Section 11

Discussion

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 (TTR) amyloidosis, the more common is the wild type, the other is an inherited TTR mutation[2,3]. AL amyloidosis is the most commonly diagnosed type of amyloidosis[2,3].

In this PEEK study, 28 participants with amyloidosis, and 8 carers to people with amyloidosis were recruited into the study. There were 18 participants with either wild type or hereditary ATTR, and 10 participants with AL amyloidosis (seven of these with cardiac involvement). There were six participants that were carers to people with AL amyloidosis and two were carers to people with ATTR.

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]. Autopsy data have indicated that amyloid deposits in about a quarter of individuals over 80 years old[5].

Risk factors include advanced age, male gender, family history, having dialysis, and African descent[2,3]. The median age for a wild type ATTR 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[6]. The median age for inherited ATTR diagnosis is 67, and the proportion of males to females is approximately 70 to 30[6]. Consistent with risk factors, of the participants in this study that were diagnosed with amyloidosis, the majority were male, and aged over 65.

Other health conditions

In addition to amyloidosis, 85% of participants had at least one other condition to manage. Most commonly arrythmias (54%), other reported conditions were sleep problems or insomnia (39%), anxiety (self or doctor diagnosed – 36%), chronic pain (32%), depression (self or doctor diagnosed – 29%), hypertension (29%), chronic heart failure (21%), chronic obstructive pulmonary disease (18%), angina (10%), and diabetes (4%).

The National Health Survey was conducted in 2017 to 2018, it is an Australia wide survey conducted by the Australian Bureau of statistics. Almost half of the Australian population have one chronic condition[7]. Common chronic health conditions experienced in Australia in 2017-18 were: mental and behavioural conditions (20%), back problems (16%), arthritis (15%), asthma (11%), diabetes mellitus (5%), heart, stroke and vascular disease (5%), osteoporosis (4%), chronic obstructive pulmonary disease (3%), cancer (2%), and kidney disease (1%)[7]. The Australian Bureau of Statistics reports that 10% of Australians have depression or feelings of depression and 13% have an anxiety-related condition[7].

Compared to the Australian population, participants in this study had higher rates of depression, anxiety, cardiovascular disease and COPD, this may be attributed in part by the advanced age of the majority of participants.

Baseline health

The Short Form Health Survey 36 (SF36) measures baseline health, or the general health of an individual[8]. The SF36 comprises nine scales: physical functioning, role functioning/physical, role functioning/emotional, energy and fatigue, emotional well-being, social function, pain, general health, and health change from one year ago. The scale ranges from 0 to 100, a higher score denotes better health or function[8].

Population norms for the SF36 dimensions in Australia were assessed in the 1995 National health survey, while this was conducted 25 years ago, it can give an indication of how the Amyloidosis community in this PEEK study compares with the Australian population[9]. Compared to the Australian population, participants in this PEEK study on average scored similar results for the energy/fatigue, emotional well-being, and social functioning domains, they had worse scores for the physical functioning, role functioning/physical, role functioning/emotional, pain and general health domains.

Compared to baseline SF36 data from 574 participants in America with AL amyloidosis, the PEEK participants scored similar results for the Role functioning/physical, pain, general health, and energy/fatigue domains, and better in the physical functioning, social functioning, role

functioning/emotional, and emotional well-being domains[10].

Other studies of health-related quality of life in people with amyloidosis in general report lower scores compared to the general American population. A large international study reported that participants with symptomatic ATTR-CM had severely reduced health related quality of life compared to the general US population[11]. In a study of 158 participants with ATTR-CM, the lowest scoring health related quality of life domains were physical limitations, social limitations and symptom stability[6], greater physical limitations were also found in this PEEK study, however social limitations were not affected. This is similar to a comparison of 31 AL amyloidosis participants with the general USA population, where health related quality of life scores were lower, in particular for physical health[12].

Symptoms

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 ATTR 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 AL amyloidosis include loss of appetite, fatigue, unintentional weight loss, and weakness. When the heart is 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, 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].

