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Original article

Ultra-rare ultra-care: Assessing the impact of caring for children with ultra rare diseases

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ABSTRACT

Background: We sought to assesses the impact of caring for children with ultra rare diseases (URDs) on family carers and to analyse the way these experiences differ among the caregivers of children diagnosed through prenatal or newborn screening, and those with symptom-based diagnosis.
Methods: A total of 200 caregivers of 219 URDs children completed an on-line survey regarding the challenges and experiences of caregivers of URDs children.
Results: The majority of URD caregivers felt burdened by their children's health problems, emotional and behavioural changes. 46.5% reported feelings of care overload, 43% coped poorly with the stress, and many experienced a variety of feelings of distress towards the role of caregiver. While most caregivers struggled with the diagnostic odyssey and were dissatisfied with the healthcare services for URD children, caregivers of children diagnosed through prenatal or newborn screening were significantly less burdened than the parents of children with symptom-based diagnoses.
Conclusion: Although caregivers of URDs children experience physical and emotional strain, they are often neglected by the healthcare system. A bio-psychosocial approach to URDs should therefore also include family caregivers' physical and psychosocial needs. Apart from financial and emotional support, enhancing access to genetic testing and newborn screening should be prioritised.

1. Introduction

As in other European countries, a condition is considered rare in Poland when it affects less than 1:2000 individuals [1,2]. Although by definition rare diseases (RDs) are scarce, it is estimated that they affect between 3.5 and 5.9% of the population worldwide [3], including between 18 and 30 million people in the European Union (EU) and between 2.3 and 3 million in Poland [2]. Their importance is further underlined by the high number of individual conditions as more than 7000 distinct RDs have been identified to date [4,5], although a recent report found there to be as many as 10 867 RDs [5]. RDs therefore constitute as many as 1/10 of all human diseases [6].

Significantly, 80% of RDs are of genetic origin, 70% affect children and 65% have serious and debilitating physical and psychological clinical manifestations. About 50% of children with RDs will die before reaching their fifth birthday and 35% will not survive the first year of life [3,6]. The reason for this is that for 95% of RDs there is currently no approved treatment and for the vast majority only the symptoms are treatable. Since RDs have been recognized as an important medical problem and an urgent public health issue [7,8], there is a growing interest in RDs, as demonstrated by the agendas of news media, government officials, policy makers and public health programmes that have led to the development of a number of national policies, plans and strategies for RDs [8–10].

At the same time, since some RDs are more common, as approximately 350 conditions account for 80% of all RD patients [7], healthcare professionals, the drug industry, health authorities and policy makers often focus on RDs, paying less attention to ultra-rare diseases (URDs), i.e. conditions with a prevalence of less than 1 per 50 000 persons [11–13]. It has been suggested, for example, that, although a *National Plan for Rare Diseases* was at last adopted by the Polish government in August 2021, rare and ultra-rare diseases should be dealt together without distinction between the two [2].

Although by definition individual URDs are extremely uncommon and are difficult to detect [13], and frequently the number of those affected by a single URD is no more than a handful, if combined they

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may include a considerable number of people and should be prioritised [12,14,15]. Even though the vast majority of URDs are chronic and life-threatening conditions, such patients are often neglected by the healthcare system [16,17]. According to Polish legislation the right to healthcare is protected constitutionally and everyone, including URD patients, is entitled to equal access to public healthcare (art. 68), but the problem is that the Polish *National Plan for Rare Diseases* neither differentiates the specificity of URDs nor contains any regulations on social support for URD caregivers and it focusses solely on the tasks assigned to the Ministry of Health.

While previous studies highlighted the multi-billion dollar burden of RDs [18–21], this study assesses the impact of caring for children with URDs on family carers. It also analyses the way these experiences differ among caregivers of children diagnosed through prenatal and newborn screening, and those with symptom-based diagnosis.

2. Material and methods

2.1. Study design

This research gathered data from an anonymous, self-administered, on-line survey regarding the experiences of family caregivers of children with URDs.

