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How to stay in balance: the impact of an inborn
 error in adults presenting with neurological
 symptoms and their partners

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Master Thesis – Klinische neuropsychologie

s3930637

September 2024

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Abstract

Inborn Errors of Metabolism (IEMs) comprise a heterogeneous group of genetic disorders that cause dysfunction of an enzyme or transporter involved in cellular metabolism. Although they often present in early life, in some patients symptoms start during adulthood. In this study, it is investigated how five patients with a late-onset IEM and their five partners stay in balance, by means of questionnaires and semi-structured interviews. The quantitative data of the interviews resulted in four major themes for the patients (consequences of the IEM, coping with the IEM, rarity of the IEM, and perceived care provision) and three major themes for the partners of the patients (relationship, coping with a partner with an IEM, and informal caregiving). The quantitative analyses showed high levels of fatigue in the patients, but this did not lead to impairments in quality of life. Only one of the five patients presented with psychiatric symptoms. All patients in the study had an active coping style, which probably contributes to successfully coping with an IEM. The partners in the study also did not report considerable limitations in daily functioning or quality of life regarding their caregiver's role. The biggest obstacle for IEM patients and their partners seems to be the lack of knowledge about the disease, therefore this study is of great value to take the first step to develop more knowledge about the psychological consequences of coping with an IEM.

Keywords: late-onset inborn errors of metabolism, interviews, caregivers, coping

Introduction

Inborn Errors of Metabolism (IEMs) comprise a heterogeneous group of genetic disorders that cause dysfunction of an enzyme or transporter involved in cellular metabolism (Ferreira et al., 2019). Since IEMs comprise a large varied group of disorders, they present with a heterogeneous group of symptoms which include for example neurological disorders, psychiatric disorders, and visceral symptoms (Koens, 2022).

Even though IEMs are inherited, the symptoms of IEMs may present at various ages. Symptoms of the disease can present early in life, even before birth or at birth (Saudubray et al., 1999). The clinical presentations of IEMs presenting at this very young age, comprise among others perinatal asphyxia, severe acidosis and severe hypoglycemia, which may lead to early death. There are also milder early-onset variants of IEMs, in these patients the symptoms may be more subtle and progressive over years (Koens, 2022).

While historically IEMs were thought to only be present during infancy or early childhood, we now know that they can be present in late adulthood as well. As many of the late-onset forms of IEM were recognized quite recently, mainly by the use of new diagnostic techniques such as next-generation sequencing, little is known about them (McNeill, 2019). Symptoms of late-onset IEMs are often quite different from the symptoms observed in classical young-onset forms (Saudubray & Mochel, 2018). For example, acute metabolic decompensation is less frequently observed in adult forms compared to children (Kölker et al., 2006). Psychiatric and neurological disorders occur frequently in late-onset IEMs and because of the more common causes of these symptoms, IEMs are often misdiagnosed (Walter, 2007). For example, the late-onset forms of urea cycle disorder (UCD) frequently presents with psychiatric diseases, which can easily be misdiagnosed as schizophrenia or alcohol or drug intoxication (Tada et al., 2013). In a study from Kuiper and colleagues (2019) on galactosemia, half of the patients suffered from psychiatric symptoms such as feeling

depressed or anxious. Also in another study, in patients with Fabry disease, it was shown that depressive symptoms were common (Körver et al., 2020). Bonnot and colleagues (2018) furthermore found that in the late-onset form of Niemann-Pick type C (NPC) psychosis occurs in up to half of the patients.

In addition to the frequently presenting psychiatric and behavioral problems, late-onset IEM patients often experience neurological problems (Lee & Lachman, 2008). These include among other: unexplained coma, peripheral neuropathy, movement disorders, dementia, epilepsy and spastic paraparesis (Tada et al., 2013). In particular, cognitive problems and movement disorders are often prevalent in late-onset IEM (Koens et al., 2021). Saudubray & Mochel (2018) found that there may be symptom variability within identical types of IEM, which suggests that there are environmental and aging influences on the clinical expression of late-onset IEM.

It could be expected that patients with a late-onset IEM are impaired in their daily functioning due to the psychiatric, behavioral, cognitive and/or neurological problems. Furthermore, Koens and colleagues (2021) found that the cognitive and neurological problems in late-onset IEM patients are often slowly progressive, which indicates that over time, the patients will get more impaired in daily functioning. From a study in adults with late-onset NPC, it became evident that specific symptoms related to perceived impaired quality of life including problems with ambulation, speech and swallowing, fine motor skills, and problems with cognition (Mengel et al., 2021). These symptoms interfere with simple activities of daily living such as getting dressed and eating and drinking. Impairments in daily functioning prevent normal social interaction or going out and therefore impair the patient's perceived quality of life. Also in the earlier mentioned study on galactosemia, it became clear that in the late-onset IEM patient cohort, it was common to experience impairments in daily functioning (Kuiper et al., 2019). Another possible issue in IEM patients may be sexual

dysfunctions, although at present there is no literature available about this considering IEMs. When looking at other disorders affecting the brain, for example TBI, patients report various cognitive, physiological and psychosocial changes that impact the patient's sexual functioning (Giacino et al., 2004). Sexuality has implications on interpersonal relationships, psychological well-being, and overall quality of life (Latella et al., 2018).

When looking at a patient's quality of life, it may be of great importance to take into account patient's coping style. Overall, there are two main styles of coping: active coping (such as problem-focused coping) and passive coping (such as negative self-targeting and avoidance) (Nielsen & Knardahl, 2014; Wood & Bhatnagar, 2015). The most effective strategy in chronic diseases, such as IEM, is that of active coping, while passive coping strategies are useful for acute situations (Urzua & Jarne, 2008). For example, in the study on Fabry disease patients, Körver and colleagues (2020) found that a positive and problem-solving coping style could alleviate the depressive symptoms in patients.

While there are some studies about the perceived quality of life of patients, there are at present no studies available that address the impact of the late-onset IEM on the partners of the patients. From studies on the impact on partners from other progressive neurological diseases, such as Alzheimer Disease (AD) it is shown that the impact on partners is significant (DiBenedetti et al., 2020). Kaplan (1996) identified common problems in emotional adjustment for family members of AD patients, these include: denial, over-involvement, anger, guilt, and acceptance. Furthermore, Kaplan (1996) identified problems that may arise for family members specifically associated with the diagnosis of AD, such as family disruptions, psychological stress, physical fatigue, social isolation, financial issues, and legal issues. Since IEMs and AD share pathophysiological mechanisms and are both progressive disorders affecting among others cognition, it may be that the classification of Kaplan is applicable to IEM family members as well (Pará et al., 2020).

Next to experiencing distress about the health of their partner and their future together, partners of patients frequently become caregivers. This significantly influences the relationship, which can shift from a balanced romantic relationship to a patient-caregiver relationship. In a study on caregiving partners of patients with Parkinson Disease (PD), it was found that they showed significant changes in both depressive symptoms and physical health. Furthermore, partners were at risk for increasing global strain, strain from worry, strain from feelings of being manipulated, and strain from increased tension (Hulshoff et al., 2021). When looking at the caregiver burden in families of a child with IEM, it turns out that 75% of their parents report a burden on their family (Gramer et al., 2014). Hurt and colleagues (2017) clearly showed that the new role of being a caregiver for, in this case a PD patient, causes much uncertainty. This uncertainty affected also issues not directly related to the disease itself and negatively impacted the caregiver's well-being. The clinical manifestation of the IEM in the patient may influence his or her sexual functioning and thereby influences the sexual functioning of the partner, which in turn has a negative impact on quality of life (Latella et al., 2018).

According to Mishel (1990), the negative impact of caregiver well-being is the consequence of inadequate coping strategies and adaptation to new situations. In various studies, it is shown that adequate coping strategies have a positive influence on the partners perceived quality of life and caregiver burden. For example, Neate and colleagues (2019) found that patients with multiple sclerosis (MS) and their partners both benefited from lifestyle modification. Aspects of this modification are seeking support, embracing wellbeing, developing commitment and making major life changes. In the study from Phongtankuel and colleagues (2023) it was shown that caregiver's self-efficacy may mitigate negative outcomes. Caregivers that expressed feelings of preparedness, so when they felt ready to take care of the patient's needs, could better control upsetting thoughts about caring for their partner.

The patients in this study had different IEMs, including Niemann-Pick type C (NPC), Krabbe disease, glutaric aciduria type 1 (GA1) and maternally inherited diabetes and deafness (MIDD). Niemann-Pick type C (NPC) is a lysosomal disease with impaired movement of cholesterol and lipids out of the lysosome and late endosome, resulting in the accumulation of lipids within the affected cell (Bolton et al., 2022). The late-onset form of NPC often presents with movement disorders, a vertical supranuclear gaze palsy, cognitive decline, and/or psychosis or mood disorders (Vanier, 2010). Adult-onset Krabbe disease or globoid cell leukodystrophy (GCL) is a demyelinating disorder resulting from deficiency of the lysosomal enzyme galactocerebrosidase (Nicholas et al., 2020). Adult-onset Krabbe disease patients present with pyramidal symptoms, resulting in a chronic progressive spastic paralysis and gait disorders, with or without peripheral nerve abnormalities, mental disorders, and cognitive disorders (Guode et al., 2022; Henderson et al., 2003; Tokushige et al., 2013; Forbes et al., 2022). In patients with GA1, putatively neurotoxic metabolites glutaric and 3-hydroxyglutaric acid accumulate in body tissues, particularly within the brain (Boy et al., 2017). Onset is often during childhood, with metabolic decompensation caused by among others infections, leading to brain damage and subsequently movement disorders (Bouchereau & Schiff, 2020). Clinical manifestations in late-onset GA1 patients include slowly progressive movement disorders (Boy et al., 2017). In MIDD there is an abnormality of glucose metabolism, associated with a gradual decrease in insulin secretion due to reduced ATP production in pancreatic cells with abnormal mitochondria (Murphy et al., 2008). The most common clinical characteristics of MIDD are progressive neurosensory deafness, early onset of diabetes and deafness, and thin and short stature. Next to that, some patients may experience secondary complications of the diabetes, such as peripheral neuropathy and retinopathy. However, the clinical manifestations in MIDD patients are variable and differ between mitochondrial mutations (Yang et al., 2021).

At present, there is no literature available about the psychological impact of late-onset IEM in adult patients and their partners. The goal of this study is to investigate, for the first time, the impact of the late-onset IEM diagnosis and how the patients and their partners stay in balance or not.

Method

Participants

Patients were included from the movement disorders outpatient clinic of the academical hospital in Groningen (University Medical Center Groningen (UMCG)). The inclusion criteria for participants were: adults with a confirmed diagnosis of an IEM, and being at least 18 years old. The exclusion criteria consisted of: having a mental disorder or being mentally incompetent, absence of having a partner or partner does not want to participate in the study, and having insufficient command over the Dutch language.

Procedure

The participants have been approached by their neurologist. Participants received the patient information folder at home, which included comprehensive information about the study concept and goals (Appendix A). After this, the patients were approached by telephone by the researcher, to answer any remaining questions, discuss their participation, and to make an appointment for taking the interviews.

Before taking the interviews, the patients signed the informed consent form. Permission was requested for participation in the study and for recording the interview (Appendix B). The interviews took place at the patients' and partners' home or at the UMCG in a room with no or minimal distractions. The interviews took place one-on-one, so while taking the interviews, the only people present in the room were the researcher and the patient or the researcher and the patient's partner. This may give the participants more self-confidence to speak more honestly and freely.

The questionnaires that had to be completed by the patients and their partners were sent by post to the patients' home. The patients and their partners filled in the questionnaires themselves, without supervision of a researcher.

The Medical Ethics Review Board of the University Medical Center Groningen (METc UMCG) has given its approval before the data collection.

