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ORIGINAL ARTICLE

Cystinosis: a truly orphan disease. Report of the Cystinosis Foundation India

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Abstract

Cystinosis is a rare disease leading to accumulation of cystine in lysosomes causing apoptotic cell death leading to organ dysfunction. Although the disease was identified 100 years ago, the history of cystinosis in India is really pathetic. Only in 2012, the Cystinosis Foundation India was formed with the initiative to pool up these unfortunate patients. Nineteen patients have been identified and registered with the foundation. Out of these, only 8 are receiving specific therapy with cysteamine. Four patients have undergone successful kidney transplantation. Eight patients have died since registering with the foundation. Seventeen patients were picked up with advanced growth retardation and renal failure. Only 2 children were picked up in early stage. This article describes the difficulties faced in the identification and management of these patients in India.

Key words

Cystinosis, renal failure, growth retardation, cysteamine, India.

Introduction

Cystinosis is an autosomal recessive disorder caused by mutation of the CTNS gene on chromosome 17 which encodes a ubiquitous cystine specific transporter in the lysosomal membrane [1]. There is massive intra lysosomal accumulation of cystine due to the transport defect leading to apoptotic cell death and progressive organ dysfunction. The disease manifests itself around 6 months of life with failure to grow. Signs of Fanconi's syndrome (polyuria, polydipsia, dehydration and acidosis) also appear as early as 6 months. Corneal crystals diagnostic of cystinosis can be present before 1 year, but is always present after the age of 16 months [2]. Untreated, the children progressively develop rickets, severe growth retardation, renal failure and die between 10-15 years of age. The treatment of the disease essentially is to identify early in the first year of life, replace the nutrients and specific treatment with cysteamine. The diagnosis is confirmed by estimating the leukocyte cystine level and identify the genetic mutation. In 1976, Crawhall reported the news of cysteamine resulting in efflux of cystine from the lysosomes [3]. Gahl showed that protracted oral therapy with cysteamine depleted the organ cystine and delayed the complication of cystinosis [4].

So far there have been hardly any reports of cystinosis from India. Phadke et al reported in 2004 a 3 year-old child who presented with Fanconi syndrome with mild renal failure and corneal crystals [5]. The child was initiated on treatment and lost follow-up. In 2014, Krishnan Swaminathan reported the agony of a boy whose diagnosis of cystinosis got delayed in spite of visiting several hospitals ultimately presenting with severe renal failure and growth retardation [6]. The sister of that patient had also died at the age of 7 of a similar condition. In 2015, Sharma reported the biopsy finding in a 3 year-old child with cystinosis and renal failure [7]. Akhilesh Kumar and Bachhawat have discussed the molecular basis of cystinosis [8]. Taosheng Huang reported the details of CTNS mutation in an Indian boy with nephropathic cystinosis [9].

The first successful kidney transplantation in a severely growth retarded child with cystinosis was reported from Chennai, India in 2010 [10]. Subsequently, when the

child attended the school, he was not able to see the black board and the eye examination confirmed the presence of crystals in the cornea. The diagnosis of cystinosis was made retrospectively and his 2 year-old brother was identified with the disease on further investigation. It was this episode that lead to the formation of Cystinosis Foundation of India in 2012. The foundation was launched on May 2012 in Chennai by a NGO Sapiens Health Foundation. Important members of the society from different professions like law, accountancy, journalism etc were made advisors of the foundation. Donations were raised from the general public to run the foundation.

Materials and methods

After the foundation was launched in Chennai, several nephrologists and ophthalmologists in leading centers throughout India were contacted to register their patients with cystinosis. Booklets were distributed in leading nephrology conferences held in the last 3 years. Once the patient was registered, the clinical details including the biochemical workup were included in the records of the registry. Approximately 1100 nephrologists were contacted throughout the country by email correspondence. This paper highlights the clinical data of these patients, the lack of treatment for cystinosis throughout the country as a whole and the difficulties faced in procuring the drug for these patients.

Results and discussion

The effort of the foundation bore fruit and 19 patients have been registered so far in the foundation. Out of the 19 children registered, 4 are females and rest males (Table 1). Only 4 children could be picked up below the age of two. All the children had growth retardation and Fanconi syndrome (Figure 1). Only in 2 children, the creatinine clearance was normal. Seventeen of them had renal impairment including 4 patients having undergone kidney transplantation. One patient continues to be on peritoneal dialysis after failed graft 12 years ago. She is the eldest with the age of 20 years. 8 patients have already died after registering in the foundation. Only 8 patients are continuing on specific treatment with cysteamine although 13 were initiated. None of the patients are using the cysteamine eye drops. Consanguinity in the parents was noted in

