Section 1 Introduction and methods

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Summary

- Mitochondrial disease is a heterogenous group of diseases that have dysfunctional mitochondrial respiratory changes that are caused by mutations to nuclear or mitochondrial DNA. The disease may affect single organ or may affect multiple organs, and usually affect organs that have the highest energy needs such as muscles, brain, eyes and heart.
- The prevalence of mitochondrial disease is estimated at 11.5 per 100,000, however this may underestimate the prevalence with reports of one in 200 healthy births having a mitochondrial DNA mutation.
- Patient Experience, Expectations and Knowledge (PEEK) is a research program developed by the International Centre for Community-Driven Research (ICCDR). The aim of PEEK is to conduct patient experience studies across several disease areas using a protocol that will allow for comparisons over time (both quantitative and qualitative components). PEEK studies give us a clear picture and historical record of what it is like to be a patient at a given point in time, and by asking patients about their expectations, PEEK studies give us a way forward to support patients and their families with treatments, information and care.
- In this PEEK study, 50 people with mitochondrial disease or their carers, throughout Australia participated in the study that included a structured interview and quantitative questionnaire. This study in mitochondrial disease is therefore the largest mixed methodology study in Australia. In addition, PEEK is a comprehensive study covering all aspects of disease experience from symptoms, diagnosis, treatment, healthcare communication, information provision, care and support, quality of life, and future treatment and care expectations.

Introduction

Mitochondrial disease is a heterogenous group of diseases that have dysfunctional mitochondrial respiratory changes that are caused by mutations to nuclear or mitochondrial DNA[1]. The disease may affect single organ or may affect multiple organs[1], and usually affect organs that have the highest energy needs such as muscles, brain, eyes and heart[2]. More commonly described clinical subtypes of mitochondrial disease include:[2]

- Chronic progressive external ophthalmoplegia (CPEO) Infantile myopathy and lactic acidosis (fatal and non-fatal forms),
- Kearns-Sayre syndrome (KSS)
- Leber hereditary optic neuropathy (LHON)
- Leigh syndrome (LS)
- Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS)
- Myoclonic epilepsy with ragged-red fibres (MERRF)
- Neurogenic weakness with ataxia and retinitis pigmentosa (NARP)
- Pearson Syndome

The prevalence of mitochondrial disease is estimated at 11.5 per 100,000[1], however this may underestimate the prevalence with reports of one in 200 healthy births having a mitochondrial DNA mutation[3].

Patient Experience, Expectations and Knowledge (PEEK)

Patient Experience, Expectations and Knowledge (PEEK) is a research program developed by the International Centre for Community-Driven Research (ICCDR). The aim of PEEK is to conduct patient experience studies across several disease areas using a protocol that will allow for comparisons over time (both quantitative and qualitative components). PEEK studies give us a clear picture and historical record of what it is like to be a patient at a given point in time, and by asking patients about their expectations, PEEK studies give us a way forward to support patients and their families with treatments, information and care.

The research protocol used in PEEK studies is independently driven by ICCDR. PEEK studies include a quantitative and qualitative component. The quantitative component is based on a series of validated tools. The qualitative component is the result of two years of protocol testing by ICCDR to develop a structured interview that solicits patient experience data and provides patients with the opportunity to provide advice on what they would like to see in relation to future treatment, information and care. The structured interview has also been designed so that the outcomes of PEEK studies can inform policy, research, care, information, supportive care services and advocacy efforts.

Methodology

Participants

To be eligible for the study, participants needed to have been diagnosed with mitochondrial disease or be a carer to someone with mitochondrial disease, have experienced the healthcare system in Australia, be 18 years of age or older, be able to speak English, and be able to give consent to participate in the study. Recruitment commenced on 19 April 2018 and the study closed for recruitment on 15 May 2018. Participants were recruited via email and social media through ICCDR and study partner the Australian Mitochondrial Disease Foundation, who sponsored the study and also sent information via electronic direct mail.

Ethics

Ethics approval for this study was granted (as a low or negligible risk research study) by the Centre for Community-Driven Research Ethics Committee (Reference CS_Q4_03).

Data collection

Data for the online questionnaire was collected using Zoho Survey (Zoho Corporation Pvt. Ltd. Pleasanton, California, USA, www.zoho.com/survey). Participants completed the survey between 19 April 2018 and 18 May 2018.

There were four researchers who conducted telephone interviews and used standardised prompts throughout the interview. The interviews were recorded and transcribed verbatim. Identifying names and locations were not included in the transcript. All transcripts were checked against the original recording for quality assurance.

Interview data was collected from 27 April 2018 to 23 May 2018.

Online questionnaire (quantitative)

The online questionnaire consisted of the 36-Item Short Form Health Survey (SF36) (RAND Health)[4], a modified Cancer Care Coordination Questionnaire for Patients (CCCQ) (Young et al 2011)[5], the Short Fear of Progression Questionnaire (FOP12) (Hinz et al)[6], and the Partners in Health version 2 (PIH) (Petov 2010)[7]. In addition investigator derived questions about demographics, diagnosis, treatment received and future treatment decisions making were included.

Structured Interview (qualitative)

Interviews were conducted via telephone by a registered nurse or researcher with a background in psychology, who were trained in qualitative research. The first set of interview questions guided the patient through their whole experience from when symptoms were noticed up to the present day.