Participants in this PEEK study had between zero and 13 symptoms (Median = 5.00), The most common symptoms for all participants were fatigue being short of breath, limb weakness, and light-headedness. Similar to the PEEK study, the most commonly patient reported symptoms in other studies were fatigue, oedema (swelling ankles and legs), short of breath, dizziness on standing, feeling full, weight loss, neuropathy, constipation/ diarrhoea, purpura (raccoon eyes), enlarged tongue, and weakness[13,14]. The most common symptom leading to diagnosis in this PEEK study population was excessive weight loss.

Diagnosis

ATTR-CM is an under-diagnosed condition, the diagnosis of ATTR-CM is difficult due the wide range of symptoms, it can mimic other conditions, there is a lack of awareness by physicians, there is limited access to genetic screening, and it is a rare disease[15,16]. Early diagnosis is important for effective management. Amyloidosis is diagnosed from biopsy; the Congo red staining of biopsy is the gold standard. Clinical assessments and imaging of involved organs, in particular, investigations of kidney (blood and urine tests), heart (blood tests, electrocardiogram (ECG) and echocardiography, MRI) and liver function (blood tests and ultrasound)[17].

Diagnosing the correct type of amyloidosis is important in all cases, monoclonal immunoglobulin abnormality testing may indicate AL amyloidosis but is not diagnostic. Assessment of the clinical presentation, genetic testing, immunohistochemistry , and mass spectrometry are used to identify the type[17].

Patient reported diagnostic tests collected in questionnaires completed by 341 AL amyloidosis participants included reported diagnostic tests include biopsy, bronchoscopies, cardiac catheterizations, cardiac magnetic resonance imaging, colonoscopies, computerized tomography scans, echocardiograms, electrocardiograms, endoscopies, nerve conduction tests, positron emission tomography scans, pulmonary functioning tests, and X-rays[13]. Often diagnostic tests were done before amyloidosis was suspected, and then more tests were conducted to confirm amyloidosis[45]. In this PEEK study, participants had between one and 11 diagnostic tests, (Median = 6.5). The most common diagnostic tests were blood tests, electrocardiogram, and echocardiogram.

Reasons for delays in diagnosis of amyloidosis from the patient perspective include their own interpretation of symptoms, and the time taken to seek medical attention[13]. From the healthcare side, delays can occur due to doctors that are not familiar with disease, delays in the healthcare system (for example, time to get a specialist appointment), symptoms similar to other conditions causing misdiagnosis, and the slow diagnostic process once amyloidosis is suspected[13].

In this PEEK study, about 10% of participants described having symptoms and not seeking medical attention initially but recognising the importance of those symptoms in hindsight. About half of the participants noticed symptoms and sought medical attention straight away, while about 20% delayed seeking medical attention. There were some participants that did not notice any symptoms.

Consistent with risk factors, of the participants in this study that were diagnosed with amyloidosis, the majority were male, and aged over 65.

A survey was completed by 533 participants with any type of amyloidosis diagnosis or their caregivers[11]. Time from symptoms to diagnosis was within a year for most participants (68%), and over a year for 38%[14]. The AL amyloidosis diagnostic journey was explored with 10 patient interviews, 4 clinician interviews and 341 patient surveys[13]. The time from symptoms to diagnosis was reported by clinicians on average 10 months, and by patients interviewed on average 3 years. Of the 341 survey respondents, over 70% reported diagnosis after 6 months from symptoms[13]. In a questionnaire of 158 participants with ATTR-CM , diagnosis was delayed in particular for wild type ATTR-CM, with over 40% being diagnosed more than four years after initial cardiac symptoms[6]. In addition, quantitative data from 341 participants with AL amyloidosis, those with cardiac involvement were more likely to receive a delayed diagnosis compared to those with kidney involvement[13]. Participants in this PEEK study, more than 40% of participants waited more than a year before being diagnosed, though the time between tests and receiving a diagnosis was most commonly between 2 and 3 weeks, or more than 4 weeks.

