018;4(6):e289. doi:10.1212/NXG.0000000000000289

69. Perrier S, Michell-Robinson MA, Bernard G. POLR3-Related Leukodystrophy: Exploring Potential Therapeutic Approaches. *Front Cell Neurosci*. 2020;14:631802. doi:10.3389/fncel.2020.631802

70. DeGasperis SM, Bernard G, Wolf NI, Miller E, Pohl D. 4H leukodystrophy: Mild clinical phenotype and comorbidity with multiple sclerosis. *Neurol Genet*. 2020;6(2):e409. doi:10.1212/NXG.0000000000000409

71. Gauquelin L, Cayami FK, Sztriha L, et al. Clinical spectrum of POLR3-related leukodystrophy caused by biallelic POLR1C pathogenic variants. *Neurol Genet*. 2019;5(6):e369. doi:10.1212/NXG.0000000000000369

72. Osterman B, La Piana R, Bernard G. Advances in the diagnosis of leukodystrophies. *Future Neurol*. 2012;7(5):595-612. doi:10.2217/fnl.12.52

73. Al Yazidi G, Tran LT, Guerrero K, et al. Dystonia in RNA Polymerase III-Related Leukodystrophy. *Mov Disord Clin Pract*. 2019;6(2):155-159. doi:10.1002/mdc3.12715

74. Wolff A, Koch MJ, Benzinger S, et al. Rare dental peculiarities associated with the hypomyelinating leukoencephalopathy 4H syndrome/ADDH. *Pediatr Dent*. 2010;32(5):386-392.

75. Pelletier F, Perrier S, Cayami FK, et al. Endocrine and Growth Abnormalities in 4H Leukodystrophy Caused by Variants in POLR3A, POLR3B, and POLR1C. *J Clin Endocrinol Metab*. 2021;106(2):e660-e674. doi:10.1210/clinem/dgaa700

76. Spasticity. National Institute of Neurological Disorders and Stroke. Accessed May 26, 2023. https://www.ninds.nih.gov/health-information/disorders/spasticity

77. Dystonia. National Institute of Neurological Disorders and Stroke. Accessed May 26, 2023. https://www.ninds.nih.gov/health-information/disorders/dystonia

78. La Piana R, Tonduti D, Gordish Dressman H, et al. Brain magnetic resonance imaging (MRI) pattern recognition in Pol III-related leukodystrophies. *J Child Neurol*. 2014;29(2):214-220. doi:10.1177/0883073813503902

79. Ghoumid J, Petit F, Boute-Benejean O, et al. Cerebellar hypoplasia with endosteal sclerosis is a POLR3-related disorder. *Eur J Hum Genet*. 2017;25(8):1011-1014. doi:10.1038/ejhg.2017.73

80. Daoud H, Tétreault M, Gibson W, et al. Mutations in POLR3A and POLR3B are a major cause of hypomyelinating leukodystrophies with or without dental abnormalities and/or hypogonadotropic hypogonadism. *J Med Genet*. 2013;50(3):194-197. doi:10.1136/jmedgenet-2012-101357

81. Harting I, Al-Saady M, Krägeloh-Mann I, et al. POLR3A variants with striatal involvement and extrapyramidal movement disorder. *Neurogenetics*. 2020;21(2):121-133. doi:10.1007/s10048-019-00602-4

82. Hiraide T, Kubota K, Kono Y, et al. POLR3A variants in striatal involvement without diffuse hypomyelination. *Brain Dev*. 2020;42(4):363-368. doi:10.1016/j.braindev.2019.12.012

83. Zhang T, Yan C, Liu Y, et al. Late-Onset Leukodystrophy Mimicking Hereditary Spastic Paraplegia without Diffuse Leukodystrophy on Neuroimaging. *Neuropsychiatr Dis Treat*. 2021;17:1451-1458. doi:10.2147/NDT.S296424

84. Gauquelin L, Tétreault M, Thiffault I, et al. POLR3A variants in hereditary spastic paraplegia and ataxia. *Brain*. 2018;141(1):e1. doi:10.1093/brain/awx290

85. Maloy S, Hughes K. *Brenner's Encyclopedia of Genetics*. 2nd ed.; 2013.

86. Paolacci S, Li Y, Agolini E, et al. Specific combinations of biallelic POLR3A variants cause Wiedemann-Rautenstrauch syndrome. *J Med Genet*. 2018;55(12):837-846. doi:10.1136/jmedgenet-2018-105528

