Eur J Health Econ (2016) 17 (Suppl 1):S89–S98
DOI 10.1007/s10198-016-0787-0

ORIGINAL PAPER

Social/economic costs and health-related quality of life of mucopolysaccharidosis patients and their caregivers in Europe

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Received: 3 May 2015 / Accepted: 13 January 2016 / Published online: 9 April 2016

Abstract

Objectives To assess the health-related quality of life (HRQOL) of patients with mucopolysaccharidosis (MPS) and their caregivers and to quantify the disease-related costs from a societal perspective.

Methods In the context of a multi-country study of rare diseases (BURQOL-RD project), a cross-sectional survey was performed among MPS patients in seven European countries. Data on demographic characteristics, health resource utilization, informal care, and loss of labor productivity were collected. The EQ-5D, Barthel index (BI), and Zarit burden interview (ZBI) questionnaires were used to assess patients' and their informal caregivers' quality of life, patients' functional ability, and caregivers' burden, respectively.

Results Altogether, 120 patients (children 62 %, females 40 %) and 66 caregivers completed the questionnaire. Patients' mean age was 16.5 years and median age at diagnosis was 3 years. Adult patients' average EQ-5D and EQ VAS scores varied across countries from 0.13 to 0.43 and 30.0 to 62.2, respectively, mean BI was 46.7, and ZBI was 32.7. Mean informal care time was 51.3 h/week. The mean total annual cost per patient (reference year 2012) was €24,520 in Hungary, €25,993 in France, €84,921 in

Members of the BURQOL-RD Research Network listed in Supplementary Annex 1.

Electronic supplementary material The online version of this article (doi:10.1007/s10198-016-0787-0) contains supplementary material, which is available to authorized users.

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Italy, €94,384 in Spain, and €209,420 in Germany. Costs are also shown to differ between children and adults. Direct costs accounted for most of the costs in all five countries (80, 100, 99, 98, and 93 %, respectively).
Conclusions MPS patients experience substantial loss of HRQOL and their families take a remarkable part in their care. Although utilization of health and social care resources varies significantly across countries, MPS incurs considerable societal costs in all the countries studied.

Keywords Mucopolysaccharidosis · Health-related quality of life · Cost-of-illness · Caregiver · EQ-5D

JEL Classification I190

Introduction

Mucopolysaccharidosis (MPS) is a group of rare metabolic diseases caused by defective activity of the lysosomal enzymes that degrade glycosaminoglycans (GAG, previously called mucopolysaccharides). MPS can be subclassified into eight types according to the deficiency of a specific lysosomal enzyme that participates in the stepwise degradation of GAGs: Hurler syndrome (MPS type I-H); Hurler-Scheie syndrome (MPS type I-H/S); Scheie syndrome (MPS type I-S); Hunter syndrome (MPS type II); Sanfilippo syndrome (MPS type III, Subtypes A, B, C and D); Morquio syndrome (MP type IV, Subtypes A and B); Maroteaux–Lamy syndrome (MPS type VI); Sly syndrome (MPS type VII). Most types of MPS are inherited in an autosomal recessive manner, with the exception of MPS type II, which has X-linked recessive inheritance [1].

MPS disorders have a chronic, progressive course, although the age of the onset of symptoms and severity of clinical disease can vary markedly [1]. Patients with MPS typically have normal development initially and abnormalities appear in infancy or sometime later in childhood [2]. The progressive systemic deposition of GAGs results in multi-organ system dysfunction that varies with the particular GAG accumulated and the specific enzyme mutation(s) present. Multiple clinical features are seen in patients, such as cardiac involvement (common and early symptom), obstructive pulmonary disease, hearing impairment, ophthalmic disorders (e.g., corneal clouding, glaucoma, retinal degenerations) and musculoskeletal symptoms (e.g., short stature, joint stiffness or hyperlaxity, peripheral nerve entrapment) [3–6].

MPS is considered a rare disease as it affects no more than five in 10,000 people in the European Union (EU) and, by nature, it is a chronically debilitating condition. However, prevalence data on MPS varies substantially across Europe and diagnostic methods and patient characteristics are often poorly reported [7]. According to a review by Jurecka et al., the prevalence of MPS (all types) per 100,000 live births was 4.50 in the Netherlands, 3.72 in the Czech Republic, 3.53 in Germany, 3.08 in Norway, 1.77 in Denmark, 1.75 in Sweden, and 1.81 in Poland [8]. The European Medicines Agency (EMA) considers a 0.03/10,000 prevalence rate in the EU as accepted in the designation of specific drugs for MPS type I and 0.02/10,000 for MPS type II (Hunter syndrome) [9].