Once diagnosed, patients have reported mixed emotions. In interviews with ten participants with AL amyloidosis some were relieved to finally have a diagnosis, while others were in shock and overwhelmed by a rare disease diagnosis[13]. A survey completed by 200 AL amyloidosis participants reported feeling frightened by the diagnosis, depressed, numb, powerless, hopeless, relieved, and angry[14].

In a survey completed by 533 participants with any amyloidosis diagnosis or their caregivers, approximately half made four or more visits to a doctor before a diagnosis was made, and most commonly, the diagnosis was made by a haematologist or oncologist.[14], another study of 341 questionnaire respondents almost two thirds reported four or more doctors before diagnosis[13]. In a questionnaire of 158 participants with ATTR-CM, diagnostic delays occurred, with patients that used hospital services reporting a median of 17 hospital visits during the three year period before diagnosis[6]. In this PEEK study, the diagnosis was given most commonly by the haematologist, followed by a cardiologist. About a quarter of participants in this PEEK study described seeing 3 or more doctors before getting a diagnosis.

Biomarkers or genetic markers

Genetic testing is important in patients with a family history to confirm the diagnosis and to identify the specific mutation[18]. The most common mutations globally are Val30Met, Val122Ile, and.8 Val30Met [19]. The European Network for TTR-FAP recommends genetic counselling for individuals and families diagnosed or at risk of ATTR to detect asymptomatic carriers and avoid misdiagnosis[18].

More than half of the participants in this PEEK study didn't have many discussions about biomarkers or genetic testing with their healthcare profession, and about half knew of any mutations that they had related to their amyloidosis. Similar to this PEEK study, qualitative interviews with ATTR participants reported that they were aware that there were several mutations responsible for their condition, but often did not know which mutation they had[20].

Understanding of disease at diagnosis

The majority of participants in this PEEK study had little to no knowledge about amyloidosis before they were diagnosed. Some participants had some knowledge due to a family history of the disease, and others noted that they understood more as they lived with the condition. A theme from 10 qualitative interviews was that participants did not consider themselves seriously ill until they received an abnormal test result[13], a general lack of knowledge about the condition could account for this.

Decision-making

The decision-making process in healthcare is an important component in care of chronic or serious illness[21]. Knowledge of prognosis, treatment options, symptom management, and how treatments are administered are important aspects of a person's ability to make decisions about their healthcare, highlighting the importance of

healthcare professional communication[22,23]. In addition, the role of family members in decision-making is important, with many making decisions following consultation with family[24].

When treatment options were presented to participants in this PEEK study, when multiple treatment options were discussed almost equal numbers participated in decision-making, some decided not to take part in decision-making, and others were not given an option to take part in treatment decision-making. The most important aspects to consider when making treatment decisions were quality of life, efficacy, and side effects.

Treatment

ATTR-CM requires a multidisciplinary approach to symptomatic treatment, in particular for neuropathy, weakness, autonomic dysfunction, changes in bowel function, and cardiac symptoms[25]. Treatment aims to prevent or delay the progression of disease and improve quality of life. The European Network for Transthyretin-Related Familial Amyloid Polyneuropathy recommends a full history and clinical examination and the assessment of sensorimotor function, autonomic dysfunction, cardiac function, and renal function[18]. National reference centres are recommended for early diagnosis, treatment and care and to ensure consistent treatment and care across different regions[16].

Hereditary and wild type ATTR, there are limited drugs available to slow the course of the disease such as diflunisal, a non-steroidal anti-inflammatory drug[25,26]. New promising treatments such as tafamidis[27-32], inotersen[33,34], and patisiran[35] are undergoing clinical trials. Selected patients may benefit from liver transplants[25]. There were five participants in this study that had diffusional to treat their ATTC-CM, quality of life with this treatment was average, consistent with a randomised clinical trial of diffusional that reported preservation of quality of life[26].

