Section 1

Introduction and methods

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About this condition

- Amyloidosis is a heterogeneous disease, where amyloid deposits form and accumulate in tissues and organs of the body. It can be acquired or hereditary, localised or systemic. The amyloid deposits can accumulate in the heart, kidneys, spleen, nerves, and blood vessels [1].

Participants

- To be eligible for the study, participants needed to have been diagnosed with ATTR-CM or AL amyloidosis, or be a carer to someone diagnosed with either condition, 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. Initial recruitment commenced in July 2019 to October 2019 and recommenced April 2020 to June 2020.

Personal Experience, Expectations and Knowledge (PEEK): Study position

- In this PEEK study, 28 people diagnosed with amyloidosis, and 8 carers to people with amyloidosis throughout Australia participated in the study that included a qualitative structured interview and quantitative questionnaire. This study in amyloidosis is therefore the largest mixed methods study reported in an Australian population, and it includes the most patient interviews worldwide. 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

Amyloidosis is a heterogeneous disease, where amyloid deposits form and accumulate in tissues and organs of the body. It can be acquired or hereditary, localised or systemic. The amyloid deposits can accumulate in the heart, kidneys, spleen, nerves, and blood vessels [1].

There are two types of transthyretin amyloidosis, the more common is the wild type, the other is an inherited transthyretin mutation[2,3]. Amyloid light-chain (AL) amyloidosis is the most commonly diagnosed type of amyloidosis.

Risk factors include advanced age, male gender, family history, having dialysis, and African descent[2,3].

Amyloidosis is a rare disease; the number of cases is not known in Australia. The incidence in Queensland was estimated at 10 cases per million per year in people aged 20 years or older[4].

The median age for a wild type transthyretin amyloidosis diagnosis is 79, though can be found in people in their forties. It is predominantly a disease found in males, with approximately 96% of cases reported in men[5]. The median age for inherited transthyretin amyloidosis diagnosis is 67, and the proportion of males to females is approximately 70:30[5].

Symptoms of amyloidosis depend on the tissues and organs affected, they are often mistaken for other more common diseases[2,3]. Symptoms of wild type and hereditary transthyretin amyloidosis include fatigue, shortness of breath, swelling of feet and legs, heart palpitations, slow heart rate that can cause dizziness or blackouts, chest pain, sleep problems, unintentional weight loss, carpel tunnel syndrome, nerve pain, and blood in urine[2,3].

General symptoms of amyloid light-chain amyloidosis include loss of appetite, fatigue, unintentional weight loss, and weakness. When the heart us involved, swollen ankles, and being short of breath. The symptoms when the kidneys are involved include swollen ankles, frothy urine, and high cholesterol[2,3].

When there is nerve involvement, symptoms can include tingling in fingers and toes, and diarrhoea. Bruising, especially around eyes occurs with blood vessel involvement, diarrhoea from gut involvement, and swollen tongue when the tongue is involved[2,3].

Personal Experience, Expectations and Knowledge (PEEK)

Personal Experience, Expectations and Knowledge (PEEK) is a research program developed by the Centre for Community-Driven Research (CCDR). 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 CCDR. 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 CCDR 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 transthyretin amyloidosis or amyloid light-chain amyloidosis, or be a carer to someone diagnosed with either condition, 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. Initial recruitment commenced in July 2019 to October 2019 and recommenced in April 2020 to June 2020.

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 from July 2017 to August 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 July 2019 to June 2020.

Online questionnaire (quantitative)

The online questionnaire consisted of the 36-Item Short Form Health Survey (SF36) (RAND Health)[6], a modified Cancer Care Coordination Questionnaire for Patients (CCCQ)[7], the Short Fear of Progression Questionnaire (FOP12)[8], and the Partners in Health version 2 (PIH)[9]. 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 registered nurses, 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.

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 participant type, gender, age, location of residence, education status and Socio-economic Indexes for Areas (SEIFA). Global scales and subscales were calculated according to reported instructions[6-9].

The **Location** of participants was evaluated by postcode using the Australian Statistical Geography Maps (ASGS) Remoteness areas accessed from the Australian Bureau of Statistics[10].

The level of social advantage of participants was evaluated by postcode using the Socio-economic Indexes for Areas (**SEIFA**) accessed from the Australian Bureau of Statistics[11].

