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An online survey of burden of illness in families with mucopolysaccharidosis type II children in the United States

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1. Introduction

Mucopolysaccharidosis type II (MPS II or Hunter's syndrome) is a rare X-linked recessive genetic disease caused by lack of the enzyme iduronate sulfatase, which leads to an accumulation of glycosaminoglycans (GAGs) throughout the body. As an X-linked disorder, MPS II occurs almost exclusively in males, although rarely females have been diagnosed. The disease has both severe and attenuated presentations, but there is a wide spectrum of clinical severity [1]. Severity of disease is usually based on the presence or absence of progressive neurological involvement and behavioral problems [2–4]. In severe MPS II children, coarse facial features, short stature, skeletal deformities, joint stiffness, cardiopulmonary disfunction, and neurocognitive deficits are typical. Disease onset occurs between two and four years of age, with somatic signs such as chronic ear infections, facial dysmorphism, enlarged tongue and tonsils, enlarged liver/spleen, and joint stiffness [2,5–7]. Cognitive development and adaptive ability begin to decline around 4 years of age, accompanied by severe speech and language delay [5,8]. Hearing loss begins around the age of 2 years, which affects speech and language development [2,9]. In addition, abnormal behavior such as hyperactivity, frustration, and impulsivity starts around 4 years of age [2,8].

Current treatment for MPS II in the United States (US) consists of enzyme replacement therapy (ERT), idursulfase, given intravenously (IV) usually on a weekly basis. The results of a phase II/III placebo-controlled clinical study of ERT with idursulfase demonstrated that weekly infusions produced significant improvements based on the six-minute walk test and pulmonary function as measured by the percentage of predicted forced vital capacity (FVC) [10]. However, these trials enrolled children with higher functioning who were likely not neuronopathic. Therefore, while ERT was shown to improve endurance and pulmonary function in these trials, the long-term effect of ERT on neurocognitive function specifically in neuronopathic children is not known, especially since IV ERT does not cross the blood-brain barrier.

As severe MPS II is a chronic and debilitating condition, families with MPS II children experience significant economic, social, and humanistic burdens. Healthcare utilization, educational needs for the child, and caregiver burden in the US have not been well documented in the literature. A few non-US studies have assessed the burden of a variety of MPS types in terms of healthcare use, cost of care, caregiver time, and impact on work and family life. In France, a study assessed healthcare utilization in 51 MPS type II patients, primarily (69.2%) those with severe subtype [11]. Among respondents, 51% of the patients had been admitted to the hospital in the last 12 months for reasons associated with their disease, with a mean length of stay of 10.4 days (range 1–120 days), and 25.5% had been to the emergency room a mean number of 2 times, primarily for respiratory symptoms. In a 12-month period, 49% had seen an ear, nose and throat specialist, 30% had seen an orthopedic surgeon, and 29% had seen an ophthalmologist at least once. Eighty-four percent had seen a physical therapist (for an average of 7.4 times/year) and 40% had seen a speech therapist (for an average of 5.3 times/year). More than two-thirds (72.5%) reported they used social services assistance for help with home care aides and financial assistance.

A study conducted by Pentek et al. in seven European countries assessed disease burden in 120 patients (74 children and 46 adults) and 66 caregivers among the MPS community, across many disease types, as part of a project referred to as BURQOL-RD (www.burqol-rd.org) [12]. Most caregivers (65 of 66) responding to the survey were the parent of the patient. These caregivers reported spending similar amounts of time per week caring for adult patients with MPS as the time reported caring for children with MPS (52 vs 51 h respectively), indicating that challenges to perform activities of daily living likely continue throughout life.

The purpose of this study was to gather, via an online survey, real-world data from families in the US caring for sons with severe MPS II to quantify children's healthcare resource use, to describe educational needs, and to assess parents' work productivity and caregiving time.

2. Methods

Parents living in the US with children younger than 18 years of age who had severe MPS II were invited to complete an online survey between December 2017 and January 2018 via ConnectMPS, an

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advocacy-supported patient registry of MPS, mucolipidosis and related glycoprotein disease families. Invitae, the parent company of ConnectMPS, recruited its members through the registry, and the National MPS Society, a patient advocacy organization, assisted with recruitment through their newsletter. Honoraria were given to families who completed the survey. An Institutional Review Board approved the study, and parents were required to provide electronic consent prior to completing the survey. Neither patient nor family identifiers were gathered in the survey itself so that respondents remained anonymous to the survey sponsor. Severity of disease was not defined in the study; parents were asked to indicate whether their child had been diagnosed with severe form of the disease.