The treatment for AL amyloidosis is chemotherapy, similar to that used for myeloma, these include traditional chemotherapy drugs (melphalan and cyclophosphamide), corticosteroids (such as dexamethasone), and targeted therapies such as bortezomib and ixazomib, and immunosuppressants such as thalidomide and lenalidomide[36]. Selected patients may benefit from stem cell transplants[36]. Consistent with these treatment guidelines, participants in this PEEK study most commonly had the following combinations for treating AL amyloidosis: melphalan and dexamethasone; bortezomib, cyclophosphamide, dexamethasone; cyclophosphamide, thalidomide, and dexamethasone.

In a survey of 181 participants with AL amyloidosis, participants reported having chemotherapy (63%), stem cell transplantation (39%), and organ transplant (8%)[14]. In this PEEK study, of the ten participants with AL amyloidosis, 90% had chemotherapy and 20% had stem cell transplantation. The average quality of life for all treatments was in the life was distressing to a little distressing range.

Affordability of healthcare

Almost half of the Australian population have private health insurance with hospital cover[37]. This can be used to partially or completely fund stays in public or private hospitals. Between 2006 and 2016, the proportion of private healthcare funded hospitalisations in public hospitals rose from about 8% to 14%[37]. In this PEEK study, 82% had private insurance, which is more than the Australian population. It should also be noted that participants in this study are grateful for the low-cost medical care and access to treatment and hospital through Medicare.

Clinical trials

Clinical trials are essential for development of new treatments. The benefits to participants include access to new treatments, an active role in healthcare, and closer monitoring of health condition. The risks to participants include new treatment may not be as effective, and side effects.

A search of the Australian New Zealand Clinical Trials Registry was conducted on 22 June 2020. The search included any study that included ATTR or amyloidosis participants, was conducted in Australia, and was open for recruitment in the last ten years. A total of eight studies were identified that had a target recruitment of between 20 and 2000 participants (Median = 218), seven studies were international drug clinical trials, and a single study was exclusively conducted in Australia and was focused on transplants.

The clinical trials were conducted across Australia, with all eight studies conducted in NSW, five were conducted in Queensland, four in Victoria, three in Western Australia, two in South Australia, and one in Tasmania. None of the clinical trials were conducted in the Australian Capital City or the Northern Territory.

A survey of 533 participants with amyloidosis and their caregivers, reported that more than 70% were poorly informed about clinical trials, almost half believed that taking part in a clinical trial would be beneficial to their health and would consider taking part, and about 20% had taken part in a clinical trial.[14] Almost all of the participants in this PEEK study had discussions about clinical trials with their doctor, indicating that they were given some information about clinical trials, nearly 80% would like to take part in a suitable clinical trial, only a single participant had taken part in a clinical trial (4%).

Self-management

Self-management of chronic disease encompasses the tasks that an individual must do to live with their condition. Self-management is supported by education, support, and healthcare interventions. It includes regular review of problems and progress, setting goals, and providing support for problem solving[38]. Components of self-management include information, activation and collaboration[38].

Information

Information is a key component of health self-management[39,40]. The types of information that help with self-management includes information about the condition, prognosis, what to expect, information about how to conduct activities of daily living with the condition, and information about lifestyle factors that can help with disease management[39,40].

In this PEEK study, information about treatment options, disease management, and disease cause were most frequently given to participants by healthcare professionals; and were also the most common topics searched for independently by the participants. In contrast, qualitative interviews with 10 ATTR-CM patients or carers, the most common topics that participants wanted to be informed about were symptoms, liver transplants, and cardiac involvement[20]. In another study of 421 questionnaire respondents, the most commonly given information was information specific to their type of amyloidosis, support groups, and clinical trial information[14]. In this PEEK study, participants accessed information most often from the hospital or clinic where treated, followed by non-profit or charities or patient organisations, consistent with reports from another amyloidosis study[14].