2.2. Research tool

Because URDs tend to manifest themselves a variety of conjunction of symptoms that affect physical, mental, cognitive, behavioural, sensory and other abilities, caregivers of URD children experience different challenges and needs. There is consequently no specific tool for assessing the burden of caregiving among parents of children with such conditions. To address the specific aspects of caregiving for URD children we have therefore developed an original open-ended questionnaire that was constructed from themes based on a review of the literature [18–21] and the study aim.

The questionnaire was developed in line with the guidelines of the European Statistical System [22] and was divided into five domains. The first included questions regarding the demographics of caregivers. The second domain asked questions concerning the challenges related to caring for a URD child. The third domain was related to caregivers' emotional experiences resulting from the role of caregiver. The fourth focused on caregivers' experiences with the healthcare system and the last domain assessed caregivers' satisfaction with life and their perceived burden. The questionnaire was constructed in simple, straightforward language. Whenever feasible, it incorporated specified response options utilising a 5-point Likert scale, ranging from 1 (indicating strong dissatisfaction or disagreement) to 5 (indicating high satisfaction or agreement).

2.3. Participants and setting

Participants were recruited through voluntary sector organizations, RD foundations and social media. The following inclusion criteria were used: participants had to be 18+ years of age and family caregivers involved in the care of child with URD between 1 and 18 years of age; they had to provide informed consent and be able to use the internet in order to participate.

Data collection took place between 13th October 2022 and 28th February 2023 using an anonymous, self-administered, computer-assisted on-line questionnaire on the psycho-social impact of URDs on family caregivers.

2.4. Ethical approval

This study was performed in line with the principles of the Declaration of Helsinki [23]. Ethics and research governance approval were obtained from the Poznań University of Medical Sciences' (PUMS) Bioethics Committee (KB – 833/22). Informed consent was obtained from all respondents enrolled in the study.

2.5. Data collection

A study coordinator contacted RD foundations to ascertain whether they were interested in participating in the study. After permission to post an invitation to participate in the study was obtained the final version of the questionnaire was posted on their websites on Facebook or sent via email and distributed among caregivers. The online consent form was included with the study invitation and placed at the top of the questionnaire and every caregiver was requested to select an "I agree" or "I do not agree" checkbox.

Once informed consent was obtained from all individuals who volunteered and were included in the study, a survey was posted on an online platform and electronically administered to study participants. Two follow-up messages were sent in January and in February. All caregivers who agreed to participate in the study completed the questionnaire using electronic devices. Completing the questionnaire took approximately 20 min and the data were collected anonymously.

2.6. Data analysis

The questionnaires were carefully reviewed in order to ensure accuracy, consistency and comprehensiveness. The information gathered was then encoded and imported into JASP (Version 0.17.2.1) for statistical analysis. In order to analyse the responses to Likert questions, the medians (M) and interquartile ranges (IQR) were computed. The findings are presented using descriptive statistics, and the relationship between variables is assessed through odds ratios (OR) or the Mann Whitney test to examine differences between groups. To determine the precision of the OR, 95% confidence intervals (CI) were computed. Differences between the groups were calculated whenever the group size allowed it and when it was logically justified. Statistical significance was determined using a significance level of $p < 0.05$.

3. Results

A total of 200 caregivers of 219 children with URDs responded and completed the survey (Table 1). The majority were women (95%), mainly mothers, male caregivers constituting a smaller proportion at 5%

Table 1
Socio-demographic characteristics of URD caregivers.

Characteristics	N (%)/M(SD)/M(95%CI)/SD(95%CI)
Total number of caregivers (N)	200
Caregiver's sex N (%)	
female	190 (95)
male	10 (5)
Caregivers' age M (SD)	
Range	19–60
M (95%CI)	37.1 (36.3–37.9)
SD (95%CI)	5.6 (5–6.3)
Relationship with URD child N (%)	
mother	189 (94.5)
father	10 (5)
grandmother	1 (0.5)
How many of your children suffer from URD? N (%)	
1	184 (92)
2 or more	16 (8)
Child's age M (SD)	
Range	0.3–18
M (95%CI)	6.4 (5.8–7)
SD (95%CI)	4.4 (3.9–4.8)
Method of diagnosis N (%)	
prenatal screening	18 (9)
newborn screening	36 (18)
symptom-based diagnosis	146 (73)

(mean age: 37.1 years, range: 19–60, SD = 5.6). While 184 respondents provided care for one URD child (92%), 16 were caring for two or more URD children (8%). The mean age of URD children was 6.4 years (range: 0.3–18, SD = 4.4). While 54 children with 17 different URDs were diagnosed during prenatal or newborn screening (7 and 10 diseases respectively, accounting for 18 (9%) and 36 (18%) parents respectively), the majority of children received symptom-based diagnosis (n = 146, 73%).