87. Wambach JA, Wegner DJ, Patni N, et al. Bi-allelic POLR3A Loss-of-Function Variants Cause Autosomal-Recessive Wiedemann-Rautenstrauch Syndrome. *Am J Hum Genet*. 2018;103(6):968-975. doi:10.1016/j.ajhg.2018.10.010

88. Devos EA, Leroy JG, Frijns JP, Van den Berghe H. The Wiedemann-Rautenstrauch or neonatal progeroid syndrome. Report of a patient with consanguineous parents. *Eur J Pediatr*. 1981;136(3):245-248. doi:10.1007/BF00442991

89. Ghamry MA, Salah R, Galal EI, Henin S, Dobs M. A Case of Wiedemann-Rautenstrauch Syndrome With Fatal Hyperkalemic Renal Faliure. *Cureus*. Published online September 19, 2022. doi:10.7759/cureus.29320

90. WHOQOL - Measuring Quality of Life| The World Health Organization. Accessed May 27, 2023. https://www.who.int/tools/whoqol

91. Burckhardt CS, Anderson KL. The Quality of Life Scale (QOLS): reliability, validity, and utilization. *Health Qual Life Outcomes*. 2003;1:60. doi:10.1186/1477-7525-1-60

92. Hand C. Measuring health-related quality of life in adults with chronic conditions in primary care settings. *Can Fam Physician*. 2016;62(7):e375-e383.

93. Cohen RD. The quality of life in patients with Crohn's disease. *Aliment Pharmacol Ther*. 2002;16(9):1603-1609. doi:10.1046/j.1365-2036.2002.01323.x

94. Thommasen HV, Zhang W. Impact of chronic disease on quality of life in the Bella Coola Valley. *Rural Remote Health*. 2006;6(2):528.

95. O'Mahony J, Salter A, Ciftci B, Fox RJ, Cutter GR, Marrie RA. Physical and Mental Health-Related Quality of Life Trajectories Among People With Multiple Sclerosis. *Neurology*. 2022;99(14):e1538-1548. doi:10.1212/WNL.0000000000200931

96. Liu E, Twilt M, Tyrrell PN, et al. Health-related quality of life in children with inflammatory brain disease. *Pediatr Rheumatol Online J*. 2018;16(1):73. doi:10.1186/s12969-018-0291-4

97. Beltran-Quintero ML, Bascou NA, Poe MD, et al. Early progression of Krabbe disease in patients with symptom onset between 0 and 5 months. *Orphanet J Rare Dis*. 2019;14(1):46. doi:10.1186/s13023-019-1018-4

98. Langan TJ, Barczykowski A, Jalal K, et al. Survey of quality of life, phenotypic expression, and response to treatment in Krabbe leukodystrophy. *JIMD Rep*. 2019;47(1):47-54. doi:10.1002/jmd2.12033

99. Boettcher J, Boettcher M, Wiegand-Grefe S, Zapf H. Being the Pillar for Children with Rare Diseases-A Systematic Review on Parental Quality of Life. *Int J Environ Res Public Health*. 2021;18(9):4993. doi:10.3390/ijerph18094993

100. Farmer AY, Lee SK. The effects of parenting stress, perceived mastery, and maternal depression on parent–child interaction. *J Soc Serv Res*. 2011;37:516-525. doi:10.1080/01488376.2011.607367

101. Casellas F, López-Vivancos J, Casado A, Malagelada JR. Factors affecting health related quality of life of patients with inflammatory bowel disease. *Qual Life Res Int J Qual Life Asp Treat Care Rehabil*. 2002;11(8):775-781. doi:10.1023/a:1020841601110

102. Samiei Siboni F, Alimoradi Z, Atashi V, Alipour M, Khatooni M. Quality of Life in Different Chronic Diseases and Its Related Factors. *Int J Prev Med*. 2019;10:65. doi:10.4103/ijpvm.IJPVM_429_17

103. Denollet J. Type D personality. A potential risk factor refined. *J Psychosom Res*. 2000;49(4):255-266. doi:10.1016/s0022-3999(00)00177-x

104. Carod-Artal J, Egido JA, González JL, Varela de Seijas E. Quality of life among stroke survivors evaluated 1 year after stroke: experience of a stroke unit. *Stroke*. 2000;31(12):2995-3000. doi:10.1161/01.str.31.12.2995