Until the early 2000s, supportive care was the only option available for the management of MPS. Since 2001, enzyme replacement therapies have been approved by the EMA for the treatment of MPS I (laronidase), II (idursulfase), IV (recombinant human *n*-acetylgalactosamine-6-sulfatase) and VI (galsulfase), resulting in substantial improvements in patients' somatic symptoms [10]. However, patients' access to costly new drugs varies geographically due to differences between national reimbursement schemes for orphan drugs [11–13]. Moreover, there is a scarcity of data on cost-of-illness and health-related quality of life (HRQOL) of patients with MPS to provide inputs for health economic analyses that could be used in health policy decisions [14].

One of the aims of the 'Social Economic Burden and Health-Related Quality of Life in patients with Rare Diseases in Europe' (BURQOL-RD) European Commission-financed project was to provide information on ten selected rare diseases in eight EU countries, including socio-economic burden and HRQOL of patients and their caregivers. Details of the project and selection of the ten rare diseases have been described elsewhere [14–17]. In this paper, we report results obtained in MPS in the context of the BURQOL-RD project.

Our study had two main objectives. First, to estimate the economic costs related to MPS from a societal perspective, including both direct costs and labor productivity losses. Second, to assess the HRQOL of MPS patients and caregivers.

Methods

Research design and subjects A cross-sectional survey was performed involving people diagnosed with MPS and their main informal caregivers. All patients and caregivers were informed about the study objectives and data

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confidentiality and were asked to state their understanding of the study conditions and agreement to participate. The survey was completely anonymous, as the patients were contacted by their patient organization (PO). The questionnaires were available online on the BURQOL-RD website (www.burqol-rd.org). Patient organizations in each country recruited patients to participate in the study via their usual information channels (the link to the questionnaire was administered by e-mail). The questionnaire did not include any identification data (name, address, e-mail) and the responses were sent electronically directly to the research database. In those sporadic cases where a paper-based version of the questionnaire was applied, the electronic data input was done by the PO. The fieldwork was carried out between September 2011 and August 2013.

Information and variables of interest The information sources used in the study were the self-completed questionnaires. The questionnaires were designed by the BURQOL-RD study group and one targeted the patients and the other the patients' main informal caregiver (if she/he had any).

Most studies of cost-of-illness and HRQOL use information gathered at a specific point in time. The questionnaire we used was detailed enough to reduce either exaggeration or underestimation. To estimate resource utilization, the questionnaire solicited information covering the 6-month period prior to the study (12 months for hospitalizations). Data for the preceding 6 months were extrapolated to the entire year. We considered 6 months to be an appropriate recall period.

Patients' questionnaire The questionnaire was presented in two versions, one for adults (including employment-related questions) and another for patients aged <18 (considering schooling issues). Demographic, clinical data, and health and social care utilization data were collected from patients diagnosed previously with MPS. Information on reductions in working time related to MPS (temporary and permanent sick leave or early retirement) was also collected and these data were used to estimate loss of labor productivity.

Caregivers' questionnaire (*designed for the main non-professional caregiver*) Demographics and reductions in working time related to the care of the patient were assessed, as well as the average time the caregiver spent helping the patient in his/her everyday activities. The following activities were surveyed on a daily basis: basic hygiene and dressing or changing, bathing or showering, feeding, helping to move, cooking and preparing meals, and the administration of drugs. Other activities (domestic tasks such as cleaning or laundry, travel, shopping, financial or administrative or legal affairs, social and leisure activities, and monitoring and supervision) were surveyed on a weekly basis. The main informal caregiver was also asked to provide data on the time spent by other informal caregivers, if any, on these activities.

Standard questionnaires Information about functioning, HRQOL, and caregivers' burden was collected using validated questionnaires (see details below).

Costing methodology We used the prevalence approach to estimate costs from a societal perspective. Disease prevalence takes into account all existing cases during a given year and all healthcare resources used for prevention, treatment, and rehabilitation, plus other resources used (formal and informal care) or lost (labor productivity) within that year as a consequence of the illness considered. Prevalence-based cost-of-illness analysis has the advantage of incorporating measurements of total annual healthcare expenditure, which is particularly relevant for chronic conditions such as a specific rare disease that requires long-term treatment. In this context, a bottom-up costing approach was used to estimate total and average annual costs [18]. Data on resource utilization were collected for each patient.

