Mental health and health related quality of life in mitochondrial POLG disease

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ARTICLE INFO
Keywords:
Epilepsy
Mental health
Mitochondrial disease
POLG
Psychological distress
Quality of life

ABSTRACT
We aimed to assess the impact of POLG disease on mental health and quality of life in 15 patients using the Symptom Checklist-90-R (SCL-90-R) and Short-Form 36 Health Survey (RAND-36). We found increased scores in all nine subscales of SCL-90-R, particularly phobic anxiety, depression and somatization. Further, patients reported considerably lower scores in all RAND-36 domains. This study revealed a global decline in mental health and poor quality of life in patients with POLG disease and highlights the need for increased awareness and systematic assessment in order to improve their quality of life and mental health.

1. Introduction
Mitochondria are essential organelles found in nearly all eukaryotic cells (Vafai and Mootha, 2012). The most vital role of mitochondria is to generate ATP via the process of oxidative phosphorylation (OXPHOS) (Smeitink et al., 2001), but they are involved in other important cellular functions including intracellular calcium regulation, phospholipid metabolism and apoptosis (Lu and Claypool, 2015; Green and Kroemer, 2004). Thirteen of the protein subunits of the OXPHOS system are encoded by the mitochondrion’s own DNA (mtDNA), while the remaining subunits, together with more than a thousand other proteins required for mitochondrial structure and function are encoded by nuclear DNA (nDNA) (Spinazzola and Zeviani, 2009).

Mitochondrial disorders are one of the most common inborn errors of metabolism with estimated prevalence of 1:5000 (Skladal et al., 2003). Clinically, affected individuals present a wide spectrum of heterogeneous phenotypes that can begin at any age often with multi-organ involvement. Organs such as brain, skeletal muscles and heart appear the most vulnerable, but any organ can be affected (Wallace et al., 2010). Curative treatments are currently lacking and management is largely based on symptomatic therapies and maximizing quality of life (Parikh et al., 2017).

Mitochondrial DNA polymerase γ (Polγ) is the enzyme responsible for mtDNA replication and repair (Longley et al., 2005). Variants in POLG, the nuclear gene encoding the catalytic subunit of Polγ, are the most common cause of inherited mitochondrial disease (Saneto and Naviaux, 2010) and can be associated with a wide spectrum of clinical manifestations ranging from devastating fatal neonatal disease to a mild late onset disease with myopathy and progressive external ophthalmoplegia (PEO) (Saneto and Naviaux, 2010; Hikmat et al., 2020;...
Hudson and Mitochondrion, 2006). We showed recently that the clinical spectrum of POLG related disease can be classified into three categories according to the age of disease onset (Hikmat et al., 2020).

The impact of POLG disease extends beyond the direct effects of each individual clinical manifestation such as seizures, ataxia or liver disease, and includes a number of challenges that lead to disability and reduced quality of life. The chronic and progressive nature of POLG disease can affect social and psychological well-being as well as physical health. Individuals with POLG disease may face diminished social support and family function, cognitive challenges, medical and psychiatric comorbidities, in addition to physical limitations in their daily activities. Little attention has been given to the psychological burden and quality of life in patients with mitochondrial diseases including POLG disease, therefore, the aim of this study was to assess the impact of POLG disease on the mental health and the health related quality of life (HRQoL).

2. Methods

2.1. Study population

Individuals were recruited from the national Norwegian POLG registry (www.polgregister.no) established in 2014 and which includes almost all individuals with genetically confirmed POLG disease in Norway. Seventy-four individuals were identified and of these, 26 were still alive.

Individuals with recessive disease and confirmed biallelic pathogenic POLG variants or dominant disease and heterozygous confirmed pathogenic variants, age older than 16 years and able/competent to provide a written informed consent to participate in the study were considered eligible. Invitation letter with information about the study, consent form and study questionnaires were sent by regular post to the 26 potential participants’ home address. Data entry was completed in June 2019.