105. Åkerblom Y, Zetterberg L, Larsson BJ, Nyholm D, Nygren I, Åsenlöf P. Pain, disease severity and associations with individual quality of life in patients with motor neuron diseases. *BMC Palliat Care*. 2021;20(1):154. doi:10.1186/s12904-021-00848-6

106. Schrag A, Selai C, Davis J, Lees AJ, Jahanshahi M, Quinn N. Health-related quality of life in patients with progressive supranuclear palsy. *Mov Disord Off J Mov Disord Soc*. 2003;18(12):1464-1469. doi:10.1002/mds.10583

107. Bakaniene I, Prasauskiene A, Vaiciene-Magistris N. Health-related quality of life in children with myelomeningocele: a systematic review of the literature. *Child Care Health Dev*. 2016;42(5):625-643. doi:10.1111/cch.12367

108. Stress. Accessed May 27, 2023. https://www.mentalhealth.org.uk/explore-mental-health/a-z-topics/stress

109. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. *J Health Soc Behav*. 1983;24(4):385-396.

110. Goldberg DP, Hillier VF. A scaled version of the General Health Questionnaire. *Psychol Med*. 1979;9(1):139-145. doi:10.1017/s0033291700021644

111. Noone PA. The Holmes-Rahe Stress Inventory. *Occup Med Oxf Engl*. 2017;67(7):581-582. doi:10.1093/occmed/kqx099

112. Cousino MK, Hazen RA. Parenting stress among caregivers of children with chronic illness: a systematic review. *J Pediatr Psychol*. 2013;38(8):809-828. doi:10.1093/jpepsy/jst049

113. Lisanti AJ. Parental stress and resilience in CHD: a new frontier for health disparities research. *Cardiol Young*. 2018;28(9):1142-1150. doi:10.1017/S1047951118000963

114. Dellve L, Samuelsson L, Tallborn A, Fasth A, Hallberg LRM. Stress and well-being among parents of children with rare diseases: a prospective intervention study. *J Adv Nurs*. 2006;53(4):392-402. doi:10.1111/j.1365-2648.2006.03736.x

115. Craig F, Operto FF, De Giacomo A, et al. Parenting stress among parents of children with Neurodevelopmental Disorders. *Psychiatry Res*. 2016;242:121-129. doi:10.1016/j.psychres.2016.05.016

116. Majnemer A, Shevell M, Law M, Poulin C, Rosenbaum P. Indicators of distress in families of children with cerebral palsy. *Disabil Rehabil*. 2012;34(14):1202-1207. doi:10.3109/09638288.2011.638035

117. Park MS, Chung CY, Lee KM, Sung KH, Choi IH, Kim TW. Parenting stress in parents of children with cerebral palsy and its association with physical function. *J Pediatr Orthop Part B*. 2012;21(5):452-456. doi:10.1097/BPB.0b013e32835470c0

118. Kaaresen PI, Rønning JA, Ulvund SE, Dahl LB. A randomized, controlled trial of the effectiveness of an early-intervention program in reducing parenting stress after preterm birth. *Pediatrics*. 2006;118(1):e9-19. doi:10.1542/peds.2005-1491

119. MacKinnon AL, Silang K, Penner K, Zalewski M, Tomfohr-Madsen L, Roos LE. Promoting Mental Health in Parents of Young Children Using eHealth Interventions: A Systematic Review and Meta-analysis. *Clin Child Fam Psychol Rev*. 2022;25(3):413-434. doi:10.1007/s10567-022-00385-5

120. Algorani EB, Gupta V. Coping Mechanisms. In: *StatPearls*. StatPearls Publishing; 2023. Accessed May 27, 2023. http://www.ncbi.nlm.nih.gov/books/NBK559031/

121. Weiten W, Lloyd MA. *Psychology Applied to Modern Life*. 9th ed. Wadsworth Cengage Learning; 2008.

122. Billings AG, Moos RH. The role of coping responses and social resources in attenuating the stress of life events. *J Behav Med*. 1981;4(2):139-157. doi:10.1007/BF00844267

123. Thompson RJ, Mata J, Jaeggi SM, Buschkuehl M, Jonides J, Gotlib IH. Maladaptive Coping, Adaptive Coping, and Depressive Symptoms: Variations across Age and Depressive State. *Behav Res Ther*. 2010;48(6):459-466. doi:10.1016/j.brat.2010.01.007