Where participants list other conditions, these were classified by the Classification of Diseases 11th Revision[12].

For comparisons by Participant type, and **Age**, a one-way analysis of variance (ANOVA) analysis was conducted. A Tukey HSD test was used post-hoc to identify the source of any differences identified in the one-way ANOVA test. Where the assumptions for the one-way ANOVA were not met, a Kruskal-Wallis rank sum test on care was conducted with post-hoc pairwise comparisons using Wilcoxon rank sum test. When the assumption of equal variances were not met, a Welch one-way test was used with post-hoc pairwise t-tests with no assumption of equal variances.

For all other 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

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 MaxQDA. Each question within the interview was individually analysed. Initial categories and definitions were identified and registered in MaxQDA. The minimum coded unit was a sentence with paragraphs and phrases 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 four times it was not included in the study results, unless this result demonstrated a significant gap or unexpected result.

Participants that did not take part in the structured interviews after completing the survey have been coded as no response, with results calculated accordingly. Non-responses have not been included in the in the study results.

Data analysis and final reporting was completed in August 2020.

Position of this study

A search was conducted in Pubmed (June 24, 2020) to identify transthyretin amyloidosis or amyloid light-chain amyloidosis quality of life or patient experience studies of adults that had been conducted in the past ten years in worldwide (Table 1.1). Meta-analysis studies, studies conducted in developing countries, and studies of less than five participants were excluded.

There were 32 studies identified that collected patient self-reported data. There were three studies using qualitative methods of between 10 and 18 participants[13-15], and 28 studies using quantitative methods of between 10 and 1,739 participants[5,16-44], and one mixed methods study of 10 interviewed participants with 341 participants completing questionnaires[45,46]. There were eight international studies[16-21,28,30,34], eight in the USA[22-24,32,35,37,41,43-45,47], six in Portugal[13,14,26,27,33,40], two in France[15,29], two in the UK[5,36], and one each in, Japan[25] and Sweden[42]. One international study included participants from Australia[28].

There were ten drug trials[16-20,25,28,30,32,34], five studies focused on quality of life[5,35,37,41,44], three nutrition studies[31,36], two studies each focused on distress[33,43], liver transplants[27,42], disease characterisation, [21-24], and a single study each focused on anxiety and depression[38], coping strategies[39], diagnosis[45,47], education[15], genetic screening[40], pharyngo-laryngeal involvement[29], stigma[13], and urinary tract dysfunction[26].

There were 28 people diagnosed with amyloidosis, and 8 carers to people with amyloidosis from throughout Australia that participated in this PEEK study. This included a qualitative structured interview and quantitative questionnaire. This study in amyloidosis is therefore the largest mixed methods study reported in an Australian population, and it includes the most patient interviews worldwide. 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.

Author, Year	Location	Number of participants	Design	Focus	PEEK Section							
					2: Health status, co-morbidities, health-related quality of life	3: Diagnosis experience, information, support and costs	4: Decision making and healthcare professional discussions	5: Treatment, healthcare system use and access, economic implications	6: Information, communication and self-management	7: Care, support and navigating healthcare system	8: Quality of life, mental health, relationships	9 Expectations, preferences and messages
McCausland et al, 2018[47], Bayliss et al, 2017[45]	USA	10 (interviews), 341 (questionnaire)	Mixed	Diagnosis		x						
Théaudin et al, 2014[15]	France	8 plus 2 carers	Qualitative (Interviews)	Education	x				x	x	x	
Oliveira et al, 2017[14]	Portugal	18	Qualitative (Interviews)	Health self-management				x	x	x	x	
Mendes et al, 2017[13]	Portugal	11	Qualitative (Interviews)	Stigma							x	
Smorti et al, 2012[38]	Italy	32	Quantitative	Anxiety and depression	x	x					x	
Waddington-Cruz et al, 2018[21]	International	172	Quantitative	Characterisation of disease	x							
Coelho et al, 2013; [22]; Wixner et al, 2014[23]; Maurer et al, 2016[24]	USA	1739	Quantitative	Characterisation of disease	x							
Smorti et al, 2014[39]	Italy	34	Quantitative	Coping strategies							x	
Lopes et al, 2018[33]	Portugal	209	Quantitative	Distress		x						
Wright et al, 2018[43]	USA	78	Quantitative	Distress							x	
Coelho et al, 2012 [16]; Keohane et al, 2017[17]	International	290	Quantitative	Drug	X							
Merlini et al, 2013[18]	International	21	Quantitative	Drug	x							
Coelho et al, 2013 [19]	International	86	Quantitative	Drug	x							
Barroso et al, 2017 [20]	International	75	Quantitative	Drug	x							
Adams et al, 2018[28]	International	225	Quantitative	Drug	x							
Berk et al, 2013[30]	International	130	Quantitative	Drug	x	x						