Materials

The presence and severity of the IEM symptoms were determined by an expert panel who scored the neurological examination that patients underwent earlier. These videos were scored through consensus discussions and by using the Global Clinical Impressions Scale (GCI; Busner & Targum, 2007). Scores on the GCI range from 1 (*functioning at or very close to full capacity*) to 7 (*unable to maintain basic functioning*).

Limitations in daily life in patients were investigated by the Health Assessment Questionnaire Disability Index (HAQ-DI; Boers et al., 2007). This questionnaire is the Dutch translation consensus of the Health Assessment Questionnaire (HAQ; Fries et al., 1980). The HAQ-DI consists of three categories with a few items in each category. In the category *activities* the patient has to fill in, on a 4-points scale, what he/she was able to do most of the time in the past few weeks, ranging from (0) = *takes no effort at all*, to (4) = *impossible to carry out*. This category consists of 8 subcategories, with a total of 20 items. In the category *tools*, the patient has to answer fifteen questions about tools he/she usually uses during the activities. The last category in the HAQ-DI is *help of others*, in which the patient has to answer eight questions about when he/she usually needs help from others. The HAQ-DI Total Score is calculated by summing the scores at the different categories and dividing this by the number of activities filled in. HAQ-DI Total Scores of 0 to 1 are generally considered to represent mild to moderate difficulty, scores of 1 to 2 moderate to severe disability, and scores of 2 to 3 severe to very severe disability (Bruce & Fries, 2003). The other questionnaire used

to investigate the limitations of daily life in patients, is the Dutch version of the Sickness Impact Profile with 68 items (SIP-68; Luttik et al., 1985). This version is the translated and abbreviated version of the traditional Sickness Impact Profile, which consists of 136 items (SIP; Bergner et al., 1981). The SIP-68 consists of three categories: physical, mental and social aspects of health-related function. Total Scores on the SIP-68 range from 0 (best health) to 68 (worst health). Post and colleagues (1996) found that in a mixed injury population the mean score was 22.8 (SD=11.1), which will be used as the cut-off score in this study.

Psychiatric and behavioral problems in patients and their partners were investigated by the Dutch versions of the Achenbach questionnaires. Patients were asked to fill in the Adult Self Report (ASR; Achenbach & Rescorla, 2003). The ASR consists of a 3-points-scale: (1) *not at all*, (2) *a little or sometimes* and (3) *obvious or often*. The scale contains 126 items about problematic behavior that occurred in the past six months. It consists of 12 syndrome scales, which can be combined into 3 overarching scales: internalizing, externalizing and total problems. Raw scores of these scales were transformed into T-scores according to the manual with a mean of 50 (SD=10). Higher T-scores indicate more problems and T-scores of 64 or higher indicate a clinical significant deviation. The partners of the patients had to fill in the Adult Behaviour Checklist, consisting of the same scales as the ASR (ABCL; Achenbach & Rescorla, 2003). Again, only the T-scores, derived from the raw data, of the overarching scales internalizing, externalizing and total problems were used. T-scores of 64 or higher indicate a clinical significant deviation.

Patient's coping style was measured by the Utrechtse Coping List – Revised (UCL-R; Scheurs & Willige, 2023). The UCL-R consists of 47 items on a 4-points scale, ranging from ‘rarely/never’ to ‘very often’, and can be subdivided into six scales: Tackle Actively, Seeking Distraction, Passive/Avoiding, Seeking Social Support, Express Negative Emotions, and Optimism. All the raw scores on the six subscales can be translated into percentile scores with

one of the six corresponding classifications, ranging from ‘very low’ ($\leq 5^{\text{th}}$ percentile) to ‘very high’ ($\geq 95^{\text{th}}$ percentile). To determine the active coping style of a patient, the mean percentile scores of the subscales Tackle Actively, Seeking Distraction, Seeking Social Support and Optimism will be calculated and classified according to the right norm groups.

Patient’s quality of life was measured by the SF-36 questionnaire (van der Zee & Sanderman, 1993). The SF-36 consists of nine subscales, and for this study, items were separately rated. As a consequence, the items 9a, 9e, 9g and 9i were used as the subscale ‘Fatigue’, the items 9b, 9c, 9d, 9f and 9h were used as the subscale ‘Mood’, and the items 1 and 11 were used as the subscale ‘General health’. To get to the total scores of the subscales, some of the raw scores had to be recoded first, after which item scores were summed to scale scores and then transformed to a 100-point scale (RAND Health Sciences Program, 1992). A high total score on the subscales corresponds with a better health and wellbeing condition.

Caregivers’ self-efficacy was measured by The Revised Scale for Caregiving Self-Efficacy, which measures three domains of caregiving self-efficacy: Obtaining Respite, Responding to Disruptive Patient Behaviors, and Controlling Upsetting Thoughts (Steffen et al., 2002). This scale was translated into Dutch for the purpose of this study. Caregivers fill in how much self-efficacy they got for specific situations, belonging to the three domains, on a continuous scale from (0) = no confidence at all to (100) = certain that you can do it. Caregivers can also choose to fill in ‘not applicable’. This scale was translated into Dutch for the purpose of this study. Caregivers scoring high on the Revised Scale for Caregiving Self-Efficacy are individuals with high self-efficacy expectations regarding their own ability to handle challenges of caregiving (Bandura, 1997).

Caregiver burden was measured by the short version of the Zarit Burden Interview (ZBI-12/ZARIT-12; Bédard et al., 2001), the used version was again in Dutch. The ZBI is useful to evaluate the burden after a period of time of caregiving for chronic patients. The

questionnaire consists of 12 items, which are statements that represent how caregivers may feel. It is measured by a 4-points-scale, ranging from (0) = *never* to (4) = *almost all the time*. A higher total score indicates a higher caregiver burden. The suggested cut-off score of 13 will be used as a reference point in this study (Gratão et al., 2019).

The semi-structured interview was taken to evaluate different topics of importance for the patients and their partners (Appendix C). Depending on the information and answers the participants gave, some topics were discussed deeper than others. The meaning of having an IEM diagnosis and the aspects of the disease that impair patients or their partners in daily life, were discussed in all interviews to at least some extent. Quality of life has also been discussed in all interviews. Furthermore, how patients and partners look at the future was considered as an important topic in the interview. Finally, it has been discussed how the patients and partners experience(d) the received care. The interviews were recorded and transcribed verbatim. The interviews of the patients lasted on average 60 minutes, the interviews of the partners lasted on average 45 minutes. To analyze the answers given by the patients and their partners, thematic analysis had been used (Braun & Clarke, 2006).

Statistical analysis

Questionnaire data were visually inspected for normality with the Shapiro-Wilk test, with regard to the small sample size (Mishra et al., 2019). When the Shapiro-Wilk test showed a significant effect, and thus normality could not be assumed, non-parametric tests were used for further analysis. Descriptive statistics were calculated by using IBM SPSS Statistics (version 29.0.1.0.). Interview data were first transcribed verbatim and subsequently analyzed using the principles of thematic analysis (Braun & Clarke, 2006). To perform the thematic analysis, ATLAS.ti 24.0.0. for Windows had been used.

Hypotheses

There are a few hypotheses investigated in this study.

Hypothesis 1 states that adults with IEM experience considerable limitations in daily functioning. This hypothesis will be investigated with the scores of the HAQ-DI and SIP-68, combined with additional information gathered in the semi-structured interview. To assume that the hypothesis is true, we expect the patients to reach a score of 2 or higher at the Total HAQ-DI, and/or a score of 22 or higher at the SIP-68.

Hypothesis 2 states that adults with IEM experience psychiatric and/or behavioral problems. This will be investigated by looking at the scales Internalizing Problems and Externalizing Problems scores of the ABCL and ASR, with a T-score of 64 or higher indicating a clinical significant deviation.

Hypothesis 3 states that adults with IEM experience a decreased quality of life compared to the general population, as measured by three constructs of the SF-36. The total scores on these subscales will be compared to the total scores in the general population.

Hypothesis 4 states that patients with a greater severity of IEM symptoms report a lower quality of life. To assume that the hypothesis is true, there should be a correlation between the scores on the GCI and the total scores on the SF-36.

Hypothesis 5 states that the higher the active coping style of a patient, the higher quality of life they report. Active coping style will be investigated by the UCL-R, indicating that a classification of 'medium' or higher ($\geq 20^{\text{th}}$ percentile) represents an active coping style. Quality of life will be investigated by 3 subscale of the SF-36, which states that the higher the score, the better the overall health and well-being condition. To state that the hypothesis is true, a correlation should be found between scores on the active coping style subscales of the UCL-R and the total scores on the SF-36.

Hypothesis 6 states that partners of adults with IEM experience a negative impact of their caregiver's role regarding quality of life. This will be investigated by the scores on the Steffens self-efficacy and ZBI-12 questionnaires, with mean scores of 49 or lower at the

Steffens self-efficacy and/or total scores of 13 or higher at the ZBI-12 indicating a negative impact of their caregiver's role regarding quality of life.

Results

Participant characteristics

A total of 10 people participated in the study, 5 patients (age range 55-69) and 5 partners (age range 58-66). Table 1 represents the characteristics of the participants.

Table 1*Participant characteristics*

Couple	Participant (1=patient, 2=partner)	Sex	Age	Duration of the relationship in years	Highest level of education*	IEM type	Movement disorders	GCI score IEM
1	1.1	Male	61	32	6	Adult-onset Krabbe disease	Spasticity	4
	1.2	Female	61	32	6			
2	2.1	Female	55	34	5	Glutaric aciduria type 1 (GA1)	Chorea, myoclonus, dystonia	3
	2.2	Male	58	34	5			

3	3.1	Female	56	35	5	Adult-onset Krabbe disease	Spasticity	3
	3.2	Male	58	35	5			
4	4.1	Male	69	41	6	Adult-onset Niemann- Pick type C	Ataxia, dystonia, myoclonus	5
	4.2	Female	66	41	6			
5	5.1	Male	56	33	5	Maternally inherited diabetes and deafness (MIDD)	None	4
	5.2	Female	53	33	5			

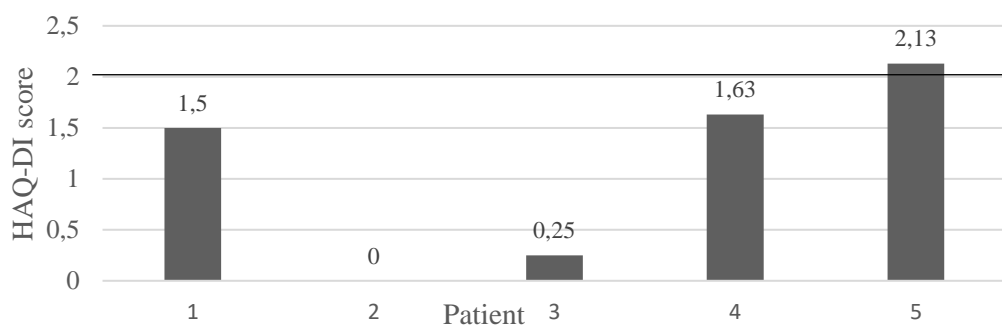
Note. *Level of education is coded by the coding system of Verhage (1964)

PART 1 – Questionnaires

Daily functioning in patients

Two of the five patients in the study experience considerable limitations in daily functioning. Those were the patients with NPC and MIDD. The mean score on the HAQ-DI in the patient sample is 1.10 (SD 0.93) with total scores ranging from 0 to 2.13, as can be seen in Figure 1.