Direct healthcare costs Direct costs were derived from healthcare utilization. Official price, tariff, and reimbursement lists were used for unit cost calculation (see Supplementary Annex 2). The value of resources used by patients was calculated in terms of the relevant unit costs and the average cost per patient in the sample. Information about the number of hospital admissions and days of inpatient care was obtained from the questionnaires.

Data for the volume of outpatient care (rehabilitation, medical tests and examinations, visits to health professionals, and home medical care) and the number of emergency visits were obtained from the questionnaires. Unit costs obtained from different sources and healthcare cost databases were then multiplied by the number of units of each resource used. Information regarding the medications used by patients was obtained from the questionnaires. The cost of drugs used by patients was calculated by determining the daily cost for each of the products used (based on the cost of each pack dispensed and the dose used) and then multiplying by duration of use. When no information concerning the number of units per pack was available, we assumed the largest pack-size was dispensed. The costs of prescription drugs used were obtained from the list of approved drugs in the different countries.

Information concerning the use of health material and healthcare-related transportation was obtained from the questionnaires. The costs of orthopedic devices were obtained from different distribution firms.

Direct non-healthcare costs Informal care is defined as the performance of tasks by non-professionals that help maintain or enhance patient independence. Therefore, informal services are defined as the group of tasks or care provided by non-professional caregivers, who are often

relatives, but may also be friends or neighbors. Information about informal care was obtained from the questionnaires, specifically from the items concerning the time spent helping the patient with his or her basic activities of daily living and the time spent helping with necessary instrumental activities of daily living (recall method). As a conservative criterion, and to prevent joint production, we have censored the time of care to a maximum of 16 h per day (112 h per week) when the time of care provided by one caregiver reported exceeded this figure.

The approach used to value the care hours was the proxy good method, which values time as an output. This method values the care provided by the informal caregiver considering that if he/she did not provide these services, their presence would have to be substituted by another person who could provide them [19]. Therefore, we took into consideration the question of how much it would cost to take on said substitution or replacement by hiring a professional caregiver [20]. The unit cost of informal care varied from €2.9 (Bulgaria) to €16.2 (Sweden) per hour across the eight countries. Thus, the maximum annual cost of informal care (112 h per week) for one caregiver would be €16,811 in Bulgaria, €29,136 in Hungary, €56,590 in Italy, €58,400 in France, €67,920 in the UK, €75,920 in Germany, €77,030 in Spain, and €94,386 in Sweden. Nevertheless, one patient could have more than one informal caregiver and we considered the sum of time of all informal caregivers in the analysis.

Information on formal paid care provided by professional caregivers and other social services was obtained from the questionnaires and comes under the social services category.

Loss of labor productivity Data on loss of labor productivity were obtained from physical units converted into monetary units with a human capital-based approach [21]. According to human capital theory, the average earnings (gross wages) of a worker can be considered a good proxy for labor productivity losses. Therefore, our calculations were based on average gross wage figures in surveys by the national statistics institutes of the participating countries. Annual losses of labor productivity were estimated for the year 2012.

Patient and caregiver self-reported outcomes Patient and main informal caregiver outcomes were obtained by means of the self-administered questionnaires: EQ-5D, Barthel index and Zarit burden interview.

The EQ-5D is a simple generic health-state instrument developed by a multidisciplinary group of researchers [22]. This questionnaire has been validated in many countries in Europe, and is commonly used in economic evaluations and health technology assessments to calculate quality-adjusted life years (QALYs). The EQ-5D consists of two parts, a descriptive system and a health thermometer. The descriptive system covers five dimensions of health: mobility, self-care, everyday activities, pain/discomfort, and anxiety/depression. Evaluations of health states described by the descriptive system have been reported for the general population, reflecting the desirability (preference or utility) of each specific health state from a societal perspective [23]. Country-specific societal value sets of the EQ-5D-3L were available for Denmark, France, Germany, Spain and the UK, but, due to lack of local values, Spain's values were applied for Italy, Denmark's for Sweden, the UK's for Bulgaria and the French for Hungary. The second part of the EQ-5D is a visual analogue scale (VAS) on which the two endpoints refer to the worst and best imaginable health states (0–100). Respondents are asked to mark their current state.

The Barthel index (BI) is a widely used tool for the assessment of disability and measures the ability of a person to perform ten basic activities of daily living, providing a quantitative estimate of the subject's degree of dependence [24, 25]. It is easy to apply, has a high degree of reliability and validity, is capable of detecting changes and is easy to interpret. The BI is recommended as the instrument of choice for measuring people's physical disability in both clinical practice and public health research. The BI was applied in our study for patients aged 6 years and older. A score of 91–99 shows mild dependence, 61–90 moderate dependence, 21–60 severe dependence, and <20 complete dependence [25].