Table 1. Details of the patients registered with the foundation and follow-up

No.	Date of registration	Age at the time of registration	Sex	Clinical manifestations*	Affected sibling	Corneal crystal	Hypothyroidism	Cysteamine treatment	Follow-up	Consanguinity in parents
1	01/03/12	12	M	GR, FS, RF, RTX	Yes	Yes	Yes	Yes	Yes	Yes
2	01/03/12	07	M	GR, FS, RF	Yes	Yes	Yes	Yes	Yes	Yes
3	May 2012	10	M	GR, FS, RF	No	Yes	Yes	No	Died	No
4	01/03/12	10	M	GR, FS, RF, RTX	No	Yes	No	No	No	No
5	01/03/12	11	M	GR, FS, RF, RTX	No	Yes	No	Yes	Yes	Yes
6	15/10/12	10	M	GR, FS, RF	No	Yes	No	Yes	Yes	No
7	06/08/12	06	M	GR, FS, RF	Yes	Yes	Yes	Yes	Died	Yes
8	20/08/12	07	M	GR, FS, RF	Yes	Yes	Yes	Yes	Died	Yes
9	29/08/12	08	F	GR, FS, RF	Yes	Yes	Yes	No	Died	Yes
10	06/10/12	01	M	GR, FS	Yes	Yes	Yes	Yes	Yes	Yes
11	06/10/12	10	M	GR, FS, RF	Yes	Yes	Yes	Yes	Died	Yes
12	27/01/13	02	M	GR, FS, RF	Yes	Yes	Yes	Yes	Died	Yes
13	27/01/13	04	F	GR, FS, RF	Yes	Yes	Yes	Yes	Died	Yes
14	16/08/13	12	M	GR, FS, RF	Yes	Yes	Yes	Yes	Yes	No
15	02/04/14	20	F	GR, FS, RF, RTX in 2002, failed graft, CAPD	No	Yes	No	No	Yes	No
16	18/04/14	02	M	GR, FS, RF	No	Yes	Yes	No	Died	Yes
17	03/10/14	03	M	GR, FS, RF	No	Yes	No	Yes	Yes	No
18	20/11/14	05	M	GR, FS, RF	No	Yes	Yes	No	Yes	No
19	03/01/15	02	F	GR, FS	No	Yes	No	Yes	Yes	No

*GR: growth retardation; RF: renal failure; FS: Fanconi's syndrome; RTX: renal transplantation.

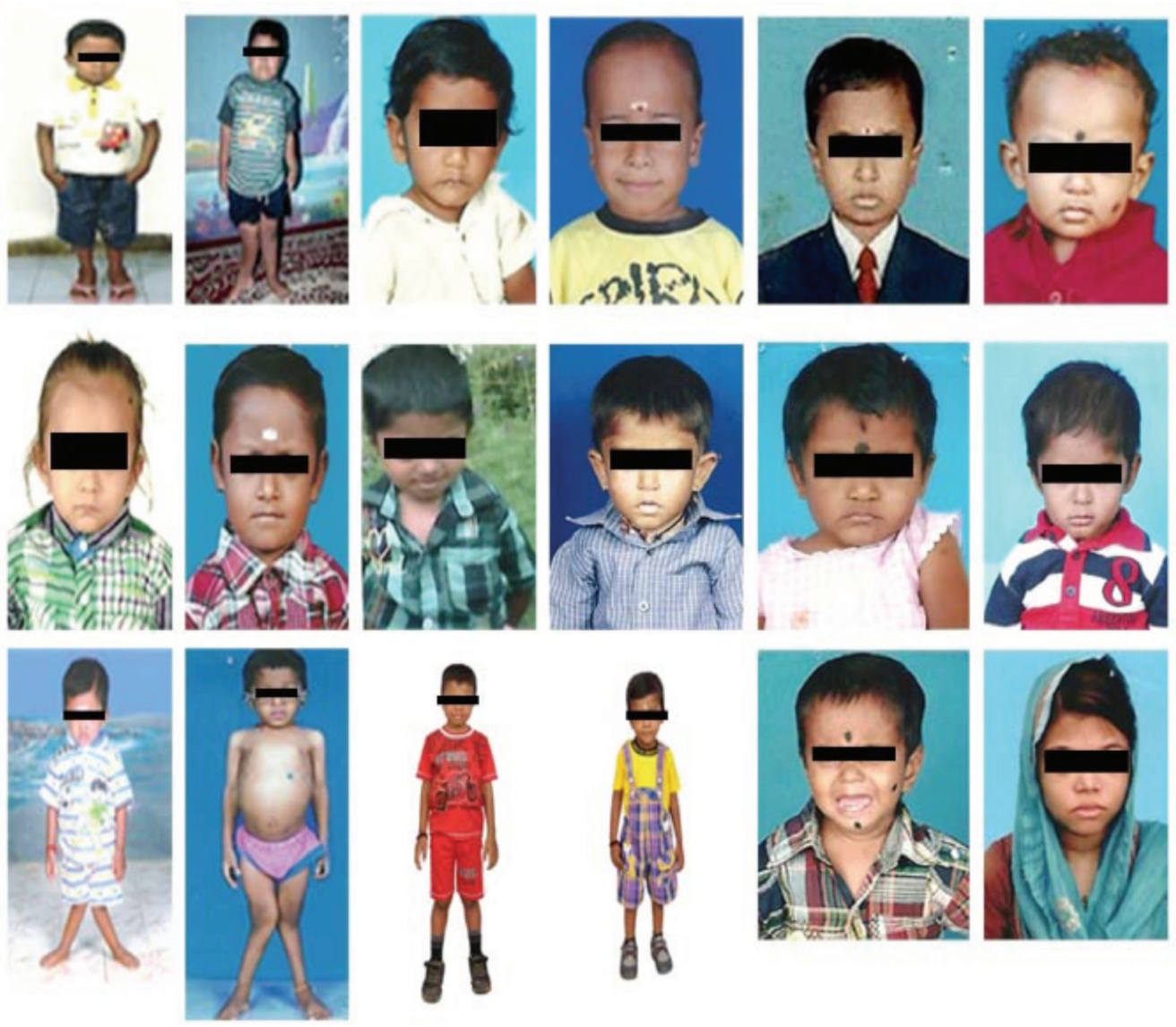

Figure 1. Photographs of the 18 children registered with the foundation.