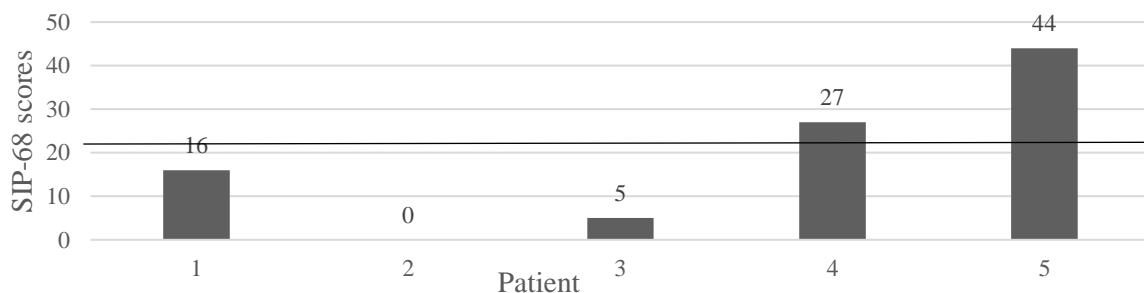
Figure 1
HAQ-DI scores of the patients



Note. Horizontal line represents HAQ-DI cut-off score of 2

The mean score on the SIP-68 in the patient sample is 18.40 (SD 17.70) with total scores ranging from 0 to 44, as can be seen in Figure 2.

Figure 2
SIP-68 scores of the patients



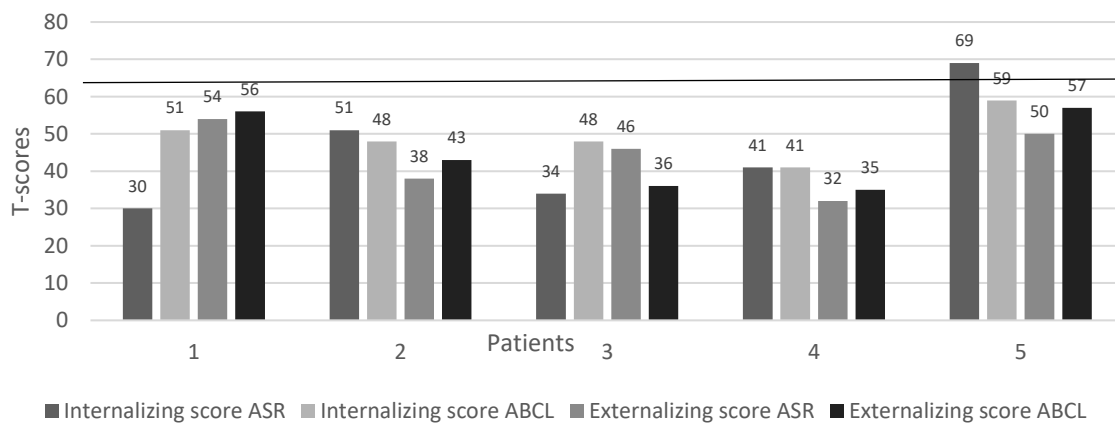
Note. Horizontal line represents SIP-68 cut-off score of 22

Psychiatric and/or behavioral problems in patients.

Based on the Internalizing Problem scales of the ASR (T-score ≥ 64), the patient with MIDD had evident psychiatric and/or behavioral internalizing problems. When looking

closely at the data of this patient, it showed that this patient scored above the cut-off score (T-score = 69.5) for the DSM scale depression (T-score patient = 77) and in the upper border in the clinical range of the DSM scale anxiety (T-score patient = 69). Table 2 shows the mean scores and range of scores in the study sample and Figure 3 gives a visual overview of the data per patient.

Figure 3
ABCL and ASR internalizing and externalizing T-scores of the patients



Note. Horizontal line represents clinically deviant T-score of 64

Table 2

Mean T-scores ABCL and ASR in the study sample

Subscale	Mean T-score (SD)	Minimum T-score	Maximum T-score
ASR internalizing problems	45 (15.60)	30	69
ABCL internalizing problems	49.40 (6.50)	41	59
ASR externalizing problems	44 (8.94)	32	54
ABCL externalizing problems	45.40 (10.60)	35	57

Quality of life in patients and partners

The mean score on the ‘fatigue’ subscale in the sample is 52.43 (SD 24.73), which is lower than the mean score in the general population of ages 55-75 (65.6, SD 21.7) according to van der Zee & Sanderman (1993). However, differences were shown to be not significant (Welch’s $t=1.35$, $p=0.25$) The median score on the ‘mood’ subscale in the patient sample is 21, with scores ranging from 8 to 80. The median score on ‘general health’ in the patient sample is 84, with scores ranging from 24 to 92.

The correlations between the GCI scores of the patients and the scores on the SF-36 subscales can be found in Table 3. There is a strong significant, negative correlation between the severity of IEM symptoms and SF-36 fatigue problems, which means that patients with more severe IEM symptoms experience more fatigue problems.

Table 3

Correlations between GCI scores and SF-36 subscales

Subscale	SF-36 Fatigue	SF-36 Mood	SF-36 General Health
GCI score	-.89*	0	-.87

Note. Spearman’s Rho correlation

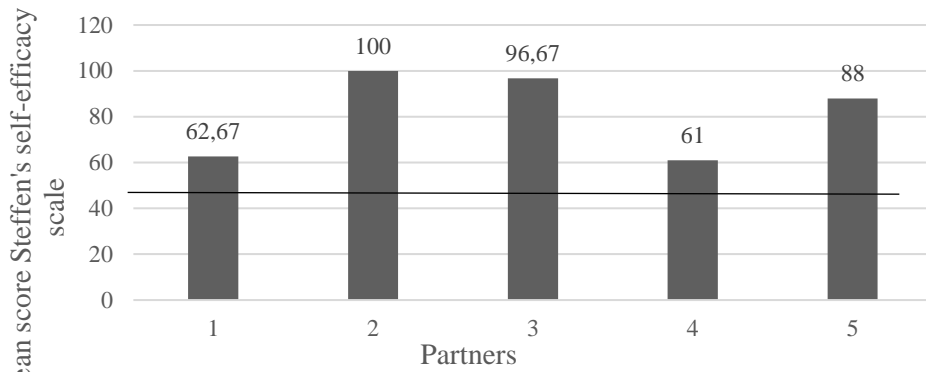
Note. * $p < 0.05$

No partner reported considerable limitations in daily functioning and quality of life regarding their caregiver’s role.

The mean score in the partners sample on the Steffens self-efficacy is 81.67 (SD 18.64), with total scores ranging from 61 to 100 (see Figure 4). The median score on the ZBI-12 was 0 with scores ranging from 0 to 10 (see Figure 5). Thus, there were no partners with

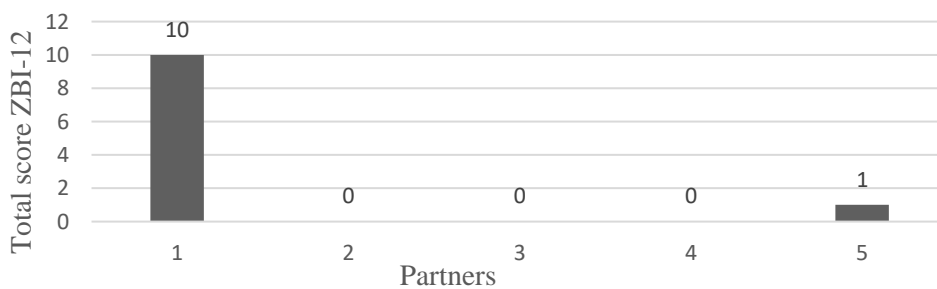
the cut-off score of 49 or lower at the Steffen's self-efficacy scale and no partners with the cut-off score of 13 or higher at the ZBI-12.

Figure 4
Steffen's self-efficacy scale mean scores in the partners of the patients



Note. Horizontal line represents Steffen's self-efficacy cut-off score of 49

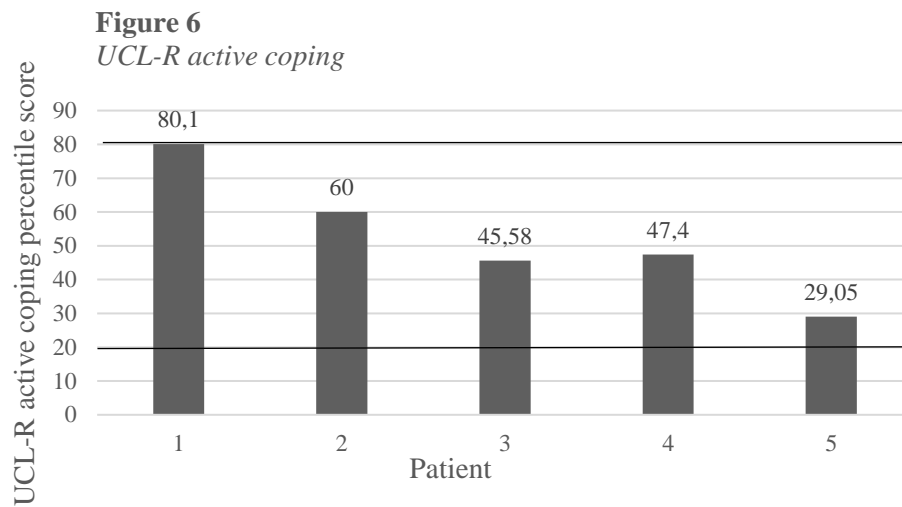
Figure 5
ZBI-12 total scores in the partners of the patients



Note. ZBI-12 cut-off score of 13 has not been reached

Coping styles of the patients

In the patient sample, the mean percentile score of the active coping style scale of the UCL-R is 52.42 (SD 18.99), with scores ranging from 29.05 to 80.10 (see Figure 6). This means that all patients in the sample have an active coping style with the classification average (between the 20th and 80th percentile) or high ($\geq 80^{\text{th}}$ percentile). The percentile score of at least 20 indicates that patients score higher on the active coping style scale than at least 20 percent of the general population.



Note. UCL-R scores between horizontal lines represent average percentile scores

The four subscales of the active coping style with corresponding percentile sample mean scores are elaborated in Table 4. In this table it becomes clear that there are no differences in classification between the mean scores on the different subscales of the Active Coping Style scale.

Table 4

Utrechtse Coping List – Revised Active Coping Style Scales

Subscale	Mean percentile score study sample (SD)	Classification
Tackle Actively	56.84 (34.90)	Average
Seeking Distraction	62.92 (28.76)	Average
Seeking Social Support	57.64 (26.61)	Average
Optimism	32.30 (22.66)	Average

Note. Classification according to the *UCL-R* guidelines (Scheurs & Willige, 2023)

When looking at the correlations between the percentile scores of the UCL-R Active Coping style and the RAND-36 subscales in Table 5, there are small to medium correlations found between these constructs, however, none of the correlations were significant. This means that having an average active coping style is not associated with reported fatigue, mood, or general health.

Table 5

Correlations between UCL-R Active Coping Style and SF-36 subscales

Subscale	SF-36 Fatigue	SF-36 Mood	SF-36 General Health
UCL-R Active Coping Style percentile	-0.40	0.20	-0.32

Note. Spearman's Rho correlations

PART 2 – Semi-structured interviews:

Main themes interview

The semi structured interviews in the adult patients with an IEM, resulted in four major themes describing how they stay in balance. These themes include: (1) consequences of the IEM, (2) coping with the IEM, (3) rarity of the IEM, (4) perceived care provision. The semi structured interviews in the partners, resulted in three major themes describing how the partners of adult patients with IEM stay in balance, including: (1) relationship (2) coping with a partner with an IEM, (3) informal caregiving. The themes are visually presented in figures 1 and 2.