The main non-professional caregiver was asked to complete the Zarit burden interview (ZBI) (22-item version), which measures the subjective burden among caregivers. Each item is a statement to which the caregiver is asked to respond using a 5-point scale, with options ranging from 0 (never) to 4 (nearly always) [26]. The total score ranges from 0 to 88, with scores under 21 corresponding to little or no burden and scores over 61 to severe burden. No validated version of the ZBI was available for Bulgaria and Hungary, therefore this measure was not applied in these two countries.

Results

A total of 120 questionnaires were collected in seven countries from patients with MPS. The largest number of questionnaires ($n = 38$; 32 %) was obtained from Italy. Spain and Germany contributed significantly to the sample, providing 29 (24 %) and 21 (18 %) filled out questionnaires, respectively. France collected data from 15 patients (13 %) and the rest was obtained from Hungary ($n = 10$; 8 %), Sweden ($n = 5$; 4 %), and Bulgaria ($n = 2$; 2 %). No data on MPS patients were obtained in the UK. The main characteristics of the overall sample and by countries are presented in Table 1.

Table 1 Main characteristics of the sample

Variables[a]	Bulgaria	France	Germany	Hungary	Italy	Spain	Sweden
Patients							
No. of responses	2	15	21	10	38	29	5
Mean age, years (SD)	14.0 (4.2)	9.4 (4.6)	21.4 (12.3)	13.5 (6.7)	22.2 (15.1)	10.2 (9.3)	16.8 (8.9)
Mean age at diagnosis, years (SD)	4.5 (2.1)	0.69 (0.5)	6.9 (9.9)	3.9 (2.2)	6.2 (9.1)	3.7 (3.2)	6.4 (6.1)
Female, %	0	53	43	30	47	32	20
Informal caregivers							
No. of responses	1	2	12	8	21	21	1
Mean age, years (SD)	39.0	21.5 (29.0)	47.3 (8.1)	42.8 (5.6)	43.1 (16.9)	39.2 (7.3)	44.0
Female, %	100	100	83	100	81	81	100
Relationship to patient, *n*							
Parent to the patient	1	2	12	8	20	21	1
Other relative to the patient	0	0	0	0	0	0	0
Partner or other	0	0	0	0	1	0	0
Informal caregivers' mean hours per week (SD)	49.8 (70.4)	3.7 (10.7)	54.0 (61.1)	75.2 (68.1)	52.0 (74.5)	70.0 (65.3)	21.9 (48.9)
Health outcomes							
Mean utility—adult patients (SD)	–	–	0.433 (0.296)	0.134 (0.433)	0.189 (0.444)	0.184 (0.458)	0.366 (0.150)
Mean utility–caregivers (SD)	0.689 (NA)	–	0.802 (0.255)	0.945 (0.106)	0.681 (0.383)	0.668 (0.422)	0.389 (NA)
Mean VAS—adult patients (SD)	–	–	45.5 (21.6)	51.3 (31.7)	62.2 (18.3)	54.8 (6.7)	30.0 (28.3)
Mean VAS–caregivers (SD)	70.0 (NA)	–	74.2 (17.2)	84.4 (12.1)	74.8 (20.5)	72.8 (19.4)	45.0 (NA)
Mean Barthel index—patients (SD)	45.0 (7.07)	50.0 (0.0)	44.0 (40.8)	35.6 (31.7)	53.8 (40.4)	44.3 (29.5)	7.8 (5.7)[b]
Mean Zarit burden interview—caregivers (SD)	–	20.5 (0.7)	34.3 (12.0)	–	31.9 (11.6)	32.7 (13.7)	54.0 (NA)

NA not applicable

[a] Results refer to the full sample, items with incomplete responses are: Age at diagnosis 117/120; Gender 119/120; Utilities of adult patients 41/46; Utilities of caregivers 44/66; VAS adult patients 40/46; VAS caregivers 57/66, ZBI (caregivers) 51/66

[b] Barthel index out of 20 and not out of 100

There were 74 children (62 %) and 46 adults (38 %) in the patient sample (percentage of children by country: Bulgaria 100 %, France 87 %, Germany 33 %, Hungary 60 %, Italy 53 %, Spain 79 %, and Sweden 60 %). The youngest and oldest patients were 1 and 56 years old, respectively. The number of household members living with the patient varied from 0 to 7.