11. Thirteen patients had hypothyroidism. Corneal crystals were found in all the patients. Three of the children had an affected sibling. Three other children gave a history of similar illness in the sibling who had died earlier. In 2 of the children, the disease was picked up early in life because of the correct diagnosis in the affected sibling.

The treating physicians were contacted, giving more information about the disease and the need for specific treatment. The test, cystine estimation in leukocyte, is not available in India. Hence samples have to be sent to USA for confirmation. Next came the biggest challenge procuring cysteamine for the patients. Cysteamine is not approved for use in India. Hence Orphan Europe could not sell the product in India. The individual patients have to apply to the drug controller for a special permission to import the drug. After that, money had to be remitted to Orphan Europe by individual patients. The cost of the drug is phenomenally expensive with none of the patients getting reimbursement from insurance. Approximately 200 euros is required for a treatment period of 3 months per child. The drug which is then sent by courier requires to be cleared from customs which again involves a 5 to 20% duty. Out of the 19 patients, only 13 were able to procure the drug. Five patients on the drug have died. At present 8 patients are continuing the drug. The Foundation raises the money by donation and is sponsoring the drug for these patients. Attempt has been made to manufacture the drug locally. The eye drops which are required to improve the corneal deposit are not available. The government does not permit the drops to be formulated by

the pharmacy. Big pharma companies are not interested in manufacturing the eye drops because of the low number of patients. It is almost impossible to import the eye drops since it is much more expensive than the oral drug. Attempts have been made to contact Orphan Europe, Raptor Pharma & Sigma Tau Pharma to apply for approval of the oral drug and eye drops in India.

This situation can be dramatically improved if pediatricians pick up the disease in the first year of life itself, so that treatment can be instituted before the child develops complications. This is possible if the test for cystinosis is made available at least in the major cities of India. The drug cysteamine should also be indigenously manufactured, bringing down the cost resulting in adequate therapy to all patients. The Indian Institute of Technology (IIT, Madras), a quasi government organization, has already produced the drug cysteamine in the laboratory and one of the pharmaceutical companies has agreed to manufacture commercially.

Conclusion

Thus, cystinosis has been a totally neglected disease in India with very poor awareness amongst the medical fraternity to pick up the disease early. Procuring cysteamine has been very expensive and difficult. The only light seen is the formation of the Cystinosis Foundation, India in 2012 with subsequent attempts in the right direction.

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ORIGINAL ARTICLE

Disability evaluation in patients with rare diseases in Spain: the importance of being in accord. BURQOL-RD Project

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Abstract

Most of rare diseases lead to a certain level of disability. In Spain, disabled persons receive long-time benefits, but only if they possess a disability evaluation that officially certifies the degree of their disability. Sometimes, the affected persons can experience disagreement with the obtained evaluation.

Our aim was to analyse the level of agreement among rare disease patients and caregivers in Spain with their official disability evaluation and its possible relationship with their health-related quality of life (HRQoL) and the general satisfaction with the national healthcare system (NHS).

Data were collected from patients (n = 123) and caregivers (n = 74) as a part of BURQOL-RD Project that measured the burden of ten rare diseases in Europe. HRQoL was evaluated by the generic instrument EQ-5D. Satisfaction with NHS was measured on a scale from 1 to 10.

Almost 30% of respondents did not agree with their disability evaluation. These persons expressed less satisfaction with NHS than those who were in accord with their evaluation (5.1 vs 6.8; p <0.0001). Patients' and caregivers' HRQoL was also worse for the disagreement group, but did not reach a statistical significance.

Correctly evaluated degree of disability is fundamental and has many consequences for all affected parties. Disability evaluation rules should reflect the specificities of rare diseases.

Key words

Disability, rare diseases, benefits, satisfaction, health-related quality of life.

Background

According to the WHO definition, disability is a complex phenomenon reflecting the interaction between features of a person's body and features of the societal context where the person lives [1]. Thus, disability is a concept, covering impairments, activity limitations, and participation restrictions. Over 1 billion persons experience some degree of disability in the world [1]. In the European Union, one in six people has a disability that ranges from mild to severe [2].

Most of rare diseases are severe and involve sensory, motor, mental and physical impairment, which leads to a disability if the environment and regulations do not take into account the special needs of people with impairment to participate in society [3]. The specificity of rare diseases is that in many cases the affected person is not seen as a disabled citizen, but just as a patient [4].

All EU countries provide long-term benefits for people who become disabled during working life, in form of disability pensions. Besides, there are also benefits for disabled children, which are mainly family benefits to cover home care, assistance, extra costs and education, as well as specific benefits for people who have never entered the labour market due to disability [5].