The next set of questions allowed patients to reflect on what they would like to see in the future in relation to treatment and care, and asked them what their messages to decision-makers would be about the care and treatment patients with their condition receive. The interview also asks patients about the advice they would give to others recently diagnosed with their condition or disease. All interviews were recorded and transcribed verbatim.

Questionnaire analysis

Statistical analysis was conducted using R included in the packages “car”, “dplyr” and “ggplot2” (R 3.3.3 GUI 1.69 Mavericks build (7328). The aim of the statistical analysis of the SF36, CCCQ, FOP12, and PIH responses was to identify variations by general health status (SF36 general health, SF36 physical functioning, SF36 social functioning, SF36 emotional well-being and SF36 social functioning), location, education status and Socio-economic Indexes for Areas (SEIFA). Global scales and sub scales were calculated according to reported instructions[4-7]. For all comparisons, a two-sample t-test was used when assumptions for normality and variance were met, or when assumptions were not met, a Wilcoxon rank sum test with continuity correction was used.

Questions where participants were asked to rank preferences were analysed using weighted averages. Weights were applied in reverse, the most preferred option was given the largest weight equal to the number of options, the least preferred option was given the lowest weight of 1.

Structured interviews analysis

A content analysis was conducted using conventional analysis to identify major themes from structured interviews. Text from the interviews were read line-by-line by the lead researcher and then imported into NVivo 8 (QSR International). Each question within the interview was individually analysed. Initial categories and definitions were identified and registered in NVivo. The minimum coded unit was a sentence however there were also paragraphs and phrases that were coded as a unit.

A second researcher verified the codes and definitions, and the text was coded until full agreement was reached using the process of consensual validation. Where a theme occurred less than 5 times it was not included in the study discussion, however these were reported in tables and graphs. A sub-group analysis was also conducted. Where there was a variation of more than 10 percent in any sub-group compared to the general population (cohort), these were reported.

Data analysis and final reporting was completed on 10 July 2018.

Position of this study

A search was conducted in Pubmed to identify mitochondrial disease quality of life or patient experience studies that had been conducted in the past ten years in developed countries (Table 1.1).

Ten studies were identified that included between six and 231 participants with mitochondrial disease or their carers. All of the studies used quantitative methods, three studies were part of clinical trials[8-10], three studies focused on parent and carer experience[11-13], two focused on physical activity[14,15], a single study of quality of life[16] and one of fatigue[15].

In this PEEK study, 39 people with mitochondrial disease and 11 parents or carers of people with mitochondrial disease throughout Australia participated in the study that included a structured interview and quantitative questionnaire. This study in mitochondrial disease is therefore the largest mixed methodology study in Australia. In addition, PEEK is a comprehensive study covering all aspects of disease experience from symptoms, diagnosis, treatment, healthcare communication, information provision, care and support, quality of life, and future treatment and care expectations.

Table 1.1: Comparative studies

Author/Country/Year	Number participants	Participant type	Study type	QL	Function	Symptoms	Anxiety/Depression	Behaviour	Diagnosis	Burden	Resources	Study Focus
Glover et al/Canada/2010[9]	30	Individual	Quantitative	✓	✓							Clinical trial
Martinelli et al/Italy/2012[8]	10	Individual	Quantitative	✓	✓							Clinical trial
Eom & Lee/Korea/2017[11]	70	Parent/Carer	Quantitative		✓	✓	✓	✓	✓			Neurodevelopment and parent stress
Kim et al/Korea/2010[12]	33	Parent/Carer	Quantitative	✓			✓			✓		Caregiver burden
Verhaak et al/Netherlands/2016[16]	72	Individual	Quantitative	✓	✓	✓	✓					QL
Martens et al/Netherlands/2014[15]	6	Individual	Quantitative	✓				✓				Physical activity (function)
Gorman et al/UK/2015[17]	132	Individual	Quantitative			✓	✓					Fatigue
Bates et al/UK/2013[14]	10	Individual	Quantitative	✓		✓						Physical activity (intervention)
Senger et al/USA/2016[13]	231	Parent/Carer	Quantitative				✓				✓	Parent experience
Enns et al/USA/2012[10]	14	Individual	Quantitative	✓	✓							Clinical trial

Abbreviations

CCDR	Centre for Community-Driven Research
dF	Degrees of Freedom. The number of values in the final calculation of a statistic that are free to vary.
IQR	Interquartile range. A measure of statistical dispersion, being equal to the difference between 75th and 25th percentiles, or between upper and lower quartiles.
FOP	Fear of Progression. Tool to measure anxiety related to progression.
MS	Mean of Squares. Estimates of variance across groups
SD	Standard Deviation. A quantity expressing by how much the members of a group differ from the mean value for the group.
SF 36	Short Form Health Survey 36
t	t-Statistic. Size of the difference relative to the variation in your sample data.
PEEK	Patient Experience, Expectations and Knowledge
PIH	Partners in Health
p	Probability value. A small *p*-value (typically ≤ 0.05) indicates strong. A large *p*-value (> 0.05) indicates weak evidence.
QoL	Quality of LIfe
W	The W statistic is the test value from the Wilcoxon Rank sum test. The theoretical range of W is between 0 and (number in group one)x(number in group 2). When W=0, the two groups are exactly the same.

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