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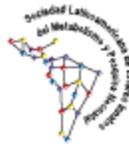
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# The Burden Endured by Caregivers of Patients With Morquio A Syndrome: Results From an International Patient-Reported Outcomes Survey

Christian J. Hendriksz, MD<sup>1</sup>, Christine Lavery<sup>2</sup>, Mahmut Coker, MD<sup>3</sup>, Sema Kalkan Ucar, MD<sup>3</sup>, Mohit Jain, PhD<sup>4</sup>, Lisa Bell, PhD<sup>5</sup>, and Christina Lampe, MD<sup>6</sup>

## Abstract

This international survey performed by direct personal interview or mail evaluated the global burden among primary caregivers of patients with Morquio A syndrome. Collected outcomes included self-reported time spent on caregiving, proportion of daily activities (from the Mucopolysaccharidosis Health Assessment Questionnaire) requiring caregiver assistance, and how the patient's age and wheelchair use affect these. In addition, the impact of caregiving on the caregivers' relationship with family and friends, physical and mental health, and employment status and income was evaluated. Caregiver burden increased with disease progression. Adult patients always using a wheelchair required substantially more caregiving time and complete assistance with a larger proportion of daily activities than more mobile patients. In children, this was less apparent. Caregivers suffered physically and emotionally and their family and social life and financial situation were considerably impacted. Improvements in patient mobility may substantially reduce the level of caregiver support and the burden of caregiving.

## Keywords

Morquio A syndrome, mucopolysaccharidosis IV, caregivers, disease burden, quality of life, wheelchairs

## Introduction

Morquio A syndrome, also known as mucopolysaccharidosis (MPS) type IVa, is an ultra-rare autosomal recessive lysosomal storage disorder caused by a deficiency in the enzyme N-acetylgalactosamine-6-sulfatase (GALNS).<sup>1</sup> More than 180 different mutations have been identified in the gene encoding GALNS (with the most common allele having an estimated prevalence of 9%), which likely explains the considerable heterogeneity and severity of clinical manifestations based on the residual GALNS activity.<sup>2</sup>

Patients with Morquio A syndrome typically present with progressive bone and joint problems that lead to short stature, pain, arthritis, fatigue, and increasing disability.<sup>3</sup> The affected patients will sooner or later need walking aids and/or a wheelchair<sup>4-6</sup> (Figure 1). Other nonskeletal organs may also be involved, often leading to significant morbidity such as respiratory compromise, obstructive sleep apnoea, valvular heart disease, hearing and visual impairment, hepatomegaly, and dental abnormalities.<sup>5,6</sup> Patients with Morquio A syndrome may survive until late childhood only.<sup>6</sup> Risks of death are clearly

correlated with the severity and effective management of cervical myelopathy and respiratory and cardiac diseases.<sup>7</sup>

## Background

Patients with Morquio A syndrome are heavily dependent on their caregivers to perform activities of daily living (ADLs).

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**Figure 1.** Pictures of patients with Morquio A syndrome.

It can be expected that this has a negative impact not only on the quality of life (QoL) of the patients but also on the QoL of their caregivers and close family. Currently, no data exist on the impact of Morquio A syndrome on the QoL of caregivers. However, several studies have shown that caregivers of patients with progressive diseases causing severe physical disability tend to have reduced QoL compared with the normal working-age population, due to an impact on their physical and psychological well-being, their social life, and their financial situation.<sup>8,9</sup> The QoL of caregivers of patients with multiple sclerosis has been shown to decrease with decreasing functioning of the patient and increasing amount of caregiving.<sup>10,11</sup> Similarly, caregivers of patients with Pompe disease reported more caregiving hours with higher disease burden and a higher burden for caregivers of patients depending on a wheelchair.<sup>12</sup>

## Aim

The present report discusses the caregiver results from a survey evaluating patient-reported outcomes (PROs; health-related QoL [HRQoL], pain, and fatigue) in children and adults ( $\geq 18$  years) with Morquio A syndrome and the burden of caregiving for these patients. The patient results of this survey have been published previously, showing a profound impact of high wheelchair reliance on the patients' HRQoL.<sup>13</sup> The aim of the caregiver part of the survey was to evaluate the time spent on caregiving, the type of daily activities requiring caregiver assistance, and how these are affected by the patient's age and wheelchair use/mobility level. In addition, it assessed the impact of caregiving on the caregivers' relationship with their family and friends, their physical and mental health, and their employment status and income.