Disability certificates are necessary to have rights applicable for disabled persons. These certificates are the result of a complex evaluation process. In Spain, the disability evaluation is a multidisciplinary process that includes medical doctors, psychologists or social workers, who carry out an interview with the disabled person and his/her family members and assess relevant documents. At the end of this process, this committee issues a disability certificate that confirms the disability level or degree. If this

level is more than 33%, the person is considered disabled [6]. However, some benefits, such as long-term care allowance, are provided only to persons with more than 75% of disability [5].

Thus, the certified level of disability has important consequences in the social benefits and support received by the affected families, and an adequate evaluation is fundamental, though not always easy for rare diseases [4]. Some patients with disabilities and their caregivers feel that the evaluation process is subjective or biased, and may experience disagreement with the degree of their disability evaluation and consequently with the received benefits.

The BURQOL-RD Project (Social Economic Burden and Health-Related Quality of Life in Patients with Rare Diseases in Europe), carried out between 2010 and 2013, reached its goal to quantify the socioeconomic burden of 10 rare diseases and also collected data on health-related quality of life (HRQoL), satisfaction, disability level and other outcomes of patients and their caregivers in eight European countries [7-12].

The aim of this paper is to analyse the level of agreement among a group of rare disease patients and caregivers in Spain with their official disability evaluation and its possible relationships either with their own health-related quality of life (HRQoL) or with the general satisfaction with the national healthcare system (NHS).

Methods

We analysed data gathered in a cross-sectional study, BURQOL-RD Project, in 2012 in Spain on persons (patients and their caregivers) affected by one of ten selected rare diseases: cystic fibrosis, epidermolysis, Prader-Willy syndrome, Duchenne muscular dystrophy, scleroderma, juvenile idiopathic arthritis, haemophilia, fragile-x syndrome, histiocytosis or mucopolysaccharidosis. This set of rare diseases was selected in order to represent the broad group of rare diseases, keeping in mind the prevalence (including ultra-rare diseases), availability of treatment or caused physical and/or mental disability [7].

Patients and caregivers were invited to participate through disease-specific patient organizations and completed a self-administered online questionnaire distributed via email [10]. Where patients were not accessible via email, postal survey was used. In case of paediatric patients, the main caregiver was taken as a proxy and answered the questions for the patient. The survey was completely anonymous, as no identification data were collected and the completed questionnaires were automatically saved in the research database.

Part of the questionnaire was dedicated to information about disability evaluation and certification by regional authorities, its level and whether the patient agreed with the evaluation (possible answers "yes" or "no"). Besides, patients' satisfaction with NHS was measured on a scale from 1 to 10, where 1 represented the answer "not at all satisfied" and 10 represented the answer "completely satisfied".

HRQoL of the patients was measured by EQ-5D, a generic instrument validated in Europe, including Spain, and commonly used in economic evaluations of health technologies [13]. This instrument covers five areas: mobility, self-care, everyday activities, pain/discomfort and anxiety/depression. A total of 245 possible health states can be defined in this way and the values oscillate between 0 and 1, where 0 represents the worst imaginable health state (death) and 1 is the value of perfect health. The second part of the EQ-5D consists of a vertical 0-100 scale (VAS), where again 0 represents the worst imaginable health state and 100 the best health state. The respondent marks a point on the scale to reflect his/her overall health on the day of the interview [14].

Barthel Index is a widely used tool for the assessment of disability; it measures the ability of a person to perform ten basic activities of daily living, obtaining a quantitative estimate of the level of dependence of the person [15].

Caregivers also completed the Zarit burden interview (22-item version), which measures their subjective burden. The total score ranges from 0 to 88, with scores under 21 corresponding to little or no burden and scores over 61 to a severe burden [16].

Descriptive analysis were used to present sample characteristics. Means and standard deviations were calculated to describe continuous variables and frequencies were used to describe categorical variables. ANOVA analysis was performed to evaluate differences between groups according to their agreement or disagreement with the disability evaluation.

Data analysis were conducted in SPSS 15 statistical software (SPSS, Inc., Chicago, IL, USA). A level of significance of 0.05 was considered in the analysis.

Results

Data of 123 patients were analysed; 35 of them suffered from fragile-x syndrome, 34 Duchenne muscular dystrophy, 20 Prader-Willi syndrome, 12 mucopolysaccharidosis, 11 epidermolysis bullosa, 6 cystic fibrosis and 5 scleroderma. No data from Spain was available for histiocytosis, juvenile idiopathic arthritis and haemophilia. Besides, 74 main informal (not contracted) caregivers of these patients, mostly parents (87%), responded questions about their situation.

Almost three quarters of the patients were males, because the two most frequent diseases in the study sample (Duchenne muscular dystrophy and fragile-x syndrome) affect more males than females [17, 18]. The average age of the patient group was 18.7 (SD: 13.5) years, due to the fact that most of these rare diseases have onset in the childhood. Average satisfaction with the Spanish NHS was 6.3 (SD: 2.3) points. Average patients' HRQoL was 63.4 (SD: 20.9) points and caregivers' HRQoL was 71.8 (SD: 17.5) points on the visual analogue scale of EQ-5D (VAS).

Characteristics of the patients and caregivers can be seen in Table 1.