Our respondents provided care for over 219 children, representing a total of 119 different URDs (see: Supplementary material). While some URDs were more prevalent than others, as caregivers of 17 (14%) diseases accounted for 41% of all respondents (13: Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency, 8: Joubert syndrome, 7: Wolf-Hirschhorn syndrome, 6: Mucopolysaccharidosi and Coffin-Siris syndrome, 5: Rubinstein-Taybi syndrome, 4: Diamond-Blackfan anemia, Gaucher disease, Maple syrup urine disease and very long-chainacyl-CoA dehydrogenase deficiency; 3: Cowden syndrome, De Grouchy syndrome, Fabry disease, FOXG1 syndrome, Isovaleric acidemia, Mowat-Wilson Syndrome and SynGAP1 Syndrome), while children with 16 diseases (13%) were cared for by two caregivers. 72% of URDs were experienced by a single caregiver.

The majority of caregivers reported that it was the child's health problems that represented the most challenging aspect of caregiving (75.5%), followed by URD children's emotional or psychological state (57%), behavioural changes (51%) and mood swings (49%) (Table 2). Almost half of caregivers consequently reported feelings of care overload (46.5%), and 43% did coped poorly with the stress. Respondents also reported experiencing anguish towards the role of caregiving. While the majority of respondents declared that their entire life was subordinated to the role of caregiver (62.5%), 60.5% felt they were not understood by others, and 51.5% believed that their needs were unimportant to others.

Table 3 presents the diagnostic odyssey experienced by children with URDs. Based on the responses regarding their diagnostic experience, respondents were divided into two groups: caregivers of URD children diagnosed during prenatal or newborn screening and those with symptom-based diagnosis. The time taken to obtain a diagnosis varied depending on the diagnostic method. While in the case of children diagnosed through prenatal or newborn screening, the time of diagnosis was relatively short, taking on average 0.5 years (95% CI: 0.2–0.8), in the case of children with symptom-based diagnoses the diagnostic journey was more prolonged, with a mean time of 2.5 years (95% CI: 2.1–3). The standard deviations (SD) for these time intervals were 1 year (95% CI: 0.6–1.4) and 2.9 years (95% CI: 1.4–6.7) respectively.

Table 3
Diagnostic odyssey in URDs.

	Prenatal and newborn screening	Symptom-based diagnosis	p
Number of caregivers (N [%])	54 (27)	146 (73)	
How long did it take to obtain a diagnosis? (in years)			
Range	0–5	0.1–18	
M(95%CI)	0.5 (0.2–0.8)	2.5 (2.1–3)	
SD(95%CI)	1 (0.6–1.4)	2.9 (1.4–6.7)	
How many doctors did you consult before receiving the diagnosis?			
Range	1–30	1–50	
M(95%CI)	2.9 (2–4.2)	7.9 (6.7–9.3)	
SD(95%CI)	4.2 (1.4–6.7)	8.1 (6.3–9.8)	
Source of information on URDs			
Internet	45 (83.3)	139 (95.2)	< **0.01**
medical specialist	39 (72.2)	55 (37.7)	< **0.001**
family doctor	5 (9.3)	5 (3.4)	
other doctor	1 (1.8)	1 (0.7)	
doctor abroad	0	2 (1.4)	
local support group	15 (27.8)	39 (26.7)	ns
genetic clinic	9 (16.7)	29 (19.9)	ns
scientific publications	19 (35.2)	78 (53.4)	< **0.05**
FB group	6 (11.1)	3 (2.1)	
associations/foundations for people with URD	9 (16.7)	42 (28.8)	ns
Children without access to a specialist center dedicated to RD	0	17 (11,6)	
How would you rate you child's health problems			
very severe	25 (46.3)	68 (46.6)	ns
severe	14 (25.9)	44 (30.1)	
moderate	13 (24.1)	27 (18.5)	
mild	2 (3.7)	5 (3.4)	
none	0	2 (1.4)	

Statistically significant differences are written in boldface; ns: not significant.