A total of 101 patients (92 %) stated that they needed help from a caregiver to perform everyday activities. Among them, 22 (22 %) received help from a professional caregiver, on average 26.9 (SD 46.7, minimum 1, maximum 168) hours per week, and all were also helped by non-professional caregivers. Altogether, 66 main non-professional caregivers completed the caregivers' questionnaire (Table 1). The mean informal care time was 51.3 (SD 65.6) hours per week for the overall sample ($n = 120$), and results were similar for children and adults (children, $n = 74$: mean 51.0, SD 64.4; adults, $n = 46$: mean 51.8, SD 68.2).

The average annual costs per patient are presented in Table 2. For further analysis of costs, we considered only those countries where data were available for at least ten patients (France, Germany, Hungary, Italy, and Spain). The average annual total cost per patient varied from €24,520 (Hungary) to €209,420 (Germany), corresponding approximately to a tenfold difference.

Drug costs were notably higher in Germany than in Italy or Spain, whilst this cost item was insignificant in France and Hungary. In contrast, inpatient care-related costs were highest in France, although only three patients had been hospitalized in the previous 12 months. None of the patients in the Hungarian sample received professional care and only one patient utilized social services, hence these costs were much lower in Hungary than in the other four countries. Informal care-related costs were similar in Hungary and Italy despite the twofold difference in unit costs.

Table 2 Cost-of-illness in mucopolysaccharidosis (mean (SD) annual costs per patient in euros, year 2012)

Costs € 2012	Bulgaria ($N = 2$)	France ($N = 15$)	Germany ($N = 21$)	Hungary ($N = 10$)	Italy ($N = 38$)	Spain ($N = 29$)	Sweden ($N = 5$)
Drugs	46,662	4	121,665	15	47,890	32,659	13,516
Medical tests	5	275	158	58	250	634	974
Medical visits	343	1055	6923	122	1702	2423	10,165
Hospitalizations	0	10,450	3076	178	4357	5476	6645
Health material	314	1056	8241	295	1770	555	3104
Healthcare transport	0	3	1867	0	0	2	20,685
Direct healthcare costs (SD)	47,369 (66,234)	12,844 (25,808)	141,928 (314,708)	668 (644)	55,967 (70,723)	41,749 (58,887)	55,090 (59,935)
Professional carer	22,461	416	258	0	753	771	64,894
Non-healthcare transport	143	47	463	109	260	139	808
Social services	1696	10,744	16,362	1	619	937	26,014
Direct non-healthcare formal costs (SD)	24,301 (33,966)	11,207 (20,445)	17,083 (27,088)	110 (278)	1633 (3514)	1847 (5138)	91,715 (103,871)
Main informal carer	7653	1 685	29,052	14,736	17,464	30,463	19,140
Other informal carers	0	258	7527	4139	8833	18,560	0
Direct non-healthcare informal costs	7653 (10,823)	1943 (5571)	36,580 (41,383)	18,875 (17,091)	26,297 (37,643)	49,023 (46,041)	19,140 (42,798)
Direct costs (SD)	79,323 (43,081)	25,993 (44,152)	195,591 (310,569)	19,654 (17,382)	83,899 (82,384)	92,619 (67,216)	165,945 (116,039)
Productivity loss, patients	0	0	103	0	0	0	0
Early retirement, patients	0	0	13,726	4866	1023	1766	0
Labor productivity losses (SD)	0	0	13,830 (17,853)	4866 (6282)	1023 (2663)	1766 (6602)	0
Total costs	79,323 (43,081)	25,993 (44,152)	209,420 (317,231)	24,520 (20,654)	84,921 (82,401)	94,385 (66,613)	165,945 (116,039)

All adult patients were of working age in the five countries ($n = 46$), however only nine patients (20 %) were employed and 16 (35 %) were on disability pension. One patient from Germany had been on sick leave (22 days), hence this type of productivity-related cost appeared only in that study sample. Unemployment occurred solely in Italy (three out of 18 adult patients) and Germany (one out of 14). In Hungary, all adult MPS patients were on disability pension (4/4) and in Germany half were (7/14). As a consequence, the highest average annual labor productivity losses occurred in these two countries (Table 2).

It is worth noting that the distribution of costs across cost categories varied substantially between countries with similar total annual costs. For instance, although we found rather similar average total annual cost per patient in Italy and Spain (€84,921 and €94,385, respectively), the percentage of informal care costs was higher in Spain. The difference in cost repartition despite similar mean total costs is even more notable between France and Hungary (total costs of €25,993 and €24,520 per patient per year, respectively), with informal care and productivity-related costs dominant in Hungary but insignificant in France (Fig. 1).