2.2. Clinical and genetic data

Clinical and genetic data of individuals who consented to participate were extracted from the registry. Age of disease onset was defined by the date of the first symptom(s) requiring medical evaluation. In this study, we focused on the most frequently reported manifestations of POLG disease and those which have impact on the morbidity and mortality (Hikmat et al., 2020; Engelsen et al., 2008). These included: seizures including status epilepticus, ataxia, stroke like episodes, the presence of liver impairment defined by the presence of two or more of the following parameters in at least two different time points - elevated aspartate aminotransferase (ASAT), gamma-glutamyltransferase (GGT), bilirubin or ammonia, low serum albumin, or pathological histological findings of liver biopsy.

Pathogenic POLG variant(s) were identified either by targeted sequence analysis (common variants c.1399G > A, p.Ala467Thr and c.2243G > C, p.Trp748Ser) or by sequence analysis of all coding regions of the POLG gene.

2.3. Mental health

We used the Symptom Checklist-90-R (SCL-90-R) to evaluate mental health status (Siqveland and Leiknes, 2016). SCL-90-R is a well-validated and widely used method to evaluate the psychological symptoms (Derogatis et al., 1973) using a self-reported questionnaire that includes 90 questions covering nine specific areas: bodily ailments, concentration problems, vulnerability, depression, anxiety, rage, phobia, worrying and alienation. Each of the nine subscales contains 6–13 items. Items are graded following a five-point Likert-scale of distress, ranging from “0 = not at all” to “4 = extremely”. The form is well-suited to measuring general psychological symptoms as well as changes in the severity. We used the Norwegian manual for administration and the T-score (Siqveland and Leiknes, 2016). A T-score above 63 is considered as abnormal and suggests the need for further assessment. In this study, the time of reference for the symptoms was the previous week.

In addition to the nine symptom-scales described above, SCL-90-R enables us to measure three global indexes: Global Severity Index (GSI) is the mean of all respondents’ answers; Positive Symptom Total (PST) indicates how many times the respondent reports a level of symptom-score more than 0, and can be interpreted as an expression of symptom width, the Positive Symptom Distress Index (PSDI) is the mean number of the questions answered with score more than 0 and can be interpreted as an expression of intensity of the reported symptoms (Siqveland and Leiknes, 2016).

2.4. Health related quality of life (HRQoL)

HRQoL was measured by RAND-36 (Short-Form 36 (SF-36) Health Survey), which is a generic measure to assess functional health and well-being in individuals of 14 years of age or older (Ware and Sherbourne, 1992). This self-reported questionnaire consists of 36 items and covers eight health domains: physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, emotional well-being, social functioning, energy/fatigue, and general health perceptions (Ware and Sherbourne, 1992). Raw domain-scores are converted to a 0–100 scale, with lower scores indicating worse HRQoL. (Ware and Sherbourne, 1992; Hays and Morales, 2001). The questionnaire has well documented validity and reliability, and is widely accepted as a generic measure of HRQoL in individuals with wide variety of chronic medical conditions (McHorney et al., 1993, 1994; Paz et al., 2009). Validated Norwegian version of the RAND-36 was used to evaluate the HRQoL in individuals with POLG disease in this study. A standard 4 weeks recall period is applied except for physical functioning and general health, which pertain to current status. Norwegian normative data of the SF-36 was used for comparative purposes (Garrett and Stavem, 2017).

2.5. Statistics

Demographic and clinical characteristics were reported as numbers and proportions. Detailed descriptive data analysis was performed on the entire study cohort using SPSS (Statistical Package of Social Sciences), Version 25.0. A two-sided P value less than 0.05 was considered to be statistically significant.

2.6. Ethical statement

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2000. Ethical approval for the study was obtained from the Regional Committee for Medical and Health Research Ethics, Western Norway (REK 2014/1783-4). Signed informed consent was obtained from each patient prior to enrolment in the study.

3. Results

3.1. Study population

Of the 26 patients who were initially invited, 15 participated in this study. Ten were females and five males. The median age at disease onset was 24 years (range = 5–71) and at which the study was conducted was 41 years (range = 16–83). All individuals included in this study were of Northern European origin.
The majority of patients had juvenile/adult or late onset disease. Eight individuals had epilepsy, and seven of these also suffered from ataxia. Five had had stroke like episodes. Ataxia without epilepsy was reported in six individuals. Evidence of liver impairment was reported in two individuals. Four individuals had late onset disease with PEO and myopathy.