Both groups of caregivers reported consulting numerous specialists before receiving a correct diagnosis. While in the case of children diagnosed through prenatal or newborn screening, the mean number of doctors consulted was 2.9 (95% CI: 2–4.2), in the case of children with symptom-based diagnoses the average was 7.9 doctors (95% CI: 6.7–9.3). The standard deviations (SD) for these numbers were 4.2 (95% CI: 1.4–6.7) and 8.1 (95% CI: 6.3–9.8) respectively. In both groups the Internet was the basic source of information about the child's disease (83.3% and 95.2% respectively) and medical specialists (72.2% and 37.7%).

Although no significant differences were found in reference to

Table 2
Challenges related to caring for URD children.

	M(IQR)	1. Never	2. Rarely	3. Sometimes	4. Often	5. Always
What makes caring for URD children challenging						
the child's health problems	4 (4–5)	2 (1)	7 (3.5)	40 (20)	58 (29)	93 (46.5)
the child's emotional/psychological state	4 (3–5)	14 (7)	25 (12.5)	47 (23.5)	39 (19.5)	75 (37.5)
changes in behaviour resulting from the disease	4 (2–5)	27 (13.5)	5 (12.5)	46 (23)	41 (20.5)	61 (30.5)
personality changes	3 (1–4)	52 (26)	25 (12.5)	48 (24)	49 (24.5)	26 (13)
mood swings	3 (2–4)	27 (13.5)	29 (14.5)	46 (23)	66 (33)	32 (16)
communication problems	3 (2–4)	34 (17)	38 (19)	51 (25.5)	39 (19.5)	38 (19)
reduced mobility	3 (1–4)	51 (15.5)	28 (14)	46 (23)	39 (19.5)	36 (18)
Feelings resulting from caring for your URD child						
care overload	3 (3–4)	13 (6.5)	30 (15)	64 (32)	70 (35)	23 (11.5)
the role of caregiver is beyond you	3 (2–4)	26 (13)	61 (30.5)	59 (29.5)	46 (23)	8 (4)
coping poorly with the stress	3 (2–4)	17 (8.5)	39 (19.5)	58 (29)	61 (30.5)	25 (12.5)
your needs are unimportant to others	4 (3–4)	9 (4.5)	35 (17.5)	53 (26.5)	67 (33.5)	36 (18)
nobody knows or understands what you are going through	4 (3–4)	7 (3.5)	17 (8.5)	55 (27.5)	83 (41.5)	38 (19)
your entire life is subordinated to the role of caregiver	4 (3–5)	12 (6)	16 (8)	47 (23.5)	68 (34)	57 (28.5)
conflict between your own needs and those of your RD child	3 (2–4)	21 (10.5)	50 (25)	68 (34)	45 (22.5)	16 (8)
difficulty in fulfilling other roles, i.e. parent, spouse, employee	3 (2–4)	15 (7.5)	37 (18.5)	67 (33.5)	60 (30)	21 (10.5)
solitude and isolation	3 (2–4)	20 (10)	36 (18)	59 (29.5)	69 (34.5)	16 (8)
stigmatisation	2 (1–3)	73 (36.5)	55 (27.5)	54 (27)	16 (8)	2 (1)
social exclusion	2 (1–3)	60 (30)	46 (23)	59 (29.5)	27 (13.5)	8 (4)

parents perception of their children's health problems, the majority of parents in both groups reported very severe (46.3% and 46.6%) or severe (25.9% vs 30.1%) health problems in their children.