Figure 1

Main themes partners

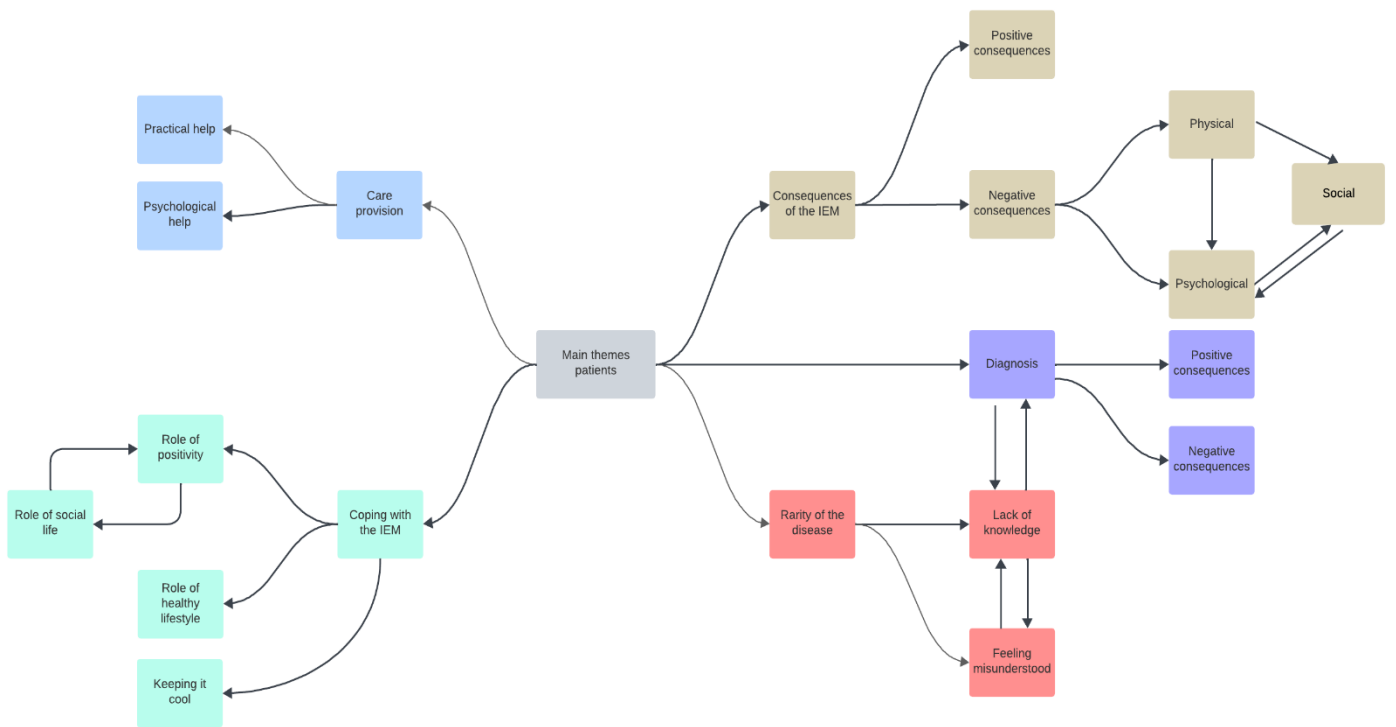
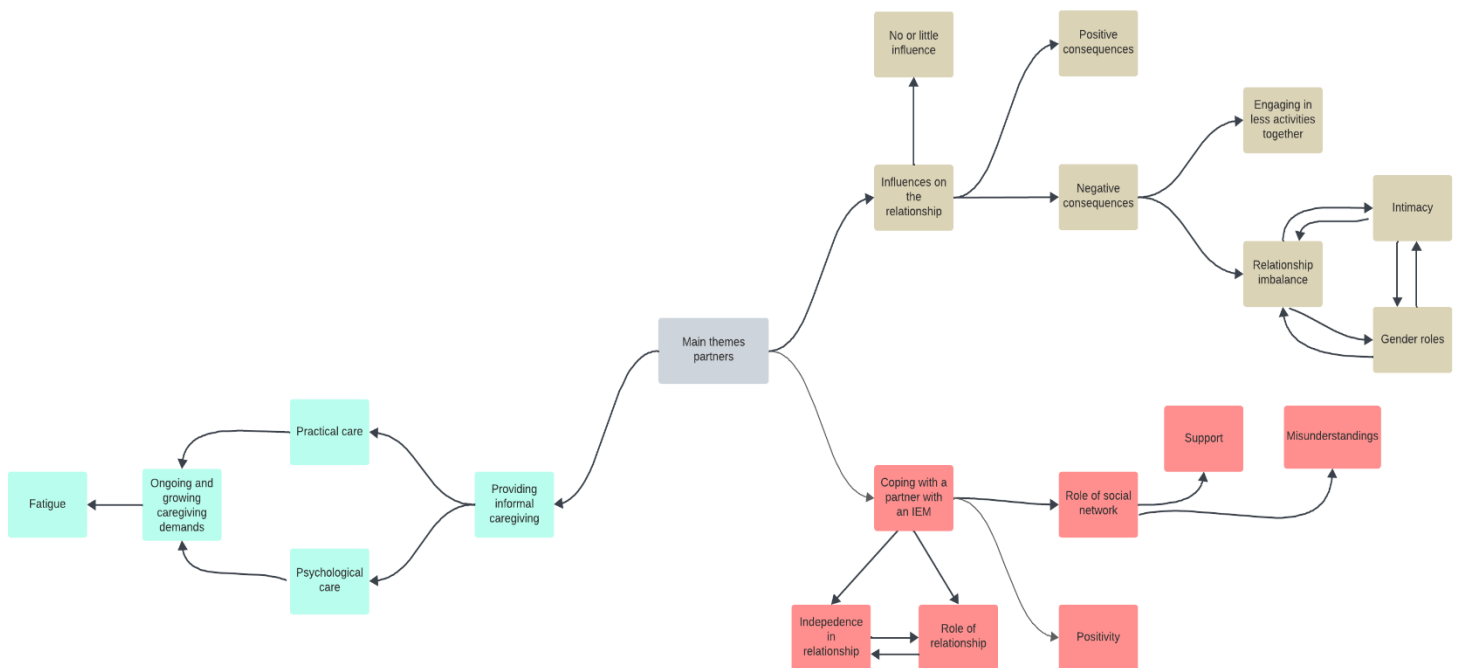


Figure 2

Main themes partners



Main themes patients

Theme 1: consequences of the IEM. Patients with an IEM mentioned a lot of IEM symptoms which impaired them in daily life. These symptoms mainly include physical problems (such as pain, movement disorders, numbness, spasticity, and fatigue). Most patients (3 out of 5) particularly mentioned to suffer from the loss of independence as a consequence of these physical problems. Since most IEMs are progressive, patients have to deal with the fact that their independence will further decline over time: *“Het lastigst aan de stofwisselingsziekte is wel gewoon het inleveren van vrijheid. Ik vind mijzelf nog steeds wel autonoom, maar je levert wel in aan autonomie. Je moet vaker aan andere mensen vragen of ze even willen helpen” (Patient 1).* Another patient mentioned the following: *“Wat de ziekte voor mij betekent, ja, dat is gewoon dat ik steeds minder kan” (Patient 4).*

The loss of independence and often unpromising future perspective, may give them a feeling of loss of control and in some patients may lead to distress, anxiety and depressive symptoms: *“Het is eigenlijk een ziekte die in principe zoveel beperkingen met zich meebrengt waardoor je voor jezelf het gevoel hebt dat het nooit ophoudt. De klachten worden steeds erger, de pijn wordt steeds erger. Dus eigenlijk heb je dan voor jezelf het gevoel dat je geen toekomst meer hebt” (Patient 5).*

The majority of patients (3 out of 5) mentioned that they get fatigued easily and they have to pay attention to keeping their energy level in balance. For some patients, one activity per day is their limit and even this requires a resting period afterwards: *“Zondag hadden we bijvoorbeeld een verjaardag, daar zijn we even geweest, anderhalf uur, langer houden we ook niet vol. En dan komen we thuis en dan moeten we eerst bijkomen daarvan” (Patient 5).* Patients may need a lot of focus, energy and time to perform a ‘simple’ movement (e.g., walking, standing up, grabbing a coffee cup) or sometimes are not able to perform the movement at all: *“Vooral 's morgens dan kom ik langzaam op gang, dan heb ik wel anderhalf uur tijd nodig voordat ik een beetje normaal functioneer” (Patient 1).* While the symptoms and possibilities differ greatly between the IEM patients, more than half of the patients (3 out of 5) mentioned that they should be aware of their energy

level balance: *“Want zoals naar het winkelcentrum zou ik de heenweg eigenlijk kunnen lopen, maar de terugweg eigenlijk niet. Dus vandaar dat ik heel goed moet uitkijken hoeveel energie dat je gaat verliezen”*(Patient 5).

Furthermore, because of the symptoms of the IEM, the loss of independence, and the energy level balance, patients may experience social limitations and difficulties in social activities such as visiting a soccer game, visiting a festival, going on a trip or holiday, or even visiting friends or family or doing groceries: *“Ik ga niet meer naar kroegjes of wat dan ook. Dat vinden we ook altijd wel heel leuk om te doen, maar dat vermijd ik, of vermijd ik, dat doe ik gewoon niet meer”* (Patient 3). Other patients, with less severe physical symptoms, do not experience these big social limitations. Yet, these patients are as well confronted with their physical limitations daily, and they are required to ask help for little things or try to avoid these certain tasks: *“Ik heb heel lang nooit iets gezegd, heel lang heb ik dat verzwegen. Dan ging ik uitwegen zoeken, zorgen dat ik dingen niet hoefde te doen, of liep ik er voor weg. Dat heb ik wel heel lang gedaan”* (Patient 2).

Some patients also mentioned the positive consequences of having a late-onset IEM. For example, one patient had been bullied because of the unexplained IEM symptoms (when the IEM was not diagnosed yet), but this patient mentioned a big mental growth as a consequence: *“Ja, dat al die factoren eigenlijk heel ongunstig waren om je als kind als een sterk en krachtig iemand te kunnen ontwikkelen. En ja, toch heb ik me wel in mijn eentje daar helemaal doorheen geslagen. En ik heb er niet veel over gesproken, ook omdat je niet precies wist van ‘wat is het?’ en ‘hoe kan het?’. Maar ik was wel veel bezig met; ‘maar ik zorg er wel voor dat mijn leven leuk is en dat ik dingen doe waar ik blij van word en ik bekijk dingen die ik wel kan’. Dus ik ben wel al vanaf heel jong mentaal heel sterk”* (Patient 2). Another patient mentioned he could now be an expert by experience in his work field. Furthermore, almost all patients (4 out of 5) stated that they were grateful to participate in this study, to eventually help other IEM patients, their partners, and healthcare professionals in the future.

Theme 2: Coping. An important question in this study is ‘how do IEM patients cope with their disorder?’. One of the most important factors to cope with the disorder seemed to be positivity, since almost all patients (4 out of 5) stated that they perceived ‘being positive’

as of big value to deal with the disorder: *“Ik heb een prima kwaliteit van leven. Maar dat komt denk ik zelf ook doordat ik heel positief ben. Ik maak er wel wat van, ook al krijg je wel beperkingen. Nee, ik ben heel gelukkig in mijn leven”* (Patient 3). Another patient mentioned the following: *“Ik denk dat er wel verschil zit in de kwaliteit van leven als mensen heel erg in de slachtofferrol zitten of als ze juist te maken hebben met positieve coping. Ik denk dat dat gewoon het verschil kan maken van en hoe mensen het op dit moment beleven, en hoe ze ook de toekomst zien. Als je op dit moment denkt dat je nog in-control bent, dan heb je ook weer een positieve kijk op de toekomst”* (Patient 1). Other patients had great difficulty with staying positive, because of all the limitations experienced and the lack of future perspective: *“Ik denk eigenlijk niet meer dat ik nog veel positieve dingen heb. Je doet dingen omdat je dat nog enigszins kwaliteit van leven vindt, maar ik heb soms ook fases dat ik denk van ‘waarvoor doe ik het nog?’. Want als ik bijvoorbeeld iets doe, dan wil ik daar ook voor 100% in gaan, en dat kan dan niet omdat je niet kan horen, of niet kan zien, of niet kan bewegen zoals je zelf wil. Nee, dan heeft dat geen perspectief”* (Patient 5).