The online survey was modified from the BURQOL-RD project (Pentek M, 2016) to be relevant for US residents and to be more specific to MPS II. The survey was made available through the ConnectMPS registry platform so that only registered members had access and was designed to take less than an hour to complete.

3. Results

A total of 74 families responded, and, of those, 24 parents reported that their son had received experimental intrathecal (IT) ERT in the last month, which is not an approved therapy in the US. Therefore, the following results did not include these 24 children in analyses, as the intent of the study was to describe children on standard care. The remaining 50 children's demographics are shown in Table 1.

Educational status: Parents were asked to describe their child's current school status. Of the 50 children, 43 were ages 5 and older, and of those, only 3 (7%) were attending school with no special support. Fig. 1 shows current school status of the 43 children 5 years of age and older.

Healthcare services: Table 2 shows outpatient healthcare resource use among the 50 children. Of these, 82% had received IV ERT in the last month. Parents were asked to recall total number of medical visits in the last six months - these were doubled to estimate annual use per patient (PPPY = per patient per year) among the 50 children. The most common types of specialists seen were cardiologists (1.43 visits PPPY), gastroenterologists (1.24 visits PPPY), and neurologists/pulmonologists (0.84 visits PPPY). Thirty-nine visits PPPY were estimated for behavioral, physical, occupational, and speech therapists, and eight visits PPPY were estimated for pediatricians or family practice physician visits.

The survey also gathered information on the frequency of emergency room/urgent care visits in the previous year. Nineteen children (40%) had sought urgent or emergency care at least once in the past year, for a total of 2.25 PPPY. Parents were asked to recall day surgeries and overnight hospitalizations in the previous 12 months. Twenty-one (44%) children had one or more day surgeries in the prior year, for a total of 0.65 surgeries PPPY. The most common reasons included removal/replacement of medical devices and tests, ear/nose/throat procedures, and orthopedic/carpal tunnel procedures. Twenty-eight (58%) children had been hospitalized at least once in the last year, for a total of 1.06 admissions PPPY averaging 6.02 days per stay. The most common reasons for overnight hospitalizations included surgical procedures and airway issues/respiratory infections. Table 3 summarizes these data.

Parents were asked to rate their satisfaction at the time of survey with the healthcare services their child received, using a numeric scale of 1 to 7, indicating very unsatisfied [1] to very satisfied [7]. Responses from the parents of 50 children are shown in Table 4. Thirty-three (66%) parents reported feeling mostly or very satisfied with the healthcare services their child received, 10 (20%) were somewhat satisfied or neutral while 7 (14%) indicated they were somewhat to very unsatisfied.

Table 1
Child demographics.

Description	*N* = 50
Current Age (Years) - Mean (Std)	9.4 (4.5)
Age at Diagnosis* (Years) – Mean (Std)	2.3 (1.3)
US Region of Residence – n (%)	
South	24 (48)
Midwest	12 (24)
West	8 (16)
Northeast	6 (12)
Healthcare Insurance Plan – n (%)	
Private/Commercial Only	16 (32)
Medicaid/CHIP Only	22 (44)
Private + Medicaid	10 (20)
Other or Combinations	2 (4)

* 1 missing; CHIP = Children's Health Insurance Program; std. = standard deviation.

4. Caregiver burden

Forty-nine (98%) of the parents said they were the child's primary caregiver. Six (12%) primary caregiving parents were between the ages of 18–29 years, 30 (61%) were between 30 and 39 years, 10 (20%) were between 40 and 49 years, and 3 (6%) were between 50 and 59 years. Among the parental caregivers, five were employed part time, eleven were employed full time, and 33 were stay-at-home parents or unemployed. Five (31%) of the 16 employed caregiving parents reported that they had reduced their work hours per week over the last six months to care for their child and 13 (81%) stated they had difficulty performing work tasks in the last six months due to their child's illness. Table 5 summarizes work status of the primary caregiving parents.

The survey requested an estimation of the number of hours per day the primary caregiver spent on activities for their child. The results are shown in Table 6. On average, caregivers reported spending nearly 11 h a day providing care to their child.