Table 4 provides an overview of caregivers' perception of various health care services for URD children and the corresponding OR. It compares the experiences of caregivers of children diagnosed via prenatal or newborn screening with those with symptom-based diagnoses. While caregivers' experiences with the healthcare system tended to be frustrating, as respondents in both groups were dissatisfied with the support from government and social institutions, access to financial help with rehabilitation and contact with psychological clinics, the findings reveal significant differences in several areas. Although the caregivers of children diagnosed via prenatal or newborn screening also reported frustration with the health care system, they showed higher levels of satisfaction in terms of the quality of medical care, access to specialists, medication and financial help with rehabilitation. They were also more satisfied with the access to information on their children's conditions, support from healthcare professionals, physicians' knowledge and practical information about the diseases. Finally, they evaluated doctors' communication skills and empathy, support received from doctors positively more often ($p < 0.01$). No statistically significant differences were observed, however, in terms of support from the government and social institutions, access to financial help, contact with genetic clinics and contact with psychological clinics.

Table 5 juxtaposes the OR for frequent emotional states experienced by the caregivers of children diagnosed via prenatal and newborn screening with those with symptom-based diagnoses. It also includes caregivers' evaluations of different aspects of quality of life. The findings reveal statistically significant differences in several emotional states. Caregivers of children diagnosed via prenatal or newborn screening reported lower levels of emotional lability, problems with emotional control, impatience/irritation and nervousness/impulsivity than caregivers of children with symptom-based diagnoses ($p < 0.01$). No statistically significant differences, however, were observed for other emotional states. Regarding the quality of life, caregivers of children diagnosed via prenatal or newborn screening showed higher ratings of satisfaction with life, self-reported health, well-being, relationship with their family and personal happiness ($p < 0.01$), but no statistically significant differences were found for other aspects of the quality of life.

Table 4
Likert-scale evaluation of perception of health care services for URD children and comparison of odds ratios: positive perception of health care services among caregivers of children diagnosed at prenatal or newborn screening vs caregivers of children with symptom-based diagnosis.

	Median (IQR)	OR	95%CI	p
Support for caregivers from government and social institutions	2 (1–3)	1.694	0.804–3.570	ns
Quality of medical care for your URD child	4 (2–4)	2.578	1.322–5.031	< **0.01**
Access to specialists (neurologist, geneticist, psychologist)	2 (1–4)	2.365	1.237–4.524	< **0.01**
Access to medications for URD children	3 (2–4)	2.461	1.248–4.850	< **0.01**
Access to financial help with rehabilitation for URD children	2 (1–3)	1.528	0.7–3.336	ns
Access to information on URD	2 (1–3)	4.182	2.067–8.460	< **0.001**
Support for URD family from healthcare professionals	2 (1–4)	3.064	1.609–5.836	< **0.001**
Doctors' knowledge about URDs	2 (1–3)	3.060	1.490–6.282	**0.001**
Doctors' practical information about URDs	2 (1–4)	4.984	2.560–9.701	< **0.001**
Doctors'/neurologists'/ geneticists' communication skills	4 (2–4)	3.066	1.555–6.043	< **0.001**
Support caregivers receive from doctors	2 (2–4)	3.821	1.978–7.381	< **0.001**
Doctors' empathy	4 (2–4)	3.560	1.785–7.103	< **0.001**
Contact with genetics clinic	4 (2–4)	1.048	0.561–1.957	ns
Contact with psychology clinic	3 (2–4)	0.838	0.414–1.697	ns

Statistically significant differences are written in boldface; ns: not significant.

Table 5
Comparative odds ratios of frequent experience of emotional states among the caregivers of children diagnosed via prenatal or newborn screening vs caregivers of children with symptom-based diagnoses.