124. Chabowski M, Jankowska-Polańska B, Lomper K, Janczak D. The effect of coping strategy on quality of life in patients with NSCLC. *Cancer Manag Res*. 2018;10:4085-4093. doi:10.2147/CMAR.S175210

125. Fairfax A, Brehaut J, Colman I, et al. A systematic review of the association between coping strategies and quality of life among caregivers of children with chronic illness and/or disability. *BMC Pediatr*. 2019;19(1):215. doi:10.1186/s12887-019-1587-3

126. Santarnecchi E, Sprugnoli G, Tatti E, et al. Brain functional connectivity correlates of coping styles. *Cogn Affect Behav Neurosci*. 2018;18(3):495-508. doi:10.3758/s13415-018-0583-7

127. Casagrande M, Boncompagni I, Mingarelli A, et al. Coping styles in individuals with hypertension of varying severity. *Stress Health J Int Soc Investig Stress*. 2019;35(4):560-568. doi:10.1002/smi.2889

128. Verberne LM, Kars MC, Schouten-van Meeteren AYN, et al. Parental experiences and coping strategies when caring for a child receiving paediatric palliative care: a qualitative study. *Eur J Pediatr*. 2019;178(7):1075-1085. doi:10.1007/s00431-019-03393-w

129. Toledano-Toledano F, Luna D. The psychosocial profile of family caregivers of children with chronic diseases: a cross-sectional study. *Biopsychosoc Med*. 2020;14:29. doi:10.1186/s13030-020-00201-y

130. Dunkel-Schetter C, Feinstein LG, Taylor SE, Falke RL. Patterns of coping with cancer. *Health Psychol Off J Div Health Psychol Am Psychol Assoc*. 1992;11(2):79-87. doi:10.1037//0278-6133.11.2.79

131. Iverson GL, Terry DP, Karr JE, Panenka WJ, Silverberg ND. Perceived Injustice and Its Correlates after Mild Traumatic Brain Injury. *J Neurotrauma*. 2018;35(10):1156-1166. doi:10.1089/neu.2017.5402

132. Carriere J, Martel MO, Kao MC, Sullivan M, Darnall B. Pain behavior mediates the relationship between perceived injustice and opioid prescription for chronic pain: a Collaborative Health Outcomes Information Registry study. *J Pain Res*. 2017;Volume 10:557-566. doi:10.2147/JPR.S128184

133. Penn TM, Overstreet DS, Aroke EN, et al. Perceived Injustice Helps Explain the Association Between Chronic Pain Stigma and Movement-Evoked Pain in Adults with Nonspecific Chronic Low Back Pain. *Pain Med Malden Mass*. 2020;21(11):3161-3171. doi:10.1093/pm/pnaa095

134. Sullivan MJL, Adams H, Yamada K, Kubota Y, Ellis T, Thibault P. The relation between perceived injustice and symptom severity in individuals with major depression: A cross-lagged panel study. *J Affect Disord*. 2020;274:289-297. doi:10.1016/j.jad.2020.05.129

135. Paré C, Thibault P, Côté P, et al. The Relationship Between Level of Catastrophizing and Mental Health Comorbidity in Individuals With Whiplash Injuries. *Clin J Pain*. 2019;35(11):880-886. doi:10.1097/AJP.0000000000000749

136. Yakobov E, Suso-Ribera C, Vrinceanu T, Adams H, Sullivan MJ. Trait Perceived Injustice Is Associated With Pain Intensity and Pain Behavior in Participants Undergoing an Experimental Pain Induction Procedure. *J Pain*. 2019;20(5):592-599. doi:10.1016/j.jpain.2018.11.007

137. Lynch J, D'Alton P, Gaynor K. Evaluating the role of perceived injustice in mental health outcomes in cervical cancer care. *Support Care Cancer*. 2022;30(7):6215-6223. doi:10.1007/s00520-022-07060-z

138. Büssing A, Ostermann T, Neugebauer EAM, Heusser P. Adaptive coping strategies in patients with chronic pain conditions and their interpretation of disease. *BMC Public Health*. 2010;10:507. doi:10.1186/1471-2458-10-507

139. Varni JW, Sherman SA, Burwinkle TM, Dickinson PE, Dixon P. The PedsQL^{TM} Family Impact Module: Preliminary reliability and validity. *Health Qual Life Outcomes*. 2004;2:55. doi:10.1186/1477-7525-2-55