5. Discussion

Studies to date have described continued needs of children with MPS II with regard to healthcare and educational services. Because IV ERT, the only approved treatment for severe MPS II in the US, does not cross the blood-brain barrier, children experience life-long health problems and cognitive challenges that may require frequent visits to specialists and costly hospitalizations [11,12]. In this study of 74 families with severe MPS II children, 24 children had received IT ERT in the previous 30 days, an experimental product not approved in the US. Therefore, analyses were conducted on the remaining 50 children to describe burden of current standard of care specifically. Of the 50 children, 82% had received IV ERT in the previous month. Among the school-aged children, almost all required special support or attended a special educational program; only 3% attended school with no support. This finding appears to confirm that severe MPS II children in the US have neurocognitive and/or behavioral challenges that require modifications to traditional educational settings.

Healthcare needs among children in this study were similar to those reported by a study in France [11] in that both French and US families reported frequent visits to medical specialists. In this US study, parents reported frequent visits to cardiologists (24% of children with 1 or more visits), gastroenterologists, pulmonologists, and neurologists (18% of children with 1 or more visits). In comparison, Guffon et al. reported that 49% of the children had seen an ear, nose and throat specialist, 30% had seen an orthopedic surgeon, and 29% had seen an ophthalmologist at least once in the previous 12 months. The differences in specialty types might be due to the populations studied: The French study combined attenuated and severe children included both children and adults. Similarly, US families reported that 40% of the children had sought emergency services at least once in the previous year, and 58% had been hospitalized at least once in the last year. In comparison,

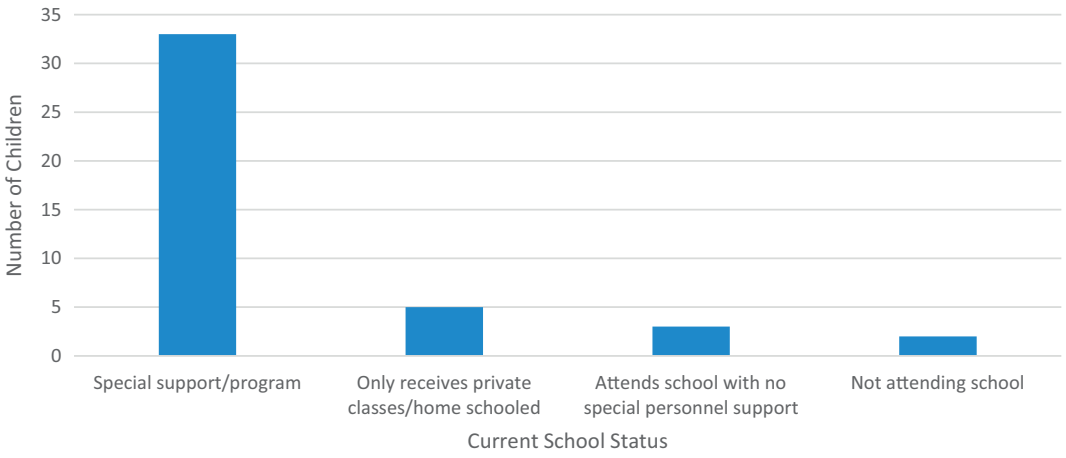

Fig. 1. School Status Among Children 5 Years and Older ($N = 43$).

Table 2
Estimated outpatient healthcare resource use among 50 children.

Resource	N = 50
IV ERT in last 30 days? - n (%)	
No	9 (18%)
Yes	41 (82%)
Specialist Visits PPPY*	8.95
Top 5 Specialists PPPY	
Cardiologist	1.43
Gastroenterologist	1.27
Neurologist	0.86
Pulmonologist	0.86
General Surgeon	0.77
Other Professional Visits PPPY**	
BT/OT/PT/ST	39.21
Family Practice/Pediatrician	8.0
Genetic Counselor	1.75
Dentist	0.95
Psychologist	0.58

BT/OT/PT/ST = behavioral/occupational/physical/speech therapy; ERT = enzyme replacement therapy; IV = intravenous; PPPY = estimated per patient per year.
* $N = 44$ (6 missing); ** $N = 48$ (2 missing).

Table 3
Outpatient emergency, day surgery, and inpatient hospital services per year*.

Resource	N = 48
ER Visits	
N (%) Children with One or More Visits	19 (40%)
Visits PPPY	2.25
Day Surgeries	
N (%) Children with One or More Day Surgeries	21 (44%)
Surgeries PPPY	0.65
Hospitalizations	
N (%) Children with One or More Inpatient Hospitalization	28 (58%)
Admissions PPPY	1.06
Inpatient Days PPPY	6.02

ER = Emergency Room; N = number; PPPY = estimated per patient per year.
* N = 48 (2 missing).