	Median (IQR)	OR	95%CI	p
Does caring for a URD child cause you to experience any of the following emotional states?				
emotional lability	4 (3–4)	0.428	0.226–0.809	< **0.01**
problems with emotional control	3 (3–4)	0.385	0.195–0.758	< **0.01**
impatience/irritation	4 (3–4)	0.472	0.249–0.897	**0.01**
nervousness/impulsivity	3 (3–4)	0.335	0.166–0.677	< **0.01**
anger	3 (2–4)	0.593	0.280–1.256	ns
anxiety/fear	4 (3–5)	0.630	0.319–1.247	ns
helplessness	4 (3.75–5)	0.497	0.250–0.985	< **0.05**
sadness/depression	4 (3–4)	0.697	0.372–1.306	ns
lack of self confidence	3 (2–4)	0.659	0.340–1.277	ns
feeling of hopelessness	3 (2–4)	0.445	0.228–0.868	< **0.01**
feelings of guilt	3 (2–4)	0.622	0.321–1.206	ns
sense of shame	2 (1–2)	0.393	0.112–1.387	ns
loneliness	3.5 (2–4)	0.599	0.318–1.128	ns
a desire to withdraw from the environment	3 (2–4)	0.573	0.282–1.166	ns
low self-esteem	3 (2–4)	0.448	0.225–0.895	< **0.05**
anticipatory loss/fear over child's premature death	3 (2–4)	0.874	0.466–1.643	ns
How do you rate the following aspects of your quality of life?				
life situation	4 (3–4)	1.797	0.884–3.653	ns
satisfaction with life	4 (2–4)	2.579	1.322–5.031	< **0.01**
your health	4 (2–4)	2.171	1.131–4.169	< **0.01**
your well-being	3 (2–4)	2.227	1.181–4.202	< **0.01**
your sense of security	3 (2–4)	1.515	0.809–2.839	ns
your financial situation	4 (2–4)	1.268	0.673–2.388	ns
your relationship with your family	4 (3–4)	3.680	1.470–9.213	< **0.01**
your social life and relationships with friends	3 (2–4)	1.138	0.601–2.152	ns
your quality of sleep	2 (2–4)	1.920	1.019–3.618	< **0.05**
time to pursue your passions/ hobbies	2 (1–4)	1.335	0.665–2.680	ns
caregiving as a source of personal satisfaction	4 (2–4)	1.424	0.759–2.672	ns
your feelings of personal happiness	4 (2–4)	3.018	1.514–6.016	< **0.001**
physical fatigue as a result of caregiving	4 (3–4)	0.758	0.399–1.439	ns
mental exhaustion as a result of caregiving	4 (3–5)	0.710	0.368–1.369	ns

Statistically significant differences are written in boldface; ns: not significant.

4. Discussion

Since most people living with a URD are children, caring for someone with such a condition has a profound impact on many aspects of family life, including physical, mental, emotional, psychological, social and economic aspects [18–21]. This research shows that specific challenges related to URDs include the complexity and severity of symptoms, which result in numerous health problems, emotional lability and behavioural changes among patients, and that these in turn lead to parents' feeling that caregiving is a burden, even claiming care overload. It also demonstrates that while caring for URD children subordinates parents totally to the role of caregiver, also resulting in social isolation as most caregivers feel misunderstood by others [24,25].

This research also confirms that one of the greatest challenges caregivers of children with URDs face relates to their encounters with the healthcare system. Indeed, while the vast majority of caregivers

enrolled in this study complained at the diagnostic and therapeutic odyssey [26–28], especially parents of children with symptom-based diagnoses who had struggled with the missed or delayed diagnoses, and reported the way it hinders access to appropriate services, specialist centres and contacts with other patients and support resources [29]. They also complained at the lack of social awareness and the ignorance of doctors and other health professionals [30–32], the limited medical expertise and lack of available treatment, including drugs [33,34]. Finally, caregivers stressed the barriers in access to the care system and lack of psychosocial support from government and social institutions and healthcare professionals [16,17,35,36].

As these findings highlight the challenges faced by caregivers of children with URDs in obtaining a timely and accurate diagnosis, this research therefore also shows that the diagnostic journey often involves consulting multiple physicians and alternative sources of information. It consequently confirms that parents of children with URDs are forced to turn into 'lay experts' on their specific condition. Since, apart from their primary and unique role as caregivers, they need to take on multiple other roles, including lawyer, case manager, medical navigator and co-ordinator, it places a huge psychological, physical, economic and logistical strain on parents [20,37]. This research therefore confirms observation made elsewhere that URD caregivers often stated that they feel alone in a crowd and describe their experiences with the healthcare system as "a jungle gym" where everything is under construction [38]. As a result of this and as reported by respondents enrolled in this study, URD caregivers experience much higher levels of emotional distress, deterioration of physical and mental health, economic burden and reduced quality of life than parents of children with other disabilities [18,19,36]. This is important since maintaining the good physical and mental health of family caregivers is crucial not only for their own well-being, but also for their ability to provide appropriate care and assistance to a child with a URD.