140. Mishra K, Ramachandran S, Firdaus S, Rath B. The impact of pediatric nephrotic syndrome on parents' health-related quality of life and family functioning: an assessment made by the PedsQL 4.0 family impact module. *Saudi J Kidney Dis Transplant Off Publ Saudi Cent Organ Transplant Saudi Arab*. 2015;26(2):285-292. doi:10.4103/1319-2442.152420

141. Chandran A, Sikka K, Thakar A, et al. The impact of pediatric tracheostomy on the quality of life of caregivers. *Int J Pediatr Otorhinolaryngol*. 2021;149:110854. doi:10.1016/j.ijporl.2021.110854

142. Ilkowitz J, Gallagher MP, Lois B, Pacheco ML, Zeleniuch-Jacquotte A. Family Impact Module and Type 1 Diabetes. *Diabetes*. 2018;67(Supplement_1):841-P. doi:10.2337/db18-841-P

143. Rozensztrauch A, Śmigiel R. Quality of Life in Children with Prader-Willi Syndrome and the Impact of the Disease on the Functioning of Families. *Int J Environ Res Public Health*. 2022;19(23):16330. doi:10.3390/ijerph192316330

144. Simpson TS, Grande LA, Kenny JJ, Wilson PE, Peterson RL. Child, Parent, and Family Adjustment for Patients Followed in a Multidisciplinary Spina Bifida Clinic. *Top Spinal Cord Inj Rehabil*. 2022;28(3):41-58. doi:10.46292/sci21-00074

145. Morcov MV, Pădure L, Morcov CG, Mirea A, Ghiță M, Onose G. Comparative Analysis of the Quality of Life in Families with Children or Adolescents Having Congenital versus Acquired Neuropathology. *Child Basel Switz*. 2022;9(5):714. doi:10.3390/children9050714

146. Medrano GR, Berlin KS, Hobart Davies W. Utility of the PedsQL™ family impact module: assessing the psychometric properties in a community sample. *Qual Life Res Int J Qual Life Asp Treat Care Rehabil*. 2013;22(10):2899-2907. doi:10.1007/s11136-013-0422-9

147. Abidin RR. Parenting Stress Index. Published online September 12, 2011. doi:10.1037/t02445-000

148. Bigras M, LaFreniere PJ, Dumas JE. Discriminant validity of the parent and child scales of the parenting stress index. *Early Educ Dev*. 1996;7:167-178. doi:10.1207/s15566935eed0702_5

149. Margalit M, Kleitman T. Mothers' stress, resilience and early intervention. *Eur J Spec Needs Educ*. 2006;21:269-283. doi:10.1080/08856250600810682

150. Kyriazos TA, Stalikas A. Positive Parenting or Positive Psychology Parenting? Towards a Conceptual Framework of Positive Psychology Parenting. *Psychology*. 2018;09(07):1761-1788. doi:10.4236/psych.2018.97104

151. Berry JO, Jones WH. The Parental Stress Scale: Initial psychometric evidence. *J Soc Pers Relatsh*. 1995;12:463-472. doi:10.1177/0265407595123009

152. Algarvio S, Leal I, Maroco J. Parental Stress Scale: Validation study with a Portuguese population of parents of children from 3 to 10 years old. *J Child Health Care Prof Work Child Hosp Community*. 2018;22(4):563-576. doi:10.1177/1367493518764337

153. McCubbin HI, McCubbin MA, Patterson JM, Cauble AE, Wilson LR, Warwick W. CHIP—Coping Health Inventory for Parents: An assessment of parental coping patterns in the care of the chronically ill child. *J Marriage Fam*. 1983;45:359-370. doi:10.2307/351514

154. Gothwal VK, Bharani S, Reddy SP. Measuring coping in parents of children with disabilities: a rasch model approach. *PloS One*. 2015;10(3):e0118189. doi:10.1371/journal.pone.0118189

155. Bak J, Zarzycka D. Coping with child's disease by children and their parents (guardians) – a systematic review of the literature. *Sciendo*. 2022;21(2):106-114. doi:https://doi.org/10.2478/pielxxiw-2022-0011

156. Aguilar-Vafaie ME. Coping-Health Inventory for Parents: Assessing Coping Among Iranian Parents in the Care of Children With Cancer and Introductory Development of an Adapted Iranian Coping-Health Inventory for Parents. *Child Health Care*. 2008;37(4):237-260. doi:10.1080/02739610802437202