Additionally, some patients (2 out of 5) seemed to cope with the IEM diagnosis and symptoms by ‘keeping it cool’. These patients seem to accept the situation as it is and try not to make a big deal out of it: *“Ik zit ook wel heel erg in elkaar zo van; ‘ik kan er wel heel erg om gaan huilen, maar het wordt er toch niet anders van’. Dus het is voor mij al een gegeven zo van, ja, het is gewoon dikke pech”* (Patient 1).

Next to being positive or ‘keeping it cool’, some patients (2 out of 5) mentioned to have a great focus on maintaining a healthy lifestyle, which they perceived to be very helpful in coping with the disorder. These patients reached for this healthy lifestyle by trying to get enough sleep, eating healthy, staying physically active as much as possible, going outside, and balancing their energy levels: *“Ik merk ook heel goed dat als ik weinig slaap of als je eens een feestje hebt gehad of een weekje minder eet omdat ik het druk heb, dat ik dan wel meer klachten krijg. Dus ik ben me nu wel bewust van ‘ik moet goed voor mijn lichaam zorgen, zodat ik goed kan lopen”* (Patient 3).

Social life moreover seemed to be of great importance in IEM patients in order to stay positive and happy in life. All patients mentioned the importance of their relationship with their partner, which in all cases had a positive influence on their life: *“Het is gewoon zo dat je door*

je beperking iemand nodig hebt die stevast naast je kan staan en dus ook weet wat de beperking inhoudt. En hoe je dus het beste met diegene moet omgaan”(Patient 5). Next to that, almost all patients (4 out of 5) found it highly important to spend time with family and friends. Not only to have fun together, but also because these people offer practically and emotionally support. Some patients (3 out of 5) stated that in the presence of their close ones (often family and friends), they did not have to be ashamed of their symptoms and they did not have to explain themselves, which does happen with people they do not know that well: “En ik vind ook wel, mijn kinderen en de vrienden die weten wat ik heb dus ik hoef me ook niet anders voor te doen – en ik doe me ook niet anders voor – maar dat is wel makkelijk, dat ze het weten, dan hoef je niks uit te leggen. Als je een keer niet met een dienblad met drinken komt, hun doen dat wel. En ik doe zelf heel veel hoor maar het is gewoon makkelijk als mensen het weten, dat ze weten dat je niet 10 kilometer met ze gaat wandelen of wat dan ook. Je hoeft het niet helemaal uit te leggen” (Patient 3).

Theme 3: Rarity of the IEM. A theme that plays a big role in the lives of patients with an IEM, is the rarity of these diseases. This rarity comes along with a lot of challenges for the patients. First of all, for some of the patients (4 out of 5) it has been a search for years to finally get diagnosed and get some kind of clarity about what is happening to them. One patient had symptoms since early childhood and only got diagnosed at middle adult-age. For this patient in particular, it had been a long search for the diagnosis. This patient felt different than others for a significant time and even developed an inferiority complex because of that: *“Toen kreeg ik die diagnose en dat was wel een enorme opluchting. Dat ik wel het gevoel had van ‘zie je wel, er is niks mis met mij, het heeft echt een fysieke oorzaak’. Er is psychisch helemaal niks mis met mij” (Patient 2).*

The majority of the other patients in the study (3 out of 4), mentioned the long search for the diagnosis too, which may come along with a lot of distress and uncertainty. While the diagnosis gives them some kind of clarity, in most patients this does not fulfill their needs. The lack of knowledge about the course of the disease makes it particularly difficult for them to cope with the disease: *“Doordat het zo onbekend is, kan niemand mij eigenlijk het antwoord geven hoe het verder gaat. Wat zijn de vooruitzichten? Mis ik straks een been? Word ik niet oud? Ten minste, minder oud*

dan in principe een normaal mens zou worden? Maar niemand kan dat zeggen” (Patient 5). When asking about their future perspective, one patient answered the following: “Ik durf er eigenlijk niet zoveel over te zeggen. Ik zie het niet positief in maar het kan ook gewoon meevallen. Ik heb ook geen idee hoe lang ik nog te leven heb” (Patient 4).

Receiving the diagnosis may cause mixed feelings in patients. On the one hand, it may give patients some kind of confirmation for their suspicions and it may feel as a relief, but on the other hand it may cause feelings of sadness, anxiety, distress and loss of control.

The importance of receiving a diagnosis is moreover stressed by the practical implications (e.g., sickness benefit and financial compensations) and ease with which it comes along: *“En dan is het wel makkelijk om te zeggen van; ‘nou, ik heb een stofwisselingsziekte, dus dat lukt mij even niet. Wil je me daar en daarin even helpen?’ En dat gaat nu veel makkelijker dan voorheen, toen had het geen naam” (Patient 2).*

Lastly, even though patients feel that the diagnosis makes their symptoms and problems more understandable for outsiders, most of them (4 out of 5) still struggle with incomprehension. Since the IEMs are often very rare, other people do not know what it means to have the disorder. This may lead to feelings of frustration, feelings of misunderstanding, and feelings of shame in the patients: *“Ja, want dat zeg ik wel eens, niemand kan begrijpen wat wij voelen in onze benen, of wat wij denken. Dat je altijd moet nadenken hoe je loopt, dat is hartstikke lastig. Maar dat kan je ook niet uitleggen. Lopen is voor iedereen vanzelfsprekend, dus ja” (Patient 3).*

Having a diagnosis does make it in some cases easier to briefly explain themselves or even to ‘justify’ their own behavior: *“Sommigen vertel ik wel over mijn hoedanigheid, om maar een beetje te voorkomen dat ze denken dat ik het bewust doe” (Patient 4).*

Theme 4: Care provision. The majority of the patients in the study (3 out of 5) mentioned the importance of the helping tools they got (e.g., walker, mobility scooter, handbike, hearing aid, blind cane, adapted toilets, and stairlift). Furthermore, all of these patients mentioned that they arranged these helping tools themselves, since the help of the

local authorities took too much time, they were not able to help, or they were inflexible in meeting their personal needs: *“We hebben het dus ook eigenlijk allebei via de gemeente aangevraagd, maar daar was zo ’n toestand omheen, dat gaat zo moeilijk. Toen hebben we gewoon zelf de leverancier opgebeld en toen was het zo voor elkaar”* (Patient 4). Some patients (2 out of 5) moreover stated that they were grateful to be in possession of enough money to arrange this for themselves and to make life more pleasurable and easy for themselves with these helping tools.

Next to the helping tools, which in most cases contributes to a better life quality for the patients, some of them (3 out of 5) furthermore mentioned the importance of (alternative) medicines: *“Bijvoorbeeld de oxazepam, die ik gebruik tegen trillen, dat is echt een heel klein pilletje, maar het is echt verschrikkelijk belangrijk voor mij”* (Patient 4). *“Nou de medicijnen hebben er in ieder geval voor gezorgd dat ik minder pijn heb, dus daar ben ik op zich al wel heel blij mee”* (Patient 5).

Overall, patients mentioned to be content with the care provision in general. The biggest shortcoming in care provision for them is the lack of knowledge about the disease and the course of the disease. Some of the patients (3 out of 5) stated to have a desire to know more about the progression of the disease and how to appropriately cope with the progression: *“Je hebt totaal geen vergelijkingsmateriaal en dat vind ik wel jammer. Dat zou wel eens fijn zijn, dat je toch een keer een soort ontmoetingsdag zou kunnen hebben. Of dat je online met elkaar zou kunnen praten over verschillende dingen”* (Patient 3). When asking about possible improvements for the care provision, one patients answered the following: *“Ja, misschien meer persoonlijke zorg. Misschien meer dat iemand mij kan vertellen, in de zorg of in de wetenschap, van ‘wat het is’. Het gaat er niet meer om dat ik een ander gehoortoestel zou krijgen of wat dan ook - dat zou ik natuurlijk ook wel willen - maar het gaat meer om persoonlijke zorg. Dus misschien kan je beter dan zeggen ‘meer wetenschappelijke zorg’”*(Patient 5).

The patient that lived for years with uncertainty and confusion about their physical condition before receiving the diagnosis, mentioned that psychological help would have been extremely helpful back then: *“Ik had als kind heel graag begeleiding willen hebben, zodat ik veel meer zelfvertrouwen kreeg”* (Patient 2). Another patient received psychological help in the past for

coping with daily life problems, but this could not help the patient cope appropriately with the uncertainty of the progression of the disease arising from the lack of knowledge and the rarity of the disease: *“Ik heb daar wel hulp bij gehad ja. Maar je komt niet echt bij de kern, omdat therapeuten, artsen, huisartsen, professoren eigenlijk niet weten hoe ze er mee om moeten gaan omdat het zo 'n zeldzame ziekte is. Dus vandaar. Het is eigenlijk zo onbekend dat er eigenlijk niks over geschreven is”* (Patient 5).

Main themes partners

Theme 1: Relationship with the patient. The influence of the IEM in the patient on the romantic relationships between patient and partner is very heterogeneous. Some partners (3 out of 5) mentioned that it has no or little influence on their relationship, while as others mentioned a significant influence on their relationship (2 out of 5). The partners that mentioned some negative influences on the relationship, especially stated that they miss engaging in activities together and tackling a (physical) task together: *“Je leert er wel mee omgaan, maar het is natuurlijk niet leuk. Je wil gewoon samen ook leuke dingen kunnen doen en van het leven kunnen genieten. Maar dat heb je gewoon moeten inleveren, voor een heel groot deel”* (Partner 5). Another partner stated the following: *“Natuurlijk vind ik het wel eens lastig, dat ik denk van wat zou het fijn zijn – we hadden altijd hele grote verjaardagen, heel veel mensen om ons heen, grote verjaardagen, heel gezellig – maar dat samen opvangen, dat is niet meer aan de orde. Dus, dan moet ik dat zelf doen. Nou dat is wel wat ik mis, samen een klus klaren”* (Partner 1).

Furthermore, partners may feel like their romantic relationship is out of balance because of the informal care they have to provide to their partners: *“Het is niet meer evenwichtig. Dus ja, daar moet je mee leren om gaan”* (Partner 1). Other patients do not share this feeling of an imbalanced relationship, even though they do give informal care in some cases: *“Het is niet anders als zeg maar 30 jaar geleden, toen wij zeg maar het huwelijksbootje instapten, nee”* (Partner 3).

All partners mentioned the need of adapting to the patient's needs, capabilities, and restraints. These adaptations differ greatly in extent and frequency between the partners. The following example describes a little adaptation in the partners life: *“Dus kijk, ze kan gewoon niet met twee kopjes tegelijk in één hand lopen. Dat gaat niet. Want dat schokt natuurlijk wel nog eens. En toen heeft*

ze mij gevraagd van 'goh, dat lukt me gewoon niet, wil jij de koffie voor me halen?'. Weet je, en dat sluipt gewoon al die jaren er gewoon zo in. Dus daar denk ik gewoon niet bij na" (Partner 2). The following example describes a bigger adaptation in the partners life: "Nou, ik denk wel het uitgaan, zoals vakanties en zo dat wordt allemaal wel wat lastiger. Want energie wordt minder, mobiliteit wordt minder, je kunt gewoon minder dingen ondernemen, je moet wel met heel veel dingen rekening houden. Dus daarmee wordt ook je sociale aspect een beetje meegenomen, want wil je in de groep wat doen, dan kun je niet met de groep mee" (Partner 4).