Most importantly, our findings suggest significant variations in both the perception of the quality of healthcare services for URD children and the emotions experienced among caregivers of children diagnosed at prenatal or newborn screening compared to caregivers of children with symptom-based diagnoses. While we cannot definitively determine whether these differences are solely influenced by the diagnostic method, it is hard to overlook the challenging diagnostic odyssey endured by the latter group over several years and its impact on their emotions and experiences. This is especially so since misdiagnoses or late diagnoses often result in many unnecessary treatments, including examinations, drugs, hospital re-admissions or surgeries, which tend to be uncomfortable, frightening and painful and may result in the deterioration in the condition of URD children's; even premature death [26]. What is equally important is that such procedures cause additional medical costs for both URD caregivers and the healthcare system. It therefore appears that for conditions where newborn screening options are available, even if effective therapies are lacking, as they often are, but treatments exist that may alleviate symptoms or prolong life, it would be beneficial to consider implementing screening programmes and providing immediate treatment.

Despite the absence of effective therapy for diseases such as Sanfilippo syndrome type A, there has been a notable and statistically significant increase in the mean age of death in recent years [39]. In the case of Fabry disease, a decade-long study has revealed that patients who began treatment at an earlier age and had less kidney involvement derived the greatest benefits from therapy. On the other hand, in patients who began treatment at more advanced ages or had advanced renal disease the disease progressed [40]. Lysosomal storage disorders have been subject to screening programmes in many countries, yielding relatively satisfactory outcomes and aiding in the early detection of many cases [41,42]. Based on an evaluation of these preliminary findings, it may be inferred that, as population screening is implemented, there may be a need to reconsider the definition of an ultra-rare disease, and possibly even a rare disease. Given the significant genetic heterogeneity observed in conditions such as Joubert syndrome, it is imperative to establish genetic testing protocols that facilitate prompt diagnosis, thereby enabling the timely initiation of necessary treatment [43]. Given this context, it is understandable that the groups we studied exhibit differences. Caregivers are well aware of the prolonged diagnostic process and its implications for the feasibility of implementing various therapeutic measures, some more or less effective.

4.1. Limitations

Although, to the best of our knowledge this is the first and by far the largest study of caregivers of children with URDs in Poland, it has some limitations. Most importantly, since to date there is no registry of URD patients in Poland the exact number of children with such conditions in the country is unknown, these findings represent no more than the opinions of those URD caregivers who participated in the study and may not be extrapolated to the entire population of URD parents in Poland. Since this study focused on experiences of caregivers of URD children, it may also be unrepresentative of the experiences of caregivers of adult patients, which may be different. Very few fathers participated and the sample tended to report the experiences of female caregivers. The study concerning the burden of caregiving is based on what the caregivers report and, even though opinion data are useful, they represent solely subjective outcomes. Another limitation rests on the fact that, while caregivers provided some general information regarding the consequences of their children's diseases, we had no diagnostic confirmation of these study variables. Finally, this study may be biased due to the online format of the study, as it may have been available only to those caregivers who are members of the online support group on Facebook.

Despite these limitations, this study provides an overview of the experiences of caregivers of children with URDS in Poland. Since URD caregivers' perspective is often neglected by researchers and the healthcare system, this survey sheds new light on their experiences and may help identify measures that need to be undertaken by the government and healthcare institutions to support URD caregivers and their children. Finally, since it allowed them to share their stories, it might have had a therapeutic value.

5. Conclusions

As most children with URDs are cared for by their parents, family caregivers of such patients are the backbone of the healthcare system, concurrently playing the role of parent, physician, nurse, social worker, case manager, disease advocate, lawyer, patient navigator and co-ordinator. At the same time, this research confirms that URDs are a prime example of a so-called family disease insofar as, while they affect URD children, leading to deterioration of their physical health and numerous mental, cognitive and behavioural disorders, caring for frail or disabled children is often a source of physical, emotional and mental strain for caregivers [21–24]. Although family caregivers of URD children are seriously impacted by their children's diseases, they frequently fail to receive appropriate services or attention to meet their needs and become what have been termed invisible patients neglected by the healthcare system.