Almost 30% of the patients or their representatives (n = 36) expressed disagreement with their disability evaluation (disagreement group), which ranges according to the disease from 8% for mucopolysaccharidosis to 60% for scleroderma (Table 2). The disagreement group had slightly higher patients' average age (23 vs 17 years; p = 0.039) and they were diagnosed later than in the agreement group (8 years old versus 4 years old; p = 0.038) (Table 3). Both groups showed similar level of performance in activities of daily living, with slightly better scores in the disagreement group but without statistical significance (63.8 vs 56.5 on Barthel score, p = 0.301). On the contrary, the subjective caregivers' overburden was higher in the disagreement group, but also without statistical significance (38.6 vs 35.5 on Zarit scale, p = 0.401).

Both satisfaction with NHS and patients' HRQoL were higher for the agreement group, although only the satisfaction variable reached the statistical significance. Those patients who were in accord with their disability evaluation expressed more satisfaction with the health-care system (6.8 vs 5.1 points, respectively; p <0.0001) and also evaluated higher their HRQoL (65.7 vs 57.8 points on the visual analogue scale of EQ-5D, respectively; p = 0.112), than those who were not in accord. Moreover, the caregivers' HRQoL was affected in the same way: caregivers of patients who agreed with the disability evaluation had somewhat better HRQoL than caregivers of those who did not agree (72.8 vs 69.7 point on the VAS; p = 0.498) (Table 3).

Table 1. Characteristics of patients and caregivers

	Patients (n = 123)	Caregivers (n = 74)
Male, n (%)	90 (73.2%)	14 (11.4%)
Age, mean ± sd	18.7 ± 13.5	45.4 ± 10.5
EQ-5D VAS, mean ± sd	63.4 ± 20.9	71.8 ± 17.5
Barthel index, mean ± sd	58.7 ± 29.5	–
Disability degree, n (%)		
<33%	3 (2.4%)	–
33%-64%	29 (23.6%)	–
65%-74%	29 (23.6%)	–
>75%	55 (44.7%)	–
No reply	7 (5.7%)	–
Years of caring, mean ± sd	–	13.3 ± 10.0
Satisfaction with NHS, mean ± sd	6.3 ± 2.3	–
Zarit scale, mean ± sd	–	36,5 ± 14,4
Relationship to patient, n (%)		
Son/Daughter	–	8 (10.8%)
Mother/Father	–	64 (86.5%)
Other	–	2 (2.7%)

sd: standard deviation; NHS: National Healthcare System; EQ-5D VAS: Visual Analogue Scale of EQ-5D questionnaire.

Table 2. Distribution of the sample (n = 123) by disease: agree vs disagree with the disability evaluation

Disease (n)	Agree	Disagree
Fragile-X syndrome (n = 35)	29 (82.9%)	6 (17.1%)
Duchenne muscular dystrophy (n = 34)	22 (64.7%)	12 (35.3%)
Prader-Willi syndrome (n = 20)	11 (55%)	9 (45%)
Mucopolysaccharidosis (n = 12)	11 (91.7%)	1 (8.3%)
Epidermolysis bullosa (n = 11)	8 (72.7%)	3 (27.3%)
Cystic fibrosis (n = 6)	4 (66.7%)	2 (33.3%)
Scleroderma (n = 5)	2 (40%)	3 (60%)
Total	87 (70.7%)	36 (29.3%)

Table 3. Comparison of groups: agree with the disability evaluation (n = 87) versus disagree with the disability evaluation (n = 36)

	Agree (n = 87)	Disagree (n = 36)	p-value
Patients			
Age, mean ± sd	17.2 ± 12.2	22.7 ± 15.8	0.039
Age at diagnosis, mean ± sd	4.4 ± 5.9	7.5 ± 10.7	0.038
Time of disease exposition, mean ± sd	12.8 ± 9.8	15.3 ± 10.9	0.228
Patient EQ-5D VAS, mean ± sd	65.7 ± 20.1	57.8 ± 22.2	0.112
Patient Barthel index, mean ± sd	56.5 ± 30.0	63.8 ± 28.2	0.301
Satisfaction with NHS, mean ± sd	6.8 ± 2.0	5.1 ± 2.5	<0.0001
Disability degree, no. (%)			
<33%	3 (3.4%)	0 (0%)	NA
33%-64%	20 (23%)	9 (25%)	
65%-74%	20 (23%)	9 (25%)	
>75%	40 (46%)	15 (41.7%)	
No reply	4 (4.6%)	3 (8.3%)	
Caregivers			
Age, mean ± sd	44.1 ± 10.7	48.4 ± 9.5	0.104
Years of caring, mean ± sd	12.0 ± 10.0	16.4 ± 9.8	0.082
Caregiver Zarit scale, mean ± sd	35.5 ± 13.3	38. 6 ± 16.7	0.401
Caregiver EQ-5D VAS, mean ± sd	72.8 ± 17.0	69.7 ± 18.8	0.498

sd: standard deviation; NHS: National Healthcare System; EQ-5D VAS: Visual Analogue Scale of EQ-5D questionnaire; NA: Not applicable.

Discussion

The European Commission has a long-term strategy on disability, which determines the main policy developments in the disability sector [2]. In the field of rare diseases, the adoption of the Commission Communication in 2008, the Council Recommendation in 2009 and the Directive on cross-border healthcare in 2011 have created a solid basis to place rare diseases in a privileged position in the health agenda of the Member States [19].