In some of the relationships in the study (2 out of 5), the disorder of the patient also has a negative influence on the intimacy and sexual life in the relationship. Patients and their partners may not be able anymore to sleep in the same bed or may experience different sexual desires. Moreover, partners may experience as if the previously more manifest gender roles, are now less evident and may fade away: "Ik hou wel van een galante man, dus even een stoel aanreiken of een jas aanreiken of weet ik veel, of even de deur voor je open doen. Nou, ik doe eigenlijk altijd de deur voor (...) open, zeker als hij in de rolstoel zit. Weet je, dat zijn verschuivingen. Is het erg? Nee. Is het soms jammer? Ja, wel eens. Het is soms wel even dat je denkt 'ah, jammer'. Maar het is niet anders" (Partner 1).

The majority of the partners furthermore mentioned a deepening of the relationship (3 out of 5). These partners state that may have conversations in the relationship in which other couples of their age may not have to engage in already (e.g., early moving to another house, talking about future possible care needed, talking about personal alarm systems in case of the patient falling): "Ik denk ook dat het wel verdiepend werkt dat je misschien dan gesprekken voert die een ander dan niet voert. En dat merken we dan ook wel, als we mensen om ons heen spreken, die houden zich natuurlijk nog niet bezig met kleiner wonen, dat komt misschien vanaf een jaar of 70 ofzo. Dus je bent een soort van vervroegd oud aan het worden. Je moet eerder over keuzes nadenken" (Partner 1).

Theme 2: Coping. The coping of partners seems to have big overlap with the coping of the patients themselves. Most important, the majority of the partners (4 out of 5) mentioned that they think it is important to stay positive, to not worry about the future, and to 'take life as it comes': "Toch proberen de kleine, positieve dingetjes te blijven zien. Het in huis zoveel mogelijk leuk en

gezellig proberen te maken. Waar mogelijk een keertje eten bestellen, als je niet uit eten kan, dan moet je maar zorgen dat het thuiskomt. Gewoon de kleine dingetjes”(Partner 5). Another partner stated: “En dan denk ik van ‘wat gebeurt, dat gebeurt’, en als het gebeurt dan zien we dat wel weer” (Partner 4).

Next to that, most of the partners (4 out of 5) mentioned the importance of engaging in activities together and to look for the possibilities together, instead of looking at the limitations: “Maar als we bijvoorbeeld zouden gaan wandelen, ik noem maar even wat, we gaan bijvoorbeeld 10 kilometer wandelen, dat is ‘not done’, dat kan niet. Maar dat weet je, dus dan ga je eigenlijk wat anders er omheen bedenken. Fietsen bijvoorbeeld, dat kan ze dan wel weer lekker lang. Nou, dat is prima. Dus je zoekt wel andere dingen dan in plaats van haar te belasten met haar lopen (Partner 3).

Additionally, clear and honest communication in the relationship seems to be of big worth in coping with the disorder of the patient, according to some of the partners (3 out of 5). The other frequently mentioned theme to stay in balance in the relationship (3 out of 5), is to set your own boundaries and to keep independent of each other as much as possible: “Wat doen wij om in balans te blijven... Ik denk praten. Afstand nemen, ook van elkaar. Dus ook weer dat eigen leven behouden, eigen energiebronnen behouden”(Partner 1). Most partners (3 out of 5) share the opinions of the patients that it is important for them to stay independent as much as possible and keep challenging yourself: “Dus dat is ook wel wat we tegen elkaar zeggen; ‘Ook al kost het veel moeite, en ook al loop je niet heel erg veel meer, probeer nu toch ook af en toe een keer extra te gaan lopen, of een keer extra naar de stad te gaan’” (Partner 4).

Some of the partners (3 out of 5) mentioned, just like the patients, that they may feel misunderstood by outsiders and even family or friends. These partners may feel like people do not really know what they are going through on a daily basis and would sometimes appreciate to receive more emotional support and real interest: “Dat niemand weet wat het precies inhoudt. En dat mensen eigenlijk nu alleen maar de effecten zien dat je instabiel loopt, maar verder kunnen ze zich er niks bij voorstellen. En niemand weet ook hoe het precies werkt. Want wat een ander ziet, dat is natuurlijk alleen nog maar een tipje van de sluier van wat er in wezen gebeurt” (Partner 4). On the other

hand, the majority of partners (3 out of 5) also stressed the importance of their social support network.

Theme 3: Informal caregiving. Some of the partners in the study (3 out of 5) are providing informal care to the patients. While these partners were mostly content with providing informal care to their partner, it sometimes may fatigue them since the need of caregiving is ongoing and never stops: *“Ja, ik ben er wel eens moe van en ik denk het te accepteren, maar is dat ook altijd zo? Of is dat weer iets van verstand en niet helemaal van gevoel? Ja, ik vergelijk het wel eens met je werk, je werk is over het algemeen leuk, maar soms heb je gewoon een prut-dag en dat hoort er ook gewoon bij. En daar geldt dit ook voor”*(Partner 1).

Furthermore, patients' abilities will only deteriorate over time, thus the demands for caregiving will only grow over time and the partners are little by little taking over tasks from the patient. This deterioration is something that not only the patients worry about, but their partners worry about this too and it may be confronting for them to see the growing struggles of the patient in daily life: *“Hij ziet nu nog wel iets, maar op termijn gaat het ook gebeuren dat hij helemaal niks meer ziet. Ik denk dat dat ook wel een angst is. Ja, de achteruitgang ook in zijn algeheel. Gaat het achteruit? Hoe snel gaat het achteruit?”*(Partner 5). Another partner stated the following after visiting a patient-day and being confronted with the more severe consequences of the IEM: *“En ja, je hoopt natuurlijk niet dat ze ook zo in een rolstoel komt of wat dan ook. Dat wil natuurlijk niemand. Ja maar goed, die ziekte die heeft ze gekregen, die is er nou eenmaal. Maar je wordt er natuurlijk wel bewust van dat je denkt van ‘ja, wat kan er gebeuren?’”* (Partner 2).

Another partner did not feel the possibility anymore to leave the house for a whole day without the patient, because of the fear that something will happen to the patient and nobody is there to help: *“Ik zou nu zeg maar iets minder snel een keer een hele dag of zo weg gaan. Voor die tijd dan deed ik dat af en toe wel eens een keer, maar ook niet zo heel vaak hoor. Maar ik heb nog wel een vriendin in (...) wonen, en daar wil ik eigenlijk wel weer een keer heen maar dan denk ik van ‘hoe ga ik dat nou doen, wanneer kom ik dan terug?’”*(Partner 4).

Some of the partners and patients (3 out of 5) are already discussing mandatory future plans to ease the informal caregiving demands of the partners, such as hiring healthcare providers or arranging an alarm system. One partner stated that it is of high importance to mostly stay a partner instead of a caregiver: *“Maar als hij volledige hulp moet hebben met douchen en aankleden en dat soort dingen, dan wil ik daar wel thuishulp voor inschakelen. Ik wil ook gewoon een partner blijven en niet alleen maar een verzorger”* (Partner 5).

Other partners (2 out of 5) are not providing informal care, since these patients are not in need for care at the moment. These patients can function (mostly) independently and the partners stated that their disorders had no or little influence on daily life: *“Nou ja, weet je, het is bij (...) gewoon, zij functioneert gewoon zoals jij en ik doen. En natuurlijk weet je dat ze dit heeft, maar gewoon in haar doen en laten merk je het niet. Ze doet ook alles wel. Gewoon zoals een ander dat zou doen”* (Partner 2).

Discussion

The objective of the current study was to explore how patients with an IEM and their partners stay in balance. The qualitative data gathered in the interviews showed that patients with a late-onset IEM experience a range of negative consequences of their disease, which are in line with an earlier study in Niemann-Pick type C (NPC) patients (Mengel et al., 2021). These negative consequences include physical problems (including movement disorders), loss of independence, fatigue, social limitations, and psychiatric symptoms such as depressive or anxiety symptoms. These negative consequences in daily life could be explained by the direct consequences of the IEM (e.g., the IEM leads to disrupted processes in the human body and brain which directly causes movement disorders or psychiatric problems) or the indirect consequences of the IEM (e.g., because of the movement disorders or psychiatric problems patients experience secondary limitations in social functioning or coping), or both. The causes for the clinical symptoms experienced by the patients, such as psychiatric disorders, may differ per patient because different IEMs were included. All late-onset IEMs have different

etiologies and clinical symptoms, which means that they cannot directly be compared to each other.

There are no studies investigating the presence of cognitive or psychiatric symptoms in Krabbe disease patients, but studies in lysosomal diseases (which Krabbe disease and NPC are both part of) do show that adult-onset lysosomal disease patients can experience depression, dementia, psychosis, and other neurological deficits (Pará et al., 2020). It is unsure which part of these psychiatric symptoms are the direct or indirect consequences of the IEM, although it is likely that some psychiatric symptoms, including psychosis, in late-onset NPC may be the direct consequence of the brain damage caused by the IEM (Rego et al., 2019). Frontotemporal lobar degeneration in late-onset glutaric aciduria type 1 (GA1) patients presents with social-emotional-behavioral and/or language changes and thus may be the direct cause of psychiatric symptoms in GA1 patients (Boy et al., 2017; Grossman et al., 2023). There are no studies showing an association between maternally inherited diabetes and deafness (MIDD) and psychiatric or cognitive symptoms, but since patients may experience central nervous system diseases, it may be assumed that the psychiatric symptoms could be a direct consequence of the IEM (Yang et al., 2021).

Furthermore, movement disorders are common in IEMs and it is shown that movement disorders may be associated with psychiatric co-morbidity due to a shared pathophysiology (Peall et al., 2017). These co-existent symptoms may be explained by the organization of sensorimotor, associative and limbic areas of the subthalamic nucleus and its interaction with the basal ganglia, but also by the involvement of neurotransmitters such as dopamine (Parent and Hazrati, 1995). Since four of the five patients in this study have at least one movement disorder, this may also influence the presence of psychiatric symptoms.

Taking into account the etiologies and symptoms of the various IEMs as discussed above, it would be expected that at least some of the patients in the study would experience

psychiatric symptoms. Additionally, patients reported to suffer from the rarity of the disease since this may lead to distress, uncertainty, anxiety, and loss of control. Surprisingly, in this study only the patient with MIDD showed psychiatric problems, although this IEM has no strong correlation with psychiatric symptoms according to the literature. This could be partially explained by the coping styles of the patients. All patients in the sample had an active coping style, however, the one patient with the psychiatric symptoms had a substantially lower active coping style compared to the other patients. This patient also stated to have difficulties with being positive and happy, while the other four patients were highly focused on staying positive in dealing with the IEM. Other frequently mentioned ways to stay in balance were; acceptance, being ‘down-to-earth’, focusing on a healthy lifestyle, and seeking support in their social networks. Neate and colleagues (2019) found that patients with the neurological disorder multiple sclerosis benefited from seeking support and embracing wellbeing and Körver and colleagues (2020) found that a positive and problem-solving coping style could alleviate depressive symptoms in Fabry disease patients. When looking at the data in this study, these ways of coping also seem to be helpful in patients with (other) IEMs, when coping with the disease.

Next to the psychiatric symptoms, some patients stated to experience limitations in daily functioning. The quantitative data showed that the two patients with NPC and MIDD experienced considerable limitations in daily life. Mengel and colleagues (2021) found that motor impairments interfere with activities of daily life. Since four of the five patients in the sample had at least one movement disorder, this finding could probably be (partly) attributed to the movement disorders. The patient without motor impairments presented with amongst other diabetes, visual, and auditory deficits, which also contribute to impairments in daily functioning (von Der Lippe et al., 2017). The finding that only two of the five patients experienced limitations in daily functioning, although all of them had symptoms that

influenced daily functioning, might be explained by the severity of the IEM symptoms. The patients who reported considerable limitations in daily functioning, were the ones with the highest severity of symptoms (GCI score 4 or 5). Another patient with a GCI score of 4 did not reach the cut-off scores, yet, this patient also reported significantly more impairments in daily life compared to the patients with a GCI score of 3. Furthermore, during the interviews, three of the five patients particularly mentioned to suffer from the loss of independence in daily life. Again, these patients were the ones with the highest severity of symptoms and the highest scores on limitations in daily life. Thus, the severity of the IEM symptoms could explain the variability in the extent of experiencing limitations in daily life.