157. Austin JK, McDermott N. Parental attitude and coping behaviors in families of children with epilepsy. *J Neurosci Nurs J Am Assoc Neurosci Nurses*. 1988;20(3):174-179. doi:10.1097/01376517-198806000-00008

158. Sullivan MJL, Adams H, Horan S, Maher D, Boland D, Gross R. The role of perceived injustice in the experience of chronic pain and disability: scale development and validation. *J Occup Rehabil*. 2008;18(3):249-261. doi:10.1007/s10926-008-9140-5

159. Palisano R, Rosenbaum P, Walter S, Russell D, Wood E, Galuppi B. Development and reliability of a system to classify gross motor function in children with cerebral palsy. *Dev Med Child Neurol*. 1997;39(4):214-223. doi:10.1111/j.1469-8749.1997.tb07414.x

160. Eliasson AC, Krumlinde-Sundholm L, Rösblad B, et al. The Manual Ability Classification System (MACS) for children with cerebral palsy: scale development and evidence of validity and reliability. *Dev Med Child Neurol*. 2006;48(7):549-554. doi:10.1017/S0012162206001162

161. Sellers D, Mandy A, Pennington L, Hankins M, Morris C. Development and reliability of a system to classify the eating and drinking ability of people with cerebral palsy. *Dev Med Child Neurol*. 2014;56(3):245-251. doi:10.1111/dmcn.12352

162. Hidecker MJC, Paneth N, Rosenbaum PL, et al. Developing and validating the Communication Function Classification System for individuals with cerebral palsy. *Dev Med Child Neurol*. 2011;53(8):704-710. doi:10.1111/j.1469-8749.2011.03996.x

163. Paulson A, Vargus-Adams J. Overview of Four Functional Classification Systems Commonly Used in Cerebral Palsy. *Child Basel Switz*. 2017;4(4):30. doi:10.3390/children4040030

164. Panepinto JA, Hoffmann RG, Pajewski NM. A psychometric evaluation of the PedsQL™ Family Impact Module in parents of children with sickle cell disease. *Health Qual Life Outcomes*. 2009;7:32. doi:10.1186/1477-7525-7-32

165. Cella D, Lai JS, Nowinski CJ, et al. Neuro-QOL: brief measures of health-related quality of life for clinical research in neurology. *Neurology*. 2012;78(23):1860-1867. doi:10.1212/WNL.0b013e318258f744

166. Vahedi S. World Health Organization Quality-of-Life Scale (WHOQOL-BREF): Analyses of Their Item Response Theory Properties Based on the Graded Responses Model. *Iran J Psychiatry*. 2010;5(4):140-153.

167. Crnic KA, Greenberg MT. Minor parenting stresses with young children. *Child Dev*. 1990;61(5):1628-1637. doi:10.1111/j.1467-8624.1990.tb02889.x

168. Brannan AM, Heflinger CA, Bickman L. The Caregiver Strain Questionnaire: Measuring the impact on the family of living with a child with serious emotional disturbance. *J Emot Behav Disord*. 1997;5:212-222. doi:10.1177/106342669700500404

169. Miodrag N, Burke M, Tanner-Smith E, Hodapp RM. Adverse health in parents of children with disabilities and chronic health conditions: a meta-analysis using the parenting stress index's health sub-domain. *J Intellect Disabil Res JIDR*. 2015;59(3):257-271. doi:10.1111/jir.12135

170. Goldberg S, Morris P, Simmons RJ, Fowler RS, Levison H. Chronic Illness in Infancy and Parenting Stress: A Comparison of Three Groups of Parents1. *J Pediatr Psychol*. 1990;15(3):347-358. doi:10.1093/jpepsy/15.3.347

171. Krulik T, Turner-Henson A, Kanematsu Y, Al-Ma'aitah R, Swan J, Holaday B. Parenting stress and mothers of young children with chronic illness: A cross-cultural study. *J Pediatr Nurs*. 1999;14(2):130-140. doi:10.1016/S0882-5963(99)80051-7

172. Epifanio MS, Genna V, Vitello MG, Roccella M, La Grutta S. Parenting Stress and Impact of Illness in Parents of Children with Coeliac Disease. *Pediatr Rep*. 2013;5(4):e19. doi:10.4081/pr.2013.e19

173. Hamby S, Grych J, Banyard V. Coping Scale. Published online 2015. doi:10.13140/RG.2.1.3094.0001

174. Crane ME, Kendall PC. Psychometric Evaluation of the Child and Parent Versions of the Coping Questionnaire. *Child Psychiatry Hum Dev*. 2020;51(5):709-720. doi:10.1007/s10578-020-00975-w

175. Monticone M, Ferrante S, Giorgi I, Galandra C, Rocca B, Foti C. The 27-item Coping Strategies Questionnaire – Revised: Confirmatory factor analysis, reliability and validity in Italian-speaking subjects with chronic pain. *Pain Res Manag J Can Pain Soc*. 2014;19(3):153-158.