However, major and arbitrary disparities exist between countries, and even between regions, in the allocation of financial aid, income support and reimbursement of medical costs [3]. Treatment costs incurred by a rare disease are often higher than they are for other common chronic diseases because of the rarity of the disease, the limited number of specialised centres and the need for continuous care. In most cases, a significant proportion of these expenses is born exclusively by the families. Travel costs to specialised centres are also high in terms of productivity losses and financial costs.

Families affected by a rare disease and health care workers frequently complain about the extreme difficulty in taking the necessary administrative steps required to receive social benefits [3]. The investigation performed by RehabCare with families and patients in Ireland brought also other elements into evidence and discussion [20]. Due to the lack of information and support for people with rare disorders many of the participants initially had great difficulty getting information on their entitlements. Some participants also felt that the caregiver's allowance was insufficient to replace the loss of a fulltime income and that they were struggling to survive.

There are many factors that can affect negatively the quality of life of a person with a rare disease [21]. Health state is certainly one of the most important factors, but others can also play a role, such as access to school or employment, existence of specialized social services or financial support and social benefits.

Our study discovered that almost one third of families affected by a rare disease in Spain were not satisfied with their officially certified disability degree. This figure is in line with the results of a survey carried out by Federación Española de Enfermedades Raras (FEDER) in 2009 [4], which observed that 35% out of 715 respondents affected by one of 29 rare diseases did not agree with their disability evaluation. The main reason, for which the patients think they did not receive a correct evaluation, is the lack of knowledge of the evaluators about the specific rare disease, its symptoms and limitations, which can lead to an underestimation of its burden and therefore a lower certified degree. Indeed, the study discovered that those patients with more prevalent rare diseases received higher disability degree than those with ultra-rare diseases (p = 0,002) [4].

Based on our results, we could add to these findings that the doubts about the correctness of the disability evalua-

tion may lead to a significantly worse perception of NHS among patients and their caregivers. Also the HRQoL of patients and caregivers from the disagreement group was affected, although not reaching a statistical significance; this impairment was not caused by the dependency level, measured by Barthel index, which was slightly higher in the agreement group. However, we cannot assure a direct connection of these variables, since there may be some confounding factors, like a higher patients' age or a higher age at diagnosis in the disagreement group. This latter variable may have a special significance, since the delayed diagnosis in rare diseases is apparently a common problem across countries [22, 23] and there is also evidence about the negative effects of this delay, which can have severe irreversible, debilitating or even life-threatening consequences [24-26]. Unfortunately, our data do not provide sufficient information to determine whether there was a delay in the diagnosis of the participants in our survey.

Other limitation of our study is the small number of participating patients and even less caregivers, without clinically confirmed diagnosis, which is a common problem of socio-economic research in rare diseases field [10] and it can limit the significance level of the analysis. The fact that BURQOL-RD project was not primarily designed to gather information on disability or satisfaction limits drawing reliable conclusions.

Conclusions

Our results suggest that the level of agreement with the disability evaluation could affect people's overall satisfaction with NHS. We also observed a non-significant impairment in patients' and caregivers' quality of life. The consequences of the correctly certified degree of disability are many: from the possibility to receive certain financial benefits, to the entitlements to social services and aids for activities of daily living. The fact, that about one third of affected persons are not in accord with the certified disability degree, is striking. Policy makers across Europe should bear in mind this fact in the moment of creating or modifying rules for disability evaluation, not only in rare diseases area.

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Authors' contribution

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Renata Linertová had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Appendix: BURQOL-RD Research Network

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Review Article

Overview of epidemiological rare diseases registries in Bulgaria

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Abstract

Background. Understanding the importance of collecting epidemiological data, Bulgarian association for promotion of education and science (BAPES) was motivated to start an important initiative in 2008, namely tracing the way for establishing a rare disease epidemiological registry in Bulgaria. This initiative was in conformity with one of the basic aims of the Bulgarian National program for development in the field of rare diseases. Till now several private initiatives on rare diseases registries have been realized in the country resulting in excellent-working databases. This is a costless experience that could be shared in order to support design, implementation, analysis, interpretation and quality evaluation.
Aim. The aim of this study was to provide up-to-date and reliable information on the epidemiological registries for rare diseases officially processing in Bulgaria.
Study design. The authors did a literature review of the available data from the existing registries for rare diseases in the country.
Material and methods. For originating the rare diseases epidemiological registries report several sequential strategies were used. The inquiry contained the following summary indicators: 1. year of launch; 2. year of latest update; 3. number of patients from latest update; 4. distribution by sex; 5. distribution by age. Also the main features of rare diseases registries were described.
Results. Consent forms and date information were provided by 13 registries on rare diseases.
Conclusion. The benefits of rare diseases registries are many and they stimulate all Bulgarian stakeholders to continue to give their best to support the management of the epidemiological rare diseases registries in the country.

Key words

Epidemiological data, epidemiological registries, rare diseases.