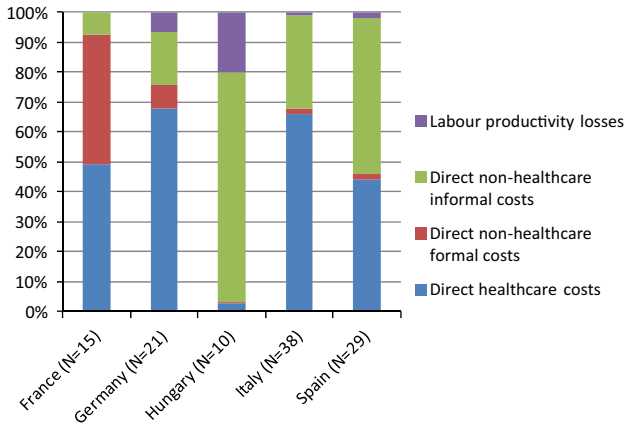

Fig. 1 Distribution of costs across cost categories in five European countries

When looking specifically at the costs incurred by adults (46 patients), which included data from Spain, France, Hungary, Germany, Sweden, and Italy (no adult patients from Bulgaria), mean annual costs ranged from €275 per patient in France to €280,932 in Germany (Table 3). Direct healthcare costs ranged from €275 per patient in France to €206,283 in Germany and direct non-healthcare costs

Table 3 Cost-of-illness in mucopolysaccharidosis adult patients (mean annual costs per adult patient in euros, year 2012)

Costs € 2012	Spain ($N = 6$)	France ($N = 2$)	Bulgaria ($N = 0$)	Hungary ($N = 4$)	Germany ($N = 14$)	Sweden ($N = 2$)	Italy ($N = 18$)
Drugs	7319	0	–	0	182,467	0	13,397
Medical tests	634	275	–	58	158	974	250
Medical visits	1362	0	–	73	6714	2122	1663
Hospitalizations	510	0	–	0	2171	707	2588
Health material	2031	0	–	311	11,973	4807	2822
Healthcare transport	4	0	–	0	2800	45,527	0
Direct healthcare costs	11,859	275	–	442	206,283	54,137	20,719
Professional carer	3727	0	–	0	386	146,535	0
Non-healthcare transport	77	0	–	22	573	106	281
Social services	1276	0	–	0	14,404	54,729	1200
Main informal carer	29,364	0	–	19,242	28,422	0	15,535
Other informal carers	9928	0	–	7858	10,119	0	7050
Direct non-healthcare costs	44,373	0	–	27,121	53,905	201,371	24,066
Direct costs	56,232	275	–	27,563	260,187	255,507	44,785
Productivity loss patients	0	0	–	0,	155	0	0
Early retirement patients	8534	0	–	12,165	20,590	0	2159
Indirect costs	8534	0	–	12,165	20,745	0	2159
Total costs	64,766	275	–	39,728	280,932	255,507	46,945

ranged from €24,066 per patient in Italy to €201,371 in Sweden (Table 3).

For the pediatric patients (74 patients from Spain, France, Bulgaria, Hungary, Germany, Sweden, and Italy), mean annual costs ranged from €14,381 per patient in Hungary to €119,100 in Italy (Table 4). Direct healthcare costs ranged from €819 per patient in Hungary to €87,693 in Italy and direct non-healthcare costs ranged from €13,562 per patient in Hungary to €53,179 in Germany (Table 4).

Patient- and caregiver-reported outcome measures are presented in Table 1. The EQ-5D utility scores (TTO tariff) were calculated for adult patients only and mean scores ranged from 0.134 (Hungary) to 0.433 (Germany), reflecting rather poor general health status among MPS patients in all countries. For comparison, the population norm is much higher even in the oldest age group in Hungary (≥85 years, mean 0.63) [27].

Assessment of general health status on the VAS resulted in better scores than with the EQ-5D in all eight countries; however, the difference was remarkable only in Hungary, Italy, and Spain. The mean VAS score for caregivers was lower in Italy, Spain, and Germany than in Hungary, despite the similar average age. Results on the BI reflected substantial disability of MPS patients in all eight countries. We obtained data from ≥10 caregivers on the ZBI in Germany, Italy, and Spain and found similar average scores (Table 1).

Discussion

In this study, we used a cross-sectional survey to assess MPS-related costs from a societal perspective in seven EU countries. The HRQOL of patients and their caregivers was also studied using standard questionnaires. Responses were obtained from 120 patients and 66 non-professional caregivers. The great majority of patients (86 %) were from four large countries (France, Germany, Italy, and Spain), whilst a reasonably sized sample was obtained only in Hungary for the Central and Eastern European (CEE) region. The percentage of children across these five countries varied from 33 to 87 % and the proportion of females from 30 to 53 %, reflecting substantial heterogeneity of the samples. All MPS types and subtypes were represented in the overall sample, however, the highest patient rates were observed in MPS type III (Sanfilippo syndrome, $N = 50$, 43 %) and MPS type II (Hunter syndrome, $N = 32$, 27 %).