During the interviews, three of the five patients stated to experience fatigue problems and an association was found between reported fatigue and severity of IEM symptoms. This means that the more severe IEM symptoms the patients have, the more fatigued they report to be. It would be logical that the more severe IEM symptoms the patient has, the more energy it will cost to function in daily life, and thus the more fatigued they get. There were however no differences found between fatigue problems in the patient sample compared to the fatigue problems in the general population of the same age group. This is surprising, since three of the five IEM patients mentioned fatigue problems as a disabling factor in daily life. It may be that the elevated levels of fatigue are connected to age rather than the IEM. Another explanation may be that the patients filled in the questionnaires overly optimistic, as a result of their active coping styles. Patients in this study were 55 till 69 years old and the healthy population at these ages may also experience fatigue problems or physical problems and thus the fatigue may not be a specific symptom or consequence of the IEM.

Despite the fatigue, four of the five patients in the sample mentioned to have a good quality of life. This is an interesting finding, as this is not the case in other neurodegenerative disorders associated with movement disorders and cognitive symptoms, such as PD.

Lubomski and colleagues (2021), who found that PD patients had a lower health related quality of life compared to their healthy caregivers. Coping styles are not taken into account in the Parkinson study even though it may be an important factor, making our patients capable to deal with fatigue without it negatively affecting their quality of life. However, there are great differences between IEMs and PD and thus it may not be completely justified to compare those diseases in health related quality of life.

In this study, not one of the partners reported a significant negative impact of their caregiver's role regarding quality of life, as measured by the questionnaires. However, there were partners that did mention the negative consequences of informal caregiving during the interviews. Three of the five partners stated to give informal care to the patients and that this may lead to feelings of fatigue, strain of worry, decreased independence, and growing caregiving demands. Next to that, two of the five partners mentioned a negative influence on the intimacy and sexual life in the relationship. These negative consequences are in line with consequences of informal caregiving of a partner with Alzheimer disease or Parkinson disease patients (Kaplan, 1996; Hulshoff et al., 2021). Even though the partners mentioned these negative consequences during the interviews, they also stated that those impacts on their daily lives and relationship do not have a significant impact on their quality of life or wellbeing. This is inconsistent with earlier studies that did find a negative impact of informal caregiving with regard to quality of life and caregiver wellbeing (Latella et al., 2018; Hurt et al., 2017). Even though the coping styles of the partners were not quantitatively measured with questionnaires, the qualitative data in this study gives indications of active coping styles in the partners since four of the five partners emphasized the importance to stay positive, to not worry about the future, and to 'take life as it comes'. It is shown that those kinds of adequate coping strategies have a positive influence on the partners perceived quality of life and caregiver burden (Mishel, 1990; Neate et al., 2019). Furthermore, Phongtankuel and

colleagues (2023) showed that caregiver's self-efficacy may mitigate the negative outcomes on quality of life and wellbeing. According to the data, it can be assumed that all the partners in the sample have an average to high self-efficacy in caregiving. Other mentioned ways to stay in balance according to the partners were: setting your own boundaries, keeping independent of each other as much as possible, engaging in activities together, clear and honest communication in the relationship, and support from their social network. All these factors may explain why the partners in this study are able to stay in balance despite giving informal care to their partner with an IEM.

Practical implications

There are some practical implications that can be made as a result of the outcomes of this study. The study results and other literature showed that having a positive, active coping style leads to positive outcomes in daily life for patients with IEM as well as their partners. It could possibly be helpful to provide psychological help to patients and partners that struggle with coping with their disease or their partner's disease. They may be taught how to deal with the uncertainty of the course of the disease and the knowledge of the probable deterioration in the patient. The results moreover showed that psychological and/or behavioral problems can occur in patients with an IEM. It is important for professionals and care providers to keep this in mind and to closely monitor the mood of their patients, so that the patients in need could be offered psychological therapy. Next to this, romantic relationships of IEM patients and their partners may be out of balance and this also may need some attention from relationship therapists or sexologists. It may be important to increase awareness for these possible problems in professionals, patients and their partners. Even though not every IEM patient and/or partner may need psychological help, the most important is the awareness of the possible secondary psychological problems that may occur as a result of for example

inappropriate coping styles, psychological and/or behavioral problems, or relationship or sexual problems.

Limitations and further research

The most prominent limitation is the small sample size. Therefore, the results in this study should be interpreted cautiously. In addition, the patient sample in this study was very heterogeneous, with four different kinds of IEMs. Every IEM represents another metabolic failure in the human body, which means that the etiologies and the symptoms differ greatly between the patients in the sample. Next to that, the severity of the IEM symptoms in the patients in the sample was heterogeneous. This makes it difficult to accordingly compare the heterogeneous diseases, symptoms, and patients to each other.

Another limitation to this study is that all patients in this sample were of ages between 55 and 69, which makes it difficult to generalize the results to younger patients. Younger patients may experience some other difficulties in daily life, such as taking care of (young) children.

Additionally, it may be that mostly the 'positive' and 'active coping' patients and partners participated in this study, leading to a selection bias. During the interviews, patients talked about family members with the same IEM who not participated in the study and who had more passive coping styles. If this was also the case for the other patients who denied to participate in the study is not clear, but one may speculate that talking about the IEM is confronting and those people try to avoid this. This may have the consequence that this study is not representative for all IEM patients and partners.

Since this study is focused on patients with an IEM, as well as partners of the patients, only patients with a partner were included. During the interviews it became clear that patients find a lot of support in their partners. Therefore, patients without a partner, probably even

struggle more with coping with the IEM and they may present with more psychiatric and/or behavioral problems, compared to patients with a partner.

There were a few limitations regarding the measurements in this study. The ABCL and ASR norm scores ranged till ages of 59 years and the UCL-R norm scores ranged till 67 years old, while some participants in this sample were older than this. Furthermore, one participant was not assessed by the neurologists in the UMCG, and thus the GCI score of this patient was established by discussion between the researcher and the neurologist. Next to that, since the participants in this study were all Dutch, all questionnaires were used in Dutch.

Unfortunately, the Steffen's self-efficacy scale had no validated Dutch version. This questionnaire had been translated by the researchers, thus validity and reliability could not be guaranteed. Next to that, the thematic analysis had been performed by one researcher while it may have been better if at least two researchers independently performed the thematic analysis, followed by discussing the outcomes, to guarantee objectivity. A remarkable finding during this study was that participants often mentioned problems during the interviews, which did not emerge as problems in the questionnaires. This may indicate that the questionnaires used in this study did not adequately measure the topics of interest. This raises the important question if questionnaires alone are giving enough information to base conclusions on.

Since this study contains a small sample size, the recommendation is to do more research on patients with an IEM with bigger sample sizes. It would be interesting to differentiate between patients with an IEM and a partner, and patients with an IEM without a partner. One of the most important recommendations is the inclusion of more IEM patients with a passive coping style or a low active coping style. Furthermore, relationship problems and sexuality problems were not extensively researched in this study, while this could provide problems in the patients and their partners. The same counts for cognitive problems, which

are not investigated in this study, while earlier studies show that they may present in IEM patients (Koens et al., 2021).

Conclusion

The qualitative analysis resulted in four major themes for the patients (consequences of the IEM, coping with the IEM, rarity of the IEM, and perceived care provision) and three major themes for the partners of the patients (relationship, coping with a partner with an IEM, and informal caregiving). The quantitative analyses showed high levels of fatigue in the patients, but this did not lead to impairments in quality of life. The partners also did not report considerable limitations in daily functioning or quality of life regarding their caregiver's role. It seems that adult patients with an IEM and their partners are able to stay in balance, in spite of high levels of fatigue and clinical symptoms in the patients. This can probably be attributed to the active coping styles observed in almost all patients and partners in this study. The biggest obstacle for IEM patients and their partners is the lack of knowledge about the disease and the course of the disease. This study is of great value to take the first step to develop more knowledge about the psychological consequences of coping with an IEM for both patients and partners.

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Appendix A

Neurologie

Hoofd Prof. dr. M.J.H. Wermer

Afd. Neuropsychologie

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Aan

Geachte,

Hierbij ontvangt u de informatiebrief voor het onderzoek 'Hoe blijf je in balans; de impact van een aangeboren stofwisselingsaandoening en bijbehorende neurologische symptomen bij volwassen patiënten en hun naasten'. Met deze informatiebrief willen wij het doel van dit onderzoek uitleggen en informatie geven over de opzet van het onderzoek.

Waarom dit onderzoek?

Tot op heden is er weinig bekend over de impact van het hebben van een stofwisselingsaandoening op volwassen leeftijd en de impact van het krijgen van deze diagnose op volwassenen leeftijd. Het doel van dit onderzoek is dan ook om beter inzicht te krijgen op de impact van een stofwisselingsaandoening op volwassen leeftijd.

Dit doen we door in dit onderzoek te kijken naar; uw ervaren kwaliteit van leven, uw ervaren beperkingen in het dagelijks leven, mogelijke symptomen van angst en depressie, wat u en uw partner van hulpverleners verwachten en wat u en uw partner zelf doen om in balans te blijven.

Datum:

Onderwerp: Hoe blijf je in balans; de impact van een aangeboren stofwisselingsaandoening en bijbehorende neurologische symptomen bij volwassen patiënten en hun naasten.

Om de impact van de stofwisselingsaandoening te onderzoeken, worden semigestructureerde interviews en vragenlijsten afgenomen bij patiënten en hun partners.

Wie zijn erbij betrokken?

Bij dit onderzoek zijn de volgende collega's betrokken:

- Lisette Koens, neuroloog
- Marina de Koning-Tijssen, neuroloog
- Tom de Koning, kinderarts metabole aandoeningen
- Joke Spikman, Klinisch Neuropsycholoog
- Maraike Coenen, GZ-psycholoog i.o.t. Klinisch Neuropsycholoog
- Isa Schonewille, psycholoog i.o.

Wat levert het op?

In dit onderzoek worden er semigestructureerde interviews afgenomen, waarbij u de kans krijgt om uw persoonlijke ervaringen te delen. Er wordt in dit onderzoek de tijd genomen om uw verhaal en ervaringen te kunnen horen. Dit onderzoek biedt u op deze manier de kans om uw verwachtingen en eventuele positieve en negatieve ervaringen wat betreft de zorg en de zorgverleners te delen.

Wat houdt het onderzoek in?

Het onderzoek bestaat uit vragenlijsten, en interviews. Het onderzoek vindt bij u thuis plaats of in combinatie met een mogelijke andere afspraak in het UMCG.

De vragenlijsten, interviews en de video zullen hieronder afzonderlijk van elkaar besproken worden.

Vragenlijsten voor uzelf:

Beperkingen in het dagelijks leven

Voor het in kaart brengen van de beperkingen in het dagelijks leven ontvangt u twee vragenlijsten (HAQ en SIP68). Het kost ongeveer 25 minuten om de lijsten in te vullen.

Stemming en gedrag

Voor het in kaart brengen van klachten over stemming en gedrag ontvangt u een vragenlijst (ASR). Het kost ongeveer 25 minuten om deze vragenlijst in te vullen.

Coping

Om een beeld te krijgen van hoe u met moeilijke situaties omgaat, vragen we u om een vragenlijst naar de Copingstijl in te vullen. Dit is de Utrechts Coping Lijst (UCL). Het duurt ongeveer 10 minuten om deze vragenlijst in te vullen.

Kwaliteit van Leven

Uw kwaliteit van leven brengen we in kaart met een vragenlijst over uw ervaringen met uw gezondheid. Dit is de SF-36. Het duurt ongeveer 5 minuten om deze vragenlijst in te vullen.