Introduction

Until recently, epidemiological registries were considered as a research tool that was exclusively used by epidemiologists. Technology progress has dramatically changed this view. Today epidemiological registries solve major problems in the field of rare diseases, most importantly the collection of information from various geographically and structurally scattered sources, and the use of these data for public health and research purposes. The combined benefits of epidemiological registries for rare diseases are widely known: producing epidemiological data about the incidence and prevalence of a disease at national and global levels; enhancing knowledge on variability, progression, and natural history of rare diseases; monitoring and evaluating patient outcomes; providing data to health authorities for planning prevention, diagnosis, treatment and follow-up in healthcare services for rare diseases and for allocation of resources[1-4].

There has been intensive work going on at EU level for joining efforts on registries for rare diseases. Different stakeholders combine their activities to achieve progress not only in pure science, but also on a number of very practical issues. The existence of well-functioning registries is itself an important prerequisite for the development and application of effective treatments for rare diseases. Patients and their families are the most interested in the consistent and proper collection of epidemiologi-

cal data, because elaboration of standards for care and treatment is greatly facilitated in this way[5]. Subsequently, this significantly improves the quality and expectancy of life, even in the absence of new therapies. These arguments logically define epidemiological registries as a key element of any reasonable policy on rare diseases and orphan drugs at national, European and international levels.

Registries as an epidemiological tool are still a relatively new concept to rare diseases, which explains the presence of some practical inconsistencies, especially the lack of a unified approach to data registration and administration[6]. This is due to many reasons:

- different number of stakeholders involved in the administration and management of the registry, as well as large variety of stakeholder needs and goals;
- failure to apply common standards, leading to fluctuations in the frequency of data collection and in quality control;
- financial instability of registries;
- lack of human, financial and structural resources to make possible maintaining separate registries for each rare disease or for each of the different stakeholder objectives.

The specificities of rare diseases represent additional challenges for the registration of patients.

- The genetic nature of most rare diseases suggests the need to investigate and track family related cases, which is not always possible.
- The combination of a small number of cases and a large geographic scope of data collection requires multiple collaborations and exchange of information, usually at international level, often constrained by legal frameworks.
- The need for resources to create and maintain registries for rare diseases. This need is almost equal to that required from the registries for common diseases, but at the same time it is much more difficult to achieve financial sustainability in the long-term for rare diseases.

Recognizing the currently existing rare disease registries, the results achieved, but also the problems encountered, the EU Committee of Experts on Rare Diseases (EUCERD) adopted at the end of its term some recommendations for the development of registries for rare diseases, focusing on compatibility of the information and the use of common codification protocols[7]. The strategic objective of the European Commission is the creation of a European Platform on Rare Diseases Registration providing common services and tools for the existing (and future) rare diseases registries in the European Union[8].

Given the importance of registries, a number of steps for international coordination of these issues have been taken in recent years. The most significant one was undoubtedly the establishment of the International Rare Diseases Research Consortium (IRDiRC). This was a joint initiative of the European Commission and the US National Institutes of Health, launched in April 2011.

Though there is overall progress at international level, the support for the launch and development of rare disease registries at national level remains a crucial point. Despite the strong support of the European Commission and the adoption of a targeted national policy for creation of national registries for rare diseases, a national registry for rare diseases does not exist yet in Bulgaria. One of the priorities of the Bulgarian National Program for Rare Diseases (2009-2013) was the collection of epidemiological data for rare diseases in Bulgaria by creation of a National registry[9]. Despite initial enthusiasm, the Program had been left without appropriate legislation, funding, organization, and management, so at present day this objective had not been implemented. Yet various private initiatives on rare diseases registries have been realized to date, resulting in several excellent-working databases.

The aim of this study is to provide up-to-date and reliable information on the epidemiological registries for rare diseases in Bulgaria. Only the epidemiological registries for rare diseases are the subject of this review while the clinical records maintained in hospitals and other medical treatment facilities are out of the review's scope.

Material and methods

The review was accomplished through:

1. description of main features of rare diseases registries and presentation of European and international recommendations and guidelines in this field;
2. summary of available data from the existing registries for rare diseases in the country.

For originating the rare diseases epidemiological registries report several sequential strategies were used:

- a literature search-keyword search in the PubMed's scientific database;
- rare diseases portal Orphanet's information on rare diseases registries;
- analysis of the scientific attainments presented during the Bulgarian National Conferences on Rare Diseases and Orphan Drugs (2010, 2011, 2012 and 2013)[10-12];
- personnel call for information on leading clinical centers in Bulgaria, recommended by rare diseases patient organizations;
- roundtables, held with a purposive sampling of rare diseases stakeholders from across Bulgaria to gain information not readily accessible from the public domain (2010, 2012).

To present the registries, the following summary indicators have been selected:

1. year of launch;
2. year of latest update;
3. number of patients from latest update;
4. distribution by sex;
5. distribution by age.

Administrators of the epidemiological registries were asked to identify the bibliography of publications, confirming the operation of the epidemiological registry. Finally an analysis of strengths and weakness of registries was performed.

Results and discussion

The Bulgarian rare disease stakeholders realized the importance and benefits of the registries as an epidemiological tool. A number of such databases were created as a result of joint activities between scientific societies, clinical centers, patient organizations and Non-Governmental Organizations (NGOs).