For the evaluation of cost-of-illness, only results from the five countries with at least ten patients were considered. The total average annual cost per patient was highest in Germany (€209,420). Results were similar in Italy and Spain (€84,920 and €94,385, respectively) and at a lower level in France and Hungary (€25,990 and €24,520, respectively). Differences in unit costs and utilization rates can be detected. Higher unit costs of disease-specific drugs, day admissions, and transportation by ambulance partly

Table 4 Cost-of-illness in mucopolysaccharidosis paediatric patients (mean annual costs per paediatric patient in euros, year 2012)

Costs € 2012	Spain ($N = 23$)	France ($N = 13$)	Bulgaria ($N = 2$)	Hungary ($N = 6$)	Germany ($N = 7$)	Sweden ($N = 3$)	Italy ($N = 20$)
Drugs	39,270	5	46,662	24	60	22,527	78,934
Medical tests	634	275	50	58	158	974	250
Medical visits	2700	1218	343	154	7338	15,527	1737
Hospitalizations	6772	12,057	0	297	4886	10,604	5949
Health material	170	1219	314	285	777	1969	823
Healthcare transport	1	4	0	0	0	4124	0
Direct healthcare costs	49,546	14,777	47,369	819	13,218	55,725	87,693
Professional carer	0	480	22,461	0	0	10,467	1430
Non-healthcare transport	155	54	143	168	244	1275	242
Social services	849	12,396	1696	1	20,278	6870	97
Main informal carer	30,750	1944	7653	11,733	30,313	31,900	19,200
Other informal carers	20,811	297	0	1660	2343	0	10,438
Direct non-healthcare costs	52,565	15,172	31,954	13,562	53,179	50,512	31,407
Direct costs	102,111	29,950	79,323	14,381	66,397	106,237	119,100
Productivity loss patients	0	0	0	0	0	0	0
Early retirement patients	0	0	0	0	0	0	0
Indirect costs	0	0	0	0	0	0	0
Total costs	102,111	29,950	79,323	14,381	66,397	106,237	119,100

explain the higher total cost-of-illness in Germany. Based on the economic characteristics of the countries and similarities in unit costs, we expected that costs in France would be closer to Italy and Spain than to Hungary. However, in France, drug utilization was insignificant and no costly disease-specific drugs were used. Moreover, costs related to loss of productivity (in paid work) were zero in the French sample, as the rate of children was highest in this country (87 %) and the two female adult patients reported on the employment-status question that they were staying at home.

Despite the differences in total costs across the five countries, the proportion of direct healthcare costs was similar in France, Germany, Italy, and Spain (from 44 to 68 %) and was much lower only in Hungary (3 %). In contrast, the proportion of costs related to informal care was the most significant in Hungary (77 %). The proportion of direct non-healthcare formal costs (involving the costs of professional caregivers, non-healthcare transport, and social services) was remarkable only in France (43 %).

In adults, drugs, medical visits, health material, direct non-healthcare formal and informal care represented the vast majority of costs, while in children, drugs, medical visits, hospitalizations and direct non-healthcare informal care were predominant.

We found that MPS had a significant impact on the HRQOL of patients and their caregivers regardless of the country. In terms of walking around, performing self-care and carrying out usual activities, 21, 30, and 29 %, respectively, of the MPS patients were unable to do these things. Moreover, 12, 7, and 8 %, respectively, had severe difficulties in these areas, reflecting the strong debilitating character of MPS. A substantial number of MPS patients reported moderate pain or discomfort (47 %) and anxiety or depression (34 %). Utility scores deduced from the EQ-5D were clearly lower than the age-matched population norms in all countries. Loss of functional abilities was also confirmed by the Barthel index, with an average score in the severe dependence range in all countries.

A significant proportion of patients needed help from others to perform everyday activities and we obtained completed questionnaires from 66 informal caregivers. All were close family members of the patients. Assessment of informal care is a major challenge in all cost-of-illness studies, although its importance cannot be overestimated in chronic diseases [20]. The task is even more complex if paediatric patients are involved as it is difficult to differentiate between age-related and disease-related needs. In this study, we adopted the conservative strategy of censoring to a maximum of 16 h per day (112 h per week). By doing this, we aimed to minimize the problem described in the literature as joint production and to offer plausible values for the estimation of informal care time.