Table 5
Primary caregiver work statistics ($N = 49$).

Currently employed?					
No – n (%)	33 (67%)				
Yes – n (%)	16 (33%)	Reduced hours in the last 6 months to care for child?		Difficulty performing work tasks due to child's illness?		Days off from work in the last 6 months to care for child?	
		Yes – n	5	Yes – n	13	0 days – n	3
		No – n	11	No – n	3	1–6 days – n	5
						7+ days – n	8

Table 6
Caregiver hours spent on daily activities for child, by age of the child.

Daily activities, hours spent	n	Mean	St Dev	Median
Basic hygiene, dressing or changing the child	47	1.9	2.2	1
0–10 years	25	2.5	2.9	2
11–17 years	22	1.4	0.7	1
Bathing or showering the child	47	1.1	0.9	1
0–10 years	25	1.2	1.3	1
11–17 years	22	1.0	0.3	1
Feeding the child	47	1.9	2.0	2
0–10 years	25	2.1	2.7	2
11–17 years	22	1.9	0.9	2
Helping the child to move	45	2.9	4.9	2
0–10 years	24	3.8	6.7	1.75
11–17 years	21	2.0	1.4	2
Cooking and preparing special meals	47	1.8	1.2	2
0–10 years	25	1.7	1.4	1.5
11–17 years	22	2.0	0.7	2
Administering drugs/treatments	47	1.7	1.7	1
0–10 years	25	1.9	2.0	1
11–17 years	22	1.6	1.2	1
TOTAL* Hours Per Day	47	10.9	8.7	9
0–10 years	25	13.0	11.0	10
11–17 years	22	8.8	3.6	8

* May be greater than 24 hours.

Table 4
Parent Satisfaction with Child's Healthcare Services ($N = 50$).

Very unsatisfied	Mostly unsatisfied	Somewhat unsatisfied	Neutral	Somewhat satisfied	Mostly satisfied	Very satisfied
2 (4%)	1 (2%)	4 (8%)	2 (4%)	8 (16%)	24 (48%)	9 (18%)

Guffon et al. reported that 25.5% of patients had sought emergency services and 51% had been admitted to hospital in the previous 12 months. The children in this US study also saw therapists (speech, behavioral, physical) almost once a week (39 visits PPPY), again indicating that current therapies do not sufficiently address the medical needs of these children.

Finally, parents in this survey who reported to be their child's primary caregiver spent significant time every day providing care to their child. In comparing parental time for younger (0–10 years) children and older (11–17 years) children, the expectation might be that older children require less parental time. However, this study did not appear to demonstrate this. For example, all children required approximately an hour per day for bathing/showering. Parents spent about an hour per day administering drugs or other treatments and about two hours a day helping their children move about.

Limitations to the study exist, primarily as general limitations of any self-reported online survey. While resources needed for distribution and administration are lessened (in comparison to oral interviews or paper surveys), and parents could start and stop the online survey as their time permitted, some respondents left questions unanswered, resulting in missing data. The survey did not include options for adding free-text comments or additional information other than the questions being asked. Parents were asked to recall healthcare resource use from as recently as a month prior to as long as 12 months prior. Finally, this online survey afforded no clinical verification that the children had a confirmed diagnosis of severe MPS II, or confirmation that the respondent was the parent or legal guardian of a child, other than the respondent's consent to participate and indication that they were a parent of a severe MPS II child.

6. Conclusion

While the devastating effects of MPS II on children are well documented, the impact on families caring for these children has not been extensively studied in the US. The findings from this survey demonstrate that even after initiation of enzyme replacement therapy (which has prolonged life and reduced morbidity), significant clinical and educational needs remain. Similarly, the impact of severe MPS II on caregiver productivity remains high. Caregiver-focused tools related to the burden of illness specific to various disease states are warranted and consistent with a growing interest among oversight agencies around the world to incorporate the patient experience into drug development programs. Likewise, the output from these tools could help the healthcare community to design support programs that better meet the needs of patients and their families. Future research might assess how burden of illness is impacted by socioeconomic status, education, and access to support systems, and whether these factors impact clinical outcome and quality of life. In conclusion, burden of illness in MPS II is quantifiable in terms of the child's healthcare resource utilization, caregivers' time, and caregiver work productivity, is significant, and does not appear to diminish as the child ages. Therefore, enormous opportunity exists for new therapies and support strategies to measurably reduce the family burden of illness in MPS II.

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