Activation (skills and knowledge)

Patient activation is the skills, knowledge, and confidence that a person has to manage their health and care; and is a key component to health self-management. Components of patient activation are support for treatment adherence and attendance at medical appointments, action plans to respond to signs and symptoms, monitoring and recording physiological measures to share with healthcare professionals, and psychological strategies such as problem solving and goal setting.

In this PEEK study, the partners in heath questionnaire was used to measure patient activation[41]. Participants scored highly in all domains which indicated that they had excellent knowledge about their condition and treatments, they had a very good ability to manage the effects of their health condition on emotional well-being, social life and healthy behaviours. They had an excellent ability to adhere to treatments and communicate with healthcare professionals, and an excellent recognition and management of symptoms. Interviews with 10 people with ATTR or their carers reported that participants had good knowledge of the disease and symptoms, but poor knowledge about disease mechanisms, they had a good knowledge of their healthcare team and what the role of each member of their healthcare team was, and they had good adherence to medication though did not always comply with dosage[20]. The participants in this PEEK study also had a good knowledge about their healthcare team roles, and the majority had complied with their treatments and medications at all times.

Communication and collaboration

Collaboration is an important part of health self-management, the components of collaboration include healthcare communication, details for available information, psychosocial and financial support[39,40]. Communication between healthcare professionals and patients can impact the treatment adherence, self-management, health outcomes, and patient satisfaction[9,42-45].

An expert panel identified the fundamental elements of healthcare communication that encourages a caring, trusting relationship for patient and healthcare professional that enables communication, information sharing, and decision-making[46].

Building a relationship with patient, families and support networks is fundamental to establishing good communication[46]. Healthcare professionals should encourage discussion with patients to understand their concerns, actively listen to patients to gather information using questions then summarising to ensure understanding[46]. It is important for healthcare professionals to understand the patient's perspective and to be sympathetic to their race, culture, beliefs, and concerns. It is important to share information using language that the patient can understand, encourage questions and make sure that the patient understands[46]. The healthcare professional should encourage patient participation in decision-making, agree on problems, check for willingness to comply with treatment and inform patient about any available support and resources[46]. Finally, the healthcare professional should provide closure, this is to summarise and confirm agreement with treatment plan and discuss follow up.

In this PEEK population, participants commonly described having a positive experience in communicating with healthcare professionals. Positive experiences were related to comprehensive, two-way, supportive conversations, and negative experiences occurred most commonly when healthcare professionals had a limited understanding of their condition. In addition, communication with health care professionals was measured using the "Care coordination: communication" scale[47]. It measures communication with healthcare professionals, measuring knowledge about all aspects of care including treatment, services available for their condition, emotional aspects, practical considerations, and financial entitlements. On average, participants had an average score for communication with healthcare professionals, and a good score for navigating the health system.

Participants in this PEEK study experienced support and care from family and friends, through hospital or clinical settings, peer support and charities though some reported the challenges of finding or accessing support, similar to other reports of supportive families[20] .

Anxiety and depression

The rates of depression and anxiety are higher in people with chronic conditions compared to the general population. In a meta-analysis of 20 qualitative studies, it was reported that people with chronic conditions experienced anxiety or depression as either as independent of their chronic condition or as a result of, or inter-related with the chronic disease, usually however, anxiety and depression develops as a consequence of being diagnosed with a chronic disease[48].

Interviews with 10 people with ATTR-CM or their carers, reported that the condition had a negative impact on mental and physical well-being, in particular, participants were worried about future reliance on family[20]. Participants in this PEEK study, also felt the burden they placed on families and experiencing changing dynamics in their relationships due to added anxiety, exacerbations and/or physical limitations, however, the most common theme in relation to impact on relationships was participants describing their relationships with family being strengthened.

In this PEEK study, anxiety associated with amyloidosis was measured by the fear of progression questionnaire[49], participants in this study had moderate anxiety.

Characterisation

There were 36 participants in the study from across Australia, 28 diagnosed with amyloidosis, and eight carers to people with amyloidosis. The majority of participants were from Queensland and New South Wales, and most lived in major cities, they lived in all levels of advantage. Most of the of participants identified as Caucasian or white, aged mostly between 65 and 74. Half of the participants had completed some university, and most were retired.