Overall, knowledge on cost-of-illness and the HRQOL of MPS patients and their close relatives has been very limited in the international literature to date. A report carried out by the London School of Economics and Political Science within the BURQOL-RD project

identified only one study that detailed costs and effectiveness of enzyme replacement therapies for MPS type I, and another report for MPS type VI [14]. The annual cost of drug treatment with laronidase for MPS type I ranged from €130,451 for a child of 20 kg to €456,581 for an adult of 70 kg (prices converted to 2010 Euros). Considering the full patient cohort ($n = 41$) of the national Society for Mucopolysaccharide Disease registry, the total national annual cost for drugs alone for MPS type I is estimated to be GBP 5.1 million in the UK [28]. Schlander and Beck (Germany) estimated the annual cost of enzyme replacement therapy (galsulfase) for MPS type VI to be an average of €350,000 per patient in 2008 (equivalent to €369,355 per patient at 2010 prices) assuming an average patient weight of 25 kg [11].

To our knowledge, only two studies have been published reporting EQ-5D results for MPS patients. Hendriksz et al. highlighted that in patients with MPS type IV Morquio A syndrome, high wheelchair reliance significantly reduced HRQOL, as mean utility values were 0.85, 0.58, and 0.06, respectively, in adults not using a wheelchair, using a wheelchair only when needed and always using a wheelchair. Moreover, employed adult patients had better EQ-5D-5L scores than unemployed patients (mean 0.64 vs. 0.28 respectively) [29]. In a study by Guffon et al., the EQ-5D scores of patients with MPS type II and idursulfase treatment were well below those for the reference (control) populations [30].

Some limitations of the study have to be mentioned. The recruitment of patients was carried out by patient organizations and patients with no contact with POs could therefore not be invited to participate in the study. We relied on patients' self-reports, thus there was no medical confirmation of disease-related data (e.g., disease subtypes, drugs, etc.). In some countries, only a very limited number of patients completed the questionnaire, hence not enough data were obtained to perform analyses and draw conclusions. Being aware of these shortcomings of the study, we believe that our research provided useful and significant information on the disease burden and HRQOL of patients with MPS.

Conclusions

To our knowledge, this study is the first to have assessed cost-of-illness and the HRQOL of patients with MPS in a multi-country survey. Our results highlight that the socio-economic burden of MPS is substantial in diverse regions of Europe both in terms of societal costs and deterioration of HRQOL.

Our research is pioneering in several aspects. Firstly, it was the first to assess healthcare and non-healthcare direct costs and labour productivity losses related to MPS. Secondly, alongside the assessment of HRQOL of MPS patients, the health status of the main informal caregiver was also explored. Thirdly, both the Barthel index and the Zarit burden interview questionnaires were used for the first time in MPS in this research. Fourthly, this was the first analysis of the relationship between diverse HRQOL outcomes and informal care time. Last, but not least, our study aimed to facilitate and promote further investigation in MPS and other rare diseases. We believe that a more extensive knowledge of the clinical and economic aspects of rare diseases can provide significant support for the improvement of patient care. Our research aimed to serve that goal.

Acknowledgments The authors wish to thank: National Alliance of People with Rare Diseases (NAPRD), Bulgaria; Alliance Maladies Rares, France; ACHSE, Germany; Hungarian Federation of People with Rare and Congenital Diseases (RIROSZ), Hungary; Federazione Italiana Malattie Rare (UNIAMO), Italy; the Consulta Nazionale delle Malattie Rare, Italy; Rare Diseases Sweden; Federación Española de Efermedades Raras (FEDER), Spain; Rare Disease UK and Rare Diseases Europe (EURORDIS); National Mucopolysaccharidosis Association, Bulgaria; Gesellschaft für Mukopolysaccharidosen e.V., Germany; Magyar Mukopoliszaccharidózis Társaság, Hungary, A.I.MPSAssociazione italiana mucopolisaccaridosi e malattie affini, Italy; Asociación Española de las Mucopolisacaridosis y Síndromes Relacionados and Asociación Valenciana de Sanfilippo i altres mucopolisacaridosis, Spain.

Compliance with ethical standards

Funding Supported by the Social/Economic Burden and Health-Related Quality of Life in Patients with Rare Diseases in Europe Project, which received funding from the European Union within the framework of the Health Programme [Grant A101205]. The Executive Agency of the European Union is not responsible for any use that may be made of the information contained herein.

Conflict of interest The authors declare that they have no conflicts of interest.

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