The majority had autosomal recessive disease and were homozygous or compound heterozygous for common pathogenic founder variants (c.1399G > A, p.Ala467Thr and c.2243G > C, p.Trp748Ser). Two individuals had autosomal dominant disease and were heterozygous for the pathogenic variant c.2864 A > G p.Tyr955Cys.

### 3.2. Clinical and genetic findings

All nine subscale-scores of SCL-90-R were increased in those participating (Table 1). Values ranged from almost abnormal to abnormal compared to the general population according to the Norwegian manual for administration and scoring (Siveland and Leiknes, 2016). Global index scores including - Global severity index, positive symptom total index and positive symptom distress index were all increased as well.

The three subscales - phobic anxiety (score = 66), depression (score = 65.7) and somatization (score = 65) had scores above normal range. Further, no significant differences were observed in the SCL-90-R subscale-scores when comparing males versus females, those with juvenile/adult versus late onset disease, or those with epilepsy versus those without.

### 3.4. Health related quality of life (HRQoL)

Individuals participating in this study reported considerably lower scores on all RAND-36 domains compared to Norwegian population norms (Fig. 1, Table 2). Further analyses showed that there were no statistically significant differences between gender, those with juvenile/adult or late onset disease, or between those with epilepsy and those without.

### 4. Discussion

In the absence of a cure, the main objectives in the management of patients with mitochondrial disease, including POLG disease, are control of symptoms, the prevention of complications and improving quality of life. Data regarding mental health and HRQoL in mitochondrial diseases is still limited, but the current study provides the first comprehensive description of mental health status and the quality of life in individuals with POLG disease.

Our study clearly identified a global decline in the mental health status of individuals with POLG disease (Table 1). Although there were no statistically significant differences between the sub-scales of SCL-90-R, symptoms such as anxiety, depression and somatization were more frequently reported in patients. The occurrence of psychiatric illness including major depression, bipolar disorder and panic/anxiety disorder has been described previously in individuals with proven mitochondrial disease (Fattal et al., 2006; Suomalainen et al., 1992). Many descriptions have however, been case reports (Van Goethem et al., 2003; Luoma et al., 2004; Hakonen et al., 2005) and this study is the first to describe, in detail, the psychological burden of POLG disease using patient/self-reported data. We show that, in addition to a large burden of somatic disease that includes progressive encephalopathy with cognitive decline and associated episodic disturbances such as in epilepsy and stroke like episodes (Hikmat et al., 2020; Luoma et al., 2004; Hakonen et al., 2005; Horvath et al., 2006; Rahman and Copeland, 2019), patients with POLG disease also have a significant burden of psychiatric symptoms.

Providing holistic, patient-centred treatment and understanding of disease burden requires the use of quality of life measures. Quality of life is a multifaceted concept based on a variety of factors that vary according to the method of measurement. Components typically include: physical health, psychological well-being, level of independence, social relationships, environment and personal beliefs. In the current study, patient/self-reported data were obtained using the well-validated RAND-36 (Short-Form 36 Health Survey) questionnaire and then compared with data obtained from a general Norwegian population. Our study revealed that POLG disease is associated with a considerably poorer quality of life (Fig. 1) compared to a general Norwegian population (Table 2). While a difference of 5–10 points on a 0–100 scale is generally considered as clinically significant (Fayers, 2007), our study showed differences of more than 30 points for almost all domains. Physical and social function and general health domains were even more impaired. These results show how disabling POLG disease can be and how it can limit the daily activities, restrict the social interaction and result in a poorer quality of life.

According to the World Health Organization (WHO), health is defined as, “A state of complete physical, mental and social well-being and not merely the absence of disease or infirmity”. The WHO developed a framework, The International Classification of Functioning, Disability and Health (ICF) for thinking about health in chronic disorders focusing on the biological aspect of human functioning. This framework comprises four major domains; body function, body structure, activities and participation and environmental factors. The ICF framework highlights the importance of using an integrated approach combining clinical data that in POLG disease includes ataxia, seizures, muscle weakness, with data reflecting the impact of disease on physical, social and mental wellbeing.