## Methods

### Study Design and Caregiver Selection

This study was a voluntary, single-assessment, cross-sectional, paper-based survey administered in person or by mail via local

staff members of advocacy/support groups of patients with Morquio A syndrome and/or physicians and clinics. The study took place from June 2012 to April 2013. Caregivers were recruited following the enrollment of their family member who had Morquio A syndrome in the PRO survey.

Caregiver burden was evaluated in adult ( $\geq 18$  years old) carers who served as the primary caregiver of at least 1 patient with Morquio A syndrome in 5 countries (Brazil, Colombia, Germany, Spain, and Turkey) with strong patient advocacy/support groups and a relatively fair number of patients. Eligible caregivers had to be able to speak, write, and understand both the verbal and the written language of their country. All caregivers were informed on all pertinent aspects of the study and were willing to participate and complete the surveys. All caregivers who met the study enrollment criteria and completed the survey were included in the analysis.

### Assessments

The caregiver questionnaire contained questions concerning demographics (eg, age and gender), family relationships, and social characteristics (education, employment status, the impact of Morquio A on relationships and finances and support received from family/friends, society, and health care professionals; Appendix 1). These questions were developed jointly by BioMarin Europe Ltd, the UK MPS Society, and some clinical experts treating patients with Morquio A syndrome.

The level of assistance the caregiver had to provide to the patient (complete assistance, moderate assistance, minimal assistance, independent [= no assistance]) to perform the following daily activities was also evaluated according to the patients' mobility level: eating, grooming, bathing, dressing, toileting, chair transfers, car transfers, bed mobility, moving around and climbing stairs. Mobility levels compared for the adult patient population ( $\geq 18$  years) were no wheelchair use, wheelchair use only when needed, and wheelchair use always. Mobility levels compared in children (7-17 years)

were no wheelchair use and wheelchair use (as only one child was always using a wheelchair, the “only when needed” and “always” wheelchair groups were combined to form a “wheelchair use” group). The daily activities were derived from the MPS Health Assessment Questionnaire (MPS HAQ) originally developed for patients with MPS I.<sup>14</sup> The caregivers also reported the time spent on caregiving per day. The Zarit Burden Interview (ZBI) was used to assess the burden experienced by the caregivers of adult patients. The ZBI is a validated and widely used self-reported questionnaire developed for caregivers of older patients, containing 22 items investigating the burden of caring in the following 5 domains: burden in the relationship, emotional well-being, social and family life, finances, and loss of control over one’s life. A higher score indicates greater caring distress.<sup>15</sup> The ZBI global score is the sum of all item scores and may range from 0 (*least burden*) to 88 (*most burden*). A global score between the range of 0 to 21 may be interpreted as little or no burden, 21 to 40 as mild to moderate burden, 41 to 60 as moderate to severe burden, and 61 to 88 as severe burden.<sup>15</sup> Caregivers of adult patients and children were also asked to indicate whether, as a result of caring for patients with Morquio A syndrome, they had clinical (stress, lack of sleep, ulcers, gastrointestinal issues, back pain from carrying) or mental (feeling burdened, anxiety, depression) health issues and whether they received therapy or medicines for their emotional and psychological health. Ethics approval was obtained in Germany, and all caregivers signed an informed consent/assent form. No ethics approval was required in the other countries due to the survey nature of the study.

### Statistical Analysis

The results were analyzed separately for caregivers providing assistance to children ( $\leq 17$  years) or adults ( $\geq 18$  years). Results of caregivers of adults and children were compared between mobility/wheelchair groups: patients never using a wheelchair, patients using a wheelchair only when needed, and patients always using a wheelchair in adults and wheelchair users and nonwheelchair users in children. Due to the limited number of patients in some of the mobility subgroups, most results are presented as descriptive statistics. A t-test was used to evaluate the statistical significance of differences in mean age between mobility/wheelchair groups for the entire patient group (both children and adults).

## Results

### Demographic and Clinical Characteristics

In total, 56 caregivers from 5 different countries completed the survey (Table 1). Most caregivers (82.1%) were mothers of patients with Morquio A syndrome, with a mean age of 42.6 years (range 16-71 years; Table 1). Most (92.9%) parents considered themselves as the primary caregiver and 73.2% cared for 1 patient with Morquio A syndrome (Table 1). However, most of them (80.3%) indicated that they were satisfied/very satisfied with the level of support they received from their

**Table 1.** Demographics and Characteristics of Caregivers of Patients With Morquio A Syndrome.