176. Wirrell EC, Wood L, Hamiwka LD, Sherman EMS. Parenting stress in mothers of children with intractable epilepsy. *Epilepsy Behav EB*. 2008;13(1):169-173. doi:10.1016/j.yebeh.2008.02.011

177. Cushner-Weinstein S, Dassoulas K, Salpekar JA, et al. Parenting stress and childhood epilepsy: the impact of depression, learning, and seizure-related factors. *Epilepsy Behav EB*. 2008;13(1):109-114. doi:10.1016/j.yebeh.2008.03.010

178. Bennett E, English MW, Rennoldson M, Starza-Smith A. Predicting parenting stress in caregivers of children with brain tumours. *Psychooncology*. 2013;22(3):629-636. doi:10.1002/pon.3047

179. Tettegah S, Espelage D. *Emotions, Technology, and Behaviors.* 16th ed. Elsevier; 2015.

180. Sullivan MJL, Scott W, Trost Z. Perceived injustice: a risk factor for problematic pain outcomes. *Clin J Pain*. 2012;28(6):484-488. doi:10.1097/AJP.0b013e3182527d13

181. Silva BKR, Quaresma FRP, Maciel E da S, Figueiredo FWDS, Sarraf JS, Adami F. Correlation Between Stress and Quality of Life Experienced by Caregivers: Perception of a

Group of Healthcare Professionals. *Open Nurs J*. 2017;11:135-141. doi:10.2174/1874434601711010135

182. Parsaei R, Roohafza H, Feizi A, Sadeghi M, Sarrafzadegan N. How Different Stressors Affect Quality of Life: An Application of Multilevel Latent Class Analysis on a Large Sample of Industrial Employees. *Risk Manag Healthc Policy*. 2020;13:1261-1270. doi:10.2147/RMHP.S256800

183. Rusli BN, Edimansyah BA, Naing L. Working conditions, self-perceived stress, anxiety, depression and quality of life: a structural equation modelling approach. *BMC Public Health*. 2008;8:48. doi:10.1186/1471-2458-8-48

184. Bialowolski P, Weziak-Bialowolska D, Lee MT, Chen Y, VanderWeele TJ, McNeely E. The role of financial conditions for physical and mental health. Evidence from a longitudinal survey and insurance claims data. *Soc Sci Med 1982*. 2021;281:114041. doi:10.1016/j.socscimed.2021.114041

185. Bailey W, Woodiel D, Turner M, Young J. The Relationship of Financial Stress to Overall Stress and Satisfaction. In: ; 1998. Accessed May 29, 2023. https://www.semanticscholar.org/paper/The-Relationship-of-Financial-Stress-to-Overall-and-Bailey-Woodiel/ff4a0b7a0ac08fcf6ed1940586e1a63673888ba0

186. Wiltshire JC, Enard KR, Colato EG, Orban BL. Problems paying medical bills and mental health symptoms post-Affordable Care Act. *AIMS Public Health*. 2020;7(2):274-286. doi:10.3934/publichealth.2020023

187. Stress in America. https://www.apa.org. Accessed May 29, 2023. https://www.apa.org/news/press/releases/stress

188. Ochieng N, Sroczynski N, Damico A, 2021. Medicare and Dental Coverage: A Closer Look. KFF. Published July 28, 2021. Accessed May 29, 2023. https://www.kff.org/medicare/issue-brief/medicare-and-dental-coverage-a-closer-look/

189. Bethune S. Money stress weighs on Americans' health. *American Psychological Association*. April 2015:38.

190. Ryu S, Fan L. The Relationship Between Financial Worries and Psychological Distress Among U.S. Adults. *J Fam Econ Issues*. 2023;44(1):16-33. doi:10.1007/s10834-022-09820-9