Vragenlijsten voor uw partner:

Stemming en gedrag

Voor het in kaart brengen van klachten over stemming en gedrag ontvangt u een vragenlijst (ABCL). Het kost ongeveer 25 minuten om de vragenlijst in te vullen.

Zelfeffectiviteit

Zelfeffectiviteit is iemands geloof in zijn/haar eigen kunnen om succesvol te zijn in bepaalde situaties. Om dit te onderzoeken, ontvangt u een vragenlijst (Steffen). Het kost ongeveer 10 minuten om de vragenlijst in te vullen.

Zorglast

Voor het in kaart brengen van de mogelijke zorglast die u ervaart, wat betreft het zorgen voor uw partner, zal u een vragenlijst ontvangen (ZBI). Het kost ongeveer 5 minuten om deze vragenlijst in te vullen.

Interview voor uzelf:

Tijdens het interview zullen wij u dingen vragen over uw dagelijkse leven. Er wordt besproken tegen welke problemen u aanloopt met betrekking tot uw ziekte en hoe u daarmee omgaat. Ook zullen we bespreken hoe u uw kwaliteit van leven ervaart en hoe u de toekomst ziet. Er zal ruimte zijn voor u om uw verhaal te doen en naar aanleiding van uw verhaal en antwoorden zullen sommige onderwerpen dieper besproken worden dan anderen. Het interview zal maximaal 60 minuten duren.

Interview voor uw partner:

Tijdens het interview zullen we de kwaliteit van leven van de patiënt bespreken uit het oogpunt van zijn/haar partner. We zullen bespreken wat de partner ziet en ervaart wat betreft het functioneren van de patiënt. Ook zullen we de kwaliteit van leven en het ervaren van een eventuele zorglast van de partner bespreken. Er zal ruimte zijn om uw verhaal te doen en naar aanleiding van uw verhaal en antwoorden zullen sommige onderwerpen dieper besproken worden dan anderen. Het interview zal maximaal 60 minuten duren.

Wat gebeurt er met de gegevens?

De gegevens die door middel van de vragenlijsten en het interview verkregen worden, zullen door de onderzoekers bestudeerd en geanalyseerd worden. Alle gegevens zullen anoniem verwerkt worden, waardoor ze niet meer herleidbaar zijn tot u. De gegevens zullen in een beveiligde database van het UMCG bewaard worden. Door middel van het combineren en analyseren van de gegevens van verschillende patiënten en partners, kunnen wij een globaal beeld krijgen over de impact van een stofwisselingsaandoening bij volwassenen en hun partners. Hiermee hopen wij uiteindelijk de zorg voor patiënten zoals u te kunnen verbeteren.

Contact

Wij hopen u met deze informatiebrief voldoende geïnformeerd te hebben. Wij zullen binnenkort contact met u opnemen om een eventuele deelname te bespreken. Mocht u vragen hebben, dan kunt u contact opnemen met Isa Schonewille op n.i.schonewille@student.rug.nl

Met vriendelijke groet,

Mw. Dr. L.H. Koens, neuroloog UMCG

Mw. prof. dr. M.A.J. de Koning-Tijssen, neuroloog; UMCG

Hr. prof. dr. T.J. de Koning, kinderarts-metabole ziekten. UMCG

Mw. Prof. Dr. J.M. Spikman, klinisch neuropsycholoog

Mw. Drs. M.A. Coenen, GZ-psycholoog i.o.t. Klinisch Neuropsycholoog

Mw. Isa Schonewille, psycholoog i.o.

Appendix B
Toestemmingsformulier proefpersoon

November 2023

Onderzoek naar de impact van een aangeboren stofwisselingsaandoening en bijbehorende neurologische symptomen bij volwassen patiënten en hun naasten.

Ik ben gevraagd om deel te nemen aan dit medisch-wetenschappelijke onderzoek.

Naam naaste:

Geboortedatum: __ / __ / __

Ik heb de informatiebrief voor proefpersonen gelezen. Ik kon aanvullende vragen stellen. Deze vragen zijn naar tevredenheid beantwoord. Ik heb voldoende tijd gehad om te beslissen of ik meedoe.

Ik weet dat meedoen helemaal vrijwillig is. Ik weet dat ik op ieder moment kan beslissen dat ik toch niet meedoe. Daarvoor hoef ik geen reden te geven.

Ik weet dat sommige mensen van bevoegde instanties de gegevens kunnen zien ter controle van de studie.

Ik geef toestemming dat de onderzoeker de geluidsopnames van het interview, de verzamelde en medische gegevens gebruikt voor de doelen die in de informatiebrief staan.

Ik geef toestemming om mijn onderzoeksgegevens 15 jaar na afloop van dit onderzoek te bewaren.

Ik wil meedoen aan dit onderzoek.

Naam:.....

Handtekening:..... Datum : __ / __ / __

* Graag doorhalen wat niet van toepassing is

Ik verklaar hierbij dat ik deze proefpersoon volledig heb geïnformeerd over het genoemde onderzoek.

Als er tijdens het onderzoek informatie bekend wordt die de toestemming van de proefpersoon zou kunnen beïnvloeden, dan breng ik hem/haar daarvan tijdig op de hoogte.

Naam onderzoeker (of diens vertegenwoordiger):

Handtekening:

Datum: __ / __ / __

Aanvullende informatie is gegeven door (indien van toepassing):

Naam:

Functie:

Handtekening:

Datum: __ / __ / __

Appendix C

TOPIC GUIDE

'Wat betekent kwaliteit van leven voor patiënten met een stofwisselingsaandoening en hun partners?'

PATIENT VERSIE

Introductie over het interview, mijn rol als onderzoeker, checken of er nog dingen zijn die de patiënt en/of familie sowieso willen bespreken en of er nog vragen zijn.

Algemene vragen: Hoe oud bent u, wat doet u in het dagelijks leven, wat is uw hoogst afgeronde opleiding? Welk type stofwisselingsziekte heeft u?

Part 1. Disease specific:

- *Wanneer heeft u de diagnose gekregen?*
- *Hoe was het voor u om de diagnose te krijgen?*
- *Wat voor klachten had u waardoor u naar de dokter bent gegaan?*
- *Hoe is uw leven veranderd sinds u de diagnose heeft gekregen?*
- Kan je vertellen wat het leven met de stofwisselingsziekte voor jou betekent?
- Als je je stofwisselingsziekte zou moeten uitleggen aan iemand, hoe leg je dat dan uit?
- Welke aspecten van de stofwisselingsziekte beperken jou het meeste in het dagelijkse leven en waarom?
- Wat is het lastigst van je stofwisselingsziekte om mee om te gaan? (Evt. wat voor veranderingen er zijn geweest, en wat goed gaat of steeds beter)
- Als er 1 aspect van de stofwisselingsziekte was waar een behandeling effect op kan hebben, wat zou jij dan willen?
- Hoe beïnvloedt het feit dat de stofwisselingsziekte zeldzaam is, jouw leven?
- Hoe ziet een goede dag eruit voor jou? En een slechte dag?
- Wat voor impact heeft het eventuele gebruik van medicijnen op jouw leven?

Part 1. Participants representation of their quality of life

- Introductie kwaliteit van leven 'In dit interview gaan we in op jouw perspectief op het dagelijkse leven met de stofwisselingsaandoening. Daarbij willen we bijvoorbeeld weten hoe het met u/jou gaat, waar jij bijvoorbeeld plezier uthaalt en waarom. Een term die met deze thema's te maken heeft in de medische wereld is Kwaliteit van Leven, heb je hier ooit van gehoord?' *Zo ja*, Wat verstaat u/ versta jij onder de term 'kwaliteit van leven'? *Zo nee*, → toelichting geven
- Hoe zou jij jouw kwaliteit van leven omschrijven? En waarom?
- Welke aspecten zijn belangrijk voor jouw kwaliteit van leven?
- Welke factoren beïnvloeden jouw kwaliteit van leven op een positieve manier?
- Welke factoren beïnvloeden jouw kwaliteit van leven op een negatieve manier?
- Wat doet u om in balans te blijven?
- Hoe ervaar jij de zorg rondom de stofwisselingsaandoening?
 - Logistieke aanpassingen in bv het huis
 - Tijd beschikbaar van zorgverleners
 - Kwaliteit van zorgverlening van hulpverleners

Part 3. Future

- Hoe zie je de toekomst?
- Wat vindt je leuk om te doen?
- Wat zou je willen worden of graag kunnen doen in de toekomst?

Part 4. Overig

- Is er iets anders onbesproken gebleven dat je graag zou willen bespreken met mij? Bijvoorbeeld over de aandoening, hoe je je voelt of wat je graag zou willen of kunnen?
- Hoe vond je dit gesprek?

PARTNER VERSIE

Algemene vragen: hoe oud bent u, hoe lang bent u al samen met uw partner, wat doet u in het dagelijks leven, opleiding?

Part 5. Only for the interview with partners

- Kunt u de periode beschrijven vanaf het moment waarop jullie besloten om met (NAAM) voor het eerst naar de dokter te gaan tot nu?
- Hoe zou jij uitleggen wat de stofwisselingsziekte inhoudt aan een nieuw gediagnosticeerde patiënt en zijn/haar partners?

Introductie kwaliteit van leven ‘In dit interview gaan we in op het persoonlijke perspectief op het dagelijkse leven met de stofwisselingsziekte. Daarbij willen we bijvoorbeeld weten hoe het met uw partner (NAAM) gaat, waar hij/zij bijvoorbeeld plezier uithaalt en waarom. Een term die hieraan verbonden is in de medische wereld is ‘kwaliteit van leven’. Heeft u hier eerder van gehoord? **Zo nee** → *leg de term kwaliteit van leven uit: Kwaliteit van leven is een subjectief begrip. Het zegt iets over hoe een persoon zijn of haar lichamelijke, psychische en sociale functioneren ervaart. We spreken daarbij meer over de mens zelf, in plaats van de patiënt. En meer over de gezondheid dan de zorg zelf. Het gaat dus meer over het persoonlijke perspectief op het dagelijks leven.* Ook willen we graag weten hoe u uw eigen kwaliteit van leven ervaart op het moment.

Zo ja:

- Wat versta jij onder de term kwaliteit van leven?
- Noem een aantal aspecten die naar jouw mening het meest belangrijk zijn voor de kwaliteit van leven van een patiënt met een stofwisselingsziekte
- Welke van deze aspecten worden het meest beïnvloed door de stofwisselingsziekte?
- Welke aspect van de stofwisselingsziekte is volgens jou het meest storend voor een patiënt?
- Welke symptomen zijn het beste onder controle te houden en welke symptomen het lastigste?
- Welk aspect van de stofwisselingsziekte zorgt met name voor stress/angst bij patiënten?
- Als er 1 aspect van de stofwisselingsziekte was waar een behandeling effect op kan hebben, wat zou u als partner dan willen?
- Hoe beïnvloedt het feit dat de stofwisselingsziekte zeldzaam is, jullie leven?
- Wat voor impact heeft de stofwisselingsziekte op jullie gezin/jullie relatie?
 - Hierbij evt seksualiteit bespreken
- Ervaart u naast de rol als partner, een rol als zorgverlener/mantelzorger?

- Is uw eigen kwaliteit van leven veranderd sinds uw partner de stofwisselingsziekte heeft gekregen?
- Wat doen u en uw partner om balans te blijven?
- Hoe ervaren jullie de zorg rondom de stofwisselingsaandoening?
 - Logistieke aanpassingen in bv het huis
 - Tijd beschikbaar van zorgverleners
 - Kwaliteit van zorgverlening van hulpverleners
- Is er nog iets anders onbesproken gebleven dat je graag zou willen aankaarten over de stofwisselingsziekte en kwaliteit van leven bij de stofwisselingsziekte?
- Hoe vond je dit gesprek?