In the population of patients included in our study, seizures and ataxia were the most common clinical manifestations, while liver impairment was reported in only two. This reflects the age of patients recruited to the study. Epilepsy and ataxia are common features in juvenile/adult onset disease, while liver impairment is a major feature of early onset disease (Hikmat et al., 2020). Only one of the individuals recruited in this study had early onset disease. Further, the majority of individuals were either homozygous or compound heterozygous of the common pathogenic founder variants; c.1399G > A, p.Ala467Thr and c.2243G > C, p.Trp748Ser. This reflects the prevalence of these founder mutations in Norway (Engelsen et al., 2008; Tzoulis et al., 2006). Lastly, the sample size making detailed comparisons difficult. Nevertheless, this study is the first to address the issues of HRQoL and mental health in POLG disease, and it adds to the existing but limited data describing the impact of mitochondrial disorders on these parameters.

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**Table 1**

Summary of the mental health scores as assessed by SCL-90-R for the Individuals (N = 15) included in this study (T-Score above 63 is considered abnormal).

| Symptom scale                | Mean T-score (SD) |
|------------------------------|-------------------|
| Somatization                 | 65.0 (11)         |
| Compulsive symptom           | 63.9 (12)         |
| Interpersonal sensitivity    | 60.1 (11)         |
| Depression                   | 65.7 (7)          |
| Anxiety                      | 60.3 (12)         |
| Hostility                    | 52.2 (12)         |
| Phobic anxiety               | 66.0 (10)         |
| Paranoid thinking            | 59.0 (8)          |
| Psychosomatic                | 59.1 (8)          |
| Global severity index        | 65.3 (7)          |
| Positive symptom total       | 61.9 (8)          |
| Positive symptom distress    | 66.1 (7)          |

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- **Global severity index**: 65.3 (7)
- **Positive symptom total**: 61.9 (8)
- **Positive symptom distress index**: 66.1 (7)

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**3.2. Clinical and genetic findings**

The majority of patients had juvenile/adult or late onset disease. Eight individuals had epilepsy, and seven of these also suffered from ataxia. Five had had stroke like episodes. Ataxia without epilepsy was reported in six individuals. Evidence of liver impairment was reported in two individuals. Four individuals had late onset disease with PEO and myopathy.

The majority had autosomal recessive disease and were homozygous or compound heterozygous for common pathogenic founder variants (c.1399G > A, p.Ala467Thr and c.2243G > C, p.Trp748Ser). Two individuals had autosomal dominant disease and were heterozygous for the pathogenic variant c.2864 A > G p.Tyr955Cys.
### Table 2

| RAND-36 domains | Individuals with POLG disease (n = 15) | Reference group |
|-----------------|--------------------------------------|------------------|
|                 | Mean (SD) | min-max | Mean (SD) |
| Physical Functioning | 34.33 (39.09) | 0–100 | 90.85 (15.39) |
| Role Physical | 18.75 (33.92) | 0–100 | 82.64 (32.77) |
| Bodily Pain | 45.00 (23.37) | 21–100 | 74.52 (25.39) |
| General Health | 36.00 (22.41) | 0–82 | 78.19 (20.70) |
| Vitality | 31.43 (23.07) | 0–65 | 62.06 (20.13) |
| Social Functioning | 41.96 (34.18) | 0–100 | 87.73 (20.11) |
| Role Emotional | 47.22 (50.17) | 0–100 | 89.04 (26.88) |
| Mental Health | 64.43 (22.71) | 16–100 | 80.67 (15.60) |

### 5. Conclusion

POLG disease has a clear negative impact on both mental health and quality of life. We suggest therefore, that systematic assessment of these parameters should be included in the standard management of these patients. Involvement of relevant expertise including psychiatrists, psychologists, occupational therapist and physical therapists in the management of patients with POLG disease is recommended.

### Source of funding

This work was supported by grants from the Western Norway Regional Health Authority (Helse-Vest, grants no.911944).

### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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