The Information Centre for Rare Diseases and Orphan Drugs called for taking part in this survey the known functioning in Bulgaria epidemiological registries for rare diseases. Consent forms and date information were provided by 13 registries (listed in alphabetical order):

- National registry of adult patients with chronic myeloid leukemia;
- National registry of patients with Becker muscular dystrophy;
- National registry of patients with Duchenne muscular dystrophy;
- National registry of patients with Gaucher disease;
- National registry of patients with mucopolysaccharidosis type II;
- National registry of patients with myotonic dystrophy type I;
- National registry of patients with myotonic dystrophy type II;
- National registry of patients with neuroendocrine tumors;
- National registry of patients with phenylketonuria;
- National registry of patients with primary immunodeficiencies;
- National registry of patients with spinal muscular atrophy;
- National registry of patients with thalassemia major;
- National registry of patients with Wilson disease.

Table 1 presents a summary of the main features of the above mentioned registries.

Although it was difficult to generalize registries' information, as they greatly differed, some common features were observed.

Strengths

- Involvement of multiple stakeholders.
- The registries are population-based.
- Provision of important public health information.
- Capacity to collect longitudinal data.

Weaknesses

- No interaction with the Bulgarian health information system.
- No long-term financial sustainability for most registries.
- Lack of a strong motivation of physicians in providing information, since this is a voluntary activity.
- No use of e-tools (e.g., they were not web-based registries).

Most of the registries started their activities during the period 2008-2011. Only one registry had been accomplished in the last 70's of the last century. This could be referred to two basic reasons. On one hand the technology achievements changed dramatically the gathering, processing and storage of information. On the other hand all stakeholders clearly realized the benefits of such registries and make every effort to create a greater number of registries for rare diseases.

The data updating is determinant for the accuracy of the submitted information. It was found that most of the investigated registries were not annually updated. The lack of an annual renewal has questioned the relevance of the information and has suggested the doubt that the registries can be used as a reliable source of information. These results raised important issues related to some factors influencing the frequency of information updating.

Legislation

At this point there are three legal acts that treat the question of the establishment and functioning of epidemiological registries for rare diseases. Health Act only defines who has the right to collect health information of individuals, and in which cases these data may be provided to third parties. The Personal Data Privacy Act limits the gathering of sensitive personal data to be done only by administrators who were registered by the Commission for protecting personal data. Last year Bulgarian Ministry of Health issued a regulation on the procedure for registration of rare diseases and centers of expertise and reference networks for rare diseases that settled the topic for National registry of rare diseases patients. The studied epidemiological registries meet the legislation requirements. Hopefully strict compliance with the new legal framework regulating the operation of registries will support data updating in shorter period of time. This will raise the data timeliness and will allow real description of a number of important indicators such as incidence, prevalence, survival, etc upon which more adequate and timely solutions could be taken for problems in the field of rare diseases.

Table 1. Bulgarian rare diseases epidemiological registries basic features summary

	Year of launch	Year of latest update	Number of patients from latest update	Distribution by sex		Distribution by age	
				men	women	under 18 years of age	above 18 years of age
Registry of adult patients with CML	2010	2012	328	163	165	0	328
Registry of patients with Becker muscular dystrophy	2008-2010	2013	33	31	2	30	3
Registry of patients with Duchenne muscular dystrophy	2008-2010	2013	87	87	0	67	20
Registry of patients with Gaucher disease	2011	2014	17	9	8	1	16
Registry of patients with mucopolysaccharidosis type II	2011	2011	7	7	0	7	0
Registry of patients with myotonic dystrophy type I	2008-2010	2013	47	23	24	3	44
Registry of patients with myotonic dystrophy type II	2008-2010	2013	3	0	3	0	3
Registry of patients with neuroendocrine tumors	2013	2013	127	57	70	4	123
Registry of patients with phenylketonuria	1977	2014	171	87	84	95	76
Registry of patients with primary immunodeficiencies	2010	2014	131	66	65	N/A	N/A
Registry of patients with spinal muscular atrophy	2008–2010	2013	52	29	23	31	21
Registry of patients with thalassemia major	2009	2012	270	141	129	104	166
Registry of patients with Wilson disease	2011	2011	162	90	72	14	148

Funding

Indirect public funding is available for some registries, established within healthcare structures of national significance. The majority of rare disease registries in Bulgaria are funded by grants, public-private partnerships or in a voluntary manner. According to regulation on the procedure for registration of rare diseases and centers of expertise and reference networks for rare diseases the future National registry of rare diseases patients will be funded by the State. Stable funding will ensure regular data updating.

Data set

It was revealed that a centralized approach to rare disease registries and rare diseases field in general was missing in Bulgaria and registries' design substantially varied. Bulgarian association for promotion of education and science, managing 7 of the identified rare diseases registries, had set a uniform data set of 18 indicators (regarding the demography, the disease, the general practitioner and the medical specialist information) for some of its registries. It was observed in the other rare disease registries that the more detailed the registry was, the wider data set was used.

Conclusions

Rare disease epidemiological registries are still a new topic for the Bulgarian public health. Yet the growing number of such initiatives shows that the rare diseases community in Bulgaria is interested and willing to participate in a registry activity. To facilitate this process and ensure better outcomes, it is recommended that:

1. the legal bases for starting and running epidemiological registries must be even more clarified and equalized;
2. the State should take the financial responsibility for the establishment and continuous work of rare diseases registries;
3. a mechanism (regulation) for mandatory registration of the rare diseases patients under surveillance should be put in place.

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