Since caring for a child with URDs has far-reaching psycho-social consequences for family caregivers, policy-makers and healthcare professionals should therefore focus on developing a bio-psychosocial approach to URD children, which should also include family caregivers' physical, mental and psycho-social needs, as it will improve the quality of care they offer their URD children. At the same time, while all URD caregivers' should be provided with financial and emotional support, this study shows that enhancing access to genetic testing and screening (gene panels, micro-arrays and exome sequencing) should be prioritised. This is especially the case since, during their encounters with the healthcare system URD patients face a double disadvantage: while due to the genetic character of most URDs there is no available

treatment, they are also discriminated against in relation to diagnosis, as genetic testing is not reimbursed. Casual diagnosis not only ends the diagnostic odyssey and enables proper care and some treatment, but it also helps parents to cope with their children's diseases and enables contacts with other patients, access to appropriate specialist centres and involvement in URD research.

All in all, as this study has identified psychosocial problems and the needs of caregivers of children with URDs, we believe that their empowerment is a huge project that requires the implementation of multilevel solutions. We therefore suggest that the following guidelines be implemented:

1. Caregivers of children with URDs require better access to psychosocial support, better financial provision for their substantive role and improved access to information regarding their children's disease.
2. Since (ultra) rare disease patient registers are essential for research, evaluation of medical care, development of clinical research and contacts with other patients, there is an urgent need to create a Polish Rare Diseases Registry.
3. Although Poland is among those European countries that have implemented many long-term screening programs identifying markers of several RDs [44], including phenylketonuria, cystic fibrosis, hypothyroidism, galactosaemia, fatty-acid oxidation disorders, organic acidemias, aminoacidurias and others, more investment in identifying markers of other URDs is required. Moreover, while appropriate screening methods should be developed it is also crucial to include more URDs into newborn screening panels.
4. In order to curb the path to URDs diagnosis the number of disease subjected to newborn screening should be extended.
5. It is essential to ensure broad accessibility to genetic sequencing for parents attempting to conceive, expectant mothers and children in the event of suspected genetic disorders. The provision of genetic testing should be free of charge and easily accessible without unnecessary delays.
6. At the same time, since many direct-to-consumer genetic tests (DTC-GT) are readily available and sold over the counter to consumers, there is a need for better regulation of the genetic testing market in Poland.
7. Since genetic counselling is essential for providing personalised information and support to URD children and their caregivers, there is a need for establishment and development of extended genetic counselling services that should be better integrated into healthcare system.
8. Because in case of some diseases early and late manifesting forms cannot be distinguished during the newborn screening pros and cons should be weighed since every diagnosis raises important ethical, psychological and medical questions [45–48]. Although early detection may allow early intervention or treatment that can, in turn, prevent or postpone irreversible health damage in the child, in later manifesting cases such diagnosis may cause serious psychological burden for URDs parents, including, anxiety related to health-related uncertainty or anticipated future death and may affect family dynamics, both between parents and parent–child relationship.
9. In order better to understand the nature of URDs and the psychosocial dimension of genetic disorders, all healthcare professionals should be trained in molecular biology, diagnostic laboratory work, clinical genetics and genetic counselling.

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Ethics approval and consent to participate

This study was performed in line with the principles of the Declaration of Helsinki. Ethics approval and research governance approval were obtained from the PUMS Bioethics Committee (KB – 833/22). Informed consent was obtained from all individual participants in the study.

Authors' contributions

Both authors contributed equally to this paper. JD and DW conceptualised the study and designed the research questionnaire. JD collected the data, conducted the literature search and drafted the manuscript. DW performed the statistical analyses and prepared the tables. JD and DW discussed the results, critically revised the article, read and approved the submitted version.

Data availability

The datasets generated during the study are available from the corresponding author on reasonable request.

Declaration of competing interest

The authors declare that they have no conflicts of interest.

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Abbreviations

EU: the European Union; RD: rare disease; URD: ultra rare disease.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejpn.2023.12.003.

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