Participants in this PEEK study were most commonly diagnosed with ATTR, either hereditary or wild type. Most of the participants also had other health conditions they had to manage, approximately 44% of the participants had anxiety and/or depression.

This is a patient population that experienced fatigue as the most common symptom leading to diagnosis. They most commonly had five or six diagnostic tests

to get their diagnosis and were diagnosed more than a year after first noticing symptoms. They had out of pocket expenses for their diagnosis, but usually the cost wasn't a significant burden. Most participants felt they had enough emotional support and information from healthcare professionals at the time of diagnosis.

This is a patient population that experienced excessive weight loss, breathlessness and tiredness as key symptoms leading to their diagnosis. Half of the participants described seeking medical attention relatively soon after they started experiencing symptoms.

This is a study cohort that described knowing nothing or very little about their condition prior to diagnosis.

This is a patient population that had conversations about treatment where multiple options were presented. They mostly took quality of life, efficacy of treatment, and side effects into consideration when making treatment decisions, their decision making had not changed over time. They commonly did not have many discussions about biomarkers and were not sure if they had any.

This is a group who felt they were treated with respect throughout their experience. They were most commonly treated for ATTR-CM with loop-acting diuretics, and doxycycline; and were most commonly treated for AL amyloidosis with melphalan and dexamethasone. Half of this study population made lifestyle changes following diagnosis, and most used complementary therapies to manage their amyloidosis

Most of the participants in this study population reported having discussions about clinical trials with their clinician and though only one had taken part in a clinical trial. Participants in this study would be willing to participate if there was a suitable trial for them.

This is a patient population that described mild side effects as fatigue and diarrhoea. They described severe side effects as pain, neuropathy, nausea and vomiting.

Within this patient population, most participants adhered to treatment at the advice of their clinician or as long as it was prescribed. They felt that evidence of stable disease and an improvement in general well-being were needed to feel like treatment was effective.

This is a patient population that primarily needed the advice of their clinician as well as information about side effects, scientific evidence and clinical advice or expertise in order to feel comfortable trying new treatments.

The cohort was split between people who did not need support to have treatment at home, and those who needed the support from family or friends, regular check-ups from a GP or nurse, and someone to call if they had a question or issue.

Participants in this study had excellent knowledge about their condition and treatments, an excellent ability to adhere to treatments and communicate with healthcare professionals, excellent recognition and management of symptoms, and a very good ability to manage the effects of their health condition on emotional well-being, social life and healthy behaviours.

This is a patient population that primarily accessed information through the internet, books, pamphlets and newsletters as well as from specific health charities. They found information from reliable sources and from their doctors helpful, and preferred to get information by talking to someone. They were most receptive to information at the time of diagnosis.

The participants in this PEEK study had very good communication, navigation and overall experience of care coordination. They mostly experienced positive communication from health care professionals with holistic, two way, and supportive conversations.

This is a patient population that experienced support and care from family and friends, through hospital or clinical settings, peer support and charities though some reported the challenges of finding or accessing support.

This is a patient population where their condition had an impact on their mental and emotional health, and it had a negative impact on their quality of life. The participants in this PEEK study had moderate levels of anxiety in relation to their condition. They managed their general health by understanding their limitations.

This is a group who would most like to control heart and lung symptoms. The most important aspect for making decisions about their own treatment was medication safety, and they thought that decision-makers should consider quality of life when making decisions about treatment for people with amyloidosis.

This is a patient population that would like future treatments to be more affordable, and more effective.

This is a study cohort did not have any recommendations for information about their condition but want more access to support services. They would like health professionals to have more knowledge of their condition.

This is a patient population that felt grateful for healthcare staff and the entire health system in general.

This is a patient population that wanted to tell patients and families in the future that they should seek peer support and join support groups, as well as seeking and accepting support in general.

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