Author, Year	Location	Number of participants	Design	Focus	PEEK Section							
					2: Health status, co-morbidities, health-related quality of life	3: Diagnosis experience, information, support and costs	4: Decision making and healthcare professional discussions	5: Treatment, healthcare system use and access, economic implications	6: Information, communication and self-management	7: Care, support and navigating healthcare system	8: Quality of life, mental health, relationships	9 Expectations, preferences and messages
Maurer et al, 2018[34]	International	441	Quantitative	Drug	x							
Ando et al, 2016[25]	Japan	10	Quantitative	Drug	x							
D'Souza et al, 2019[32]	USA	31	Quantitative	Drug	x							
Valdrez et al, 2014[40]	Portugal	111	Quantitative	Genetic screening		x						
Lane et al, 2019[5]	UK	158	Quantitative	Health related quality of life	x	x						
Sanchorawala et al, 2017[35]	USA	574	Quantitative	Health related quality of life	X							
Shu et al, 2016[37]	USA	1226	Quantitative	Health related quality of life	x							
Warsame et al, 2017[41]	USA	302	Quantitative	Health related quality of life	x							
Yarlas et al, 2019[44]	USA	172	Quantitative	Health related quality of life	x							
Telles-Correia and Moreira, 2014[27]	Portugal	10	Quantitative	Liver transplant							x	
Wixner et al, 2015[42]	Sweden	77	Quantitative	Liver transplant	x	x						
Caccialanza et al, 2012[31]	Italy	150	Quantitative	Nutrition	x							
Caccialanza et al, 2015 [31]	Italy	143	Quantitative	Nutrition	x							
Sattianayagam et al, 2013[36]	UK	110	Quantitative	Nutrition	x							
Bartier et al, 2019[29]	France	95	Quantitative	Pharyngo-laryngeal involvement	x							
Gomes et al, 2014[26]	Portugal	23	Quantitative	Urinary tract dysfunction	x						x	

Abbreviations and terminology

AL amyloidosis	Amyloid light-chain amyloidosis
Amyloidosis	Refers to transthyretin amyloidosis or amyloid light-chain amyloidosis
ANOVA	Analysis of variance (ANOVA). This is used to analyze the differences among group means in a sample.
ASGS	The Australian Statistical Geography Standard from the Australian Bureau of Statistics, defines remoteness and urban/rural definitions in Australia
ATTR	Transthyretin amyloidosis
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.
f	The F ratio is the ratio of two mean square values, used in an ANOVA comparison. A large F ratio means that the variation among group means is more than you'd expect to see by chance.
FOP	Fear of Progression. Tool to measure anxiety related to progression
IQR	Interquartile range. A measure of statistical dispersion, being equal to the difference between 75th and 25th percentiles, or between upper and lower quartiles.
p	Probability value. A small *p*-value (typically ≤ 0.05) indicates strong. A large *p*-value (> 0.05) indicates weak evidence.
PEEK	Patient Experience, Expectations and Knowledge
PIH	Partners in Health
SD	Standard deviation. A quantity expressing by how much the members of a group digger from the mean value for the group/
SEIFA	Socio-Economic Indexes for Areas (SEIFA) ranks areas in Australia according to relative socio-economic advantage and disadvantage. This is developed by the Australian Bureau of Statistics.
SF36	Short Form Health Survey 36
t	t-Statistic. Size of the difference relative to the variation in your sample data.
Tukey HSD	Tukey's honestly significant difference test. It is used in this study to find 6significantly different means following an ANOVA test.
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.
X^2	Chi-squared. Kruskal-Wallis test statistic approximates a chi-square distribution. The Chi-square test is intended to test how likely it is that an observed distribution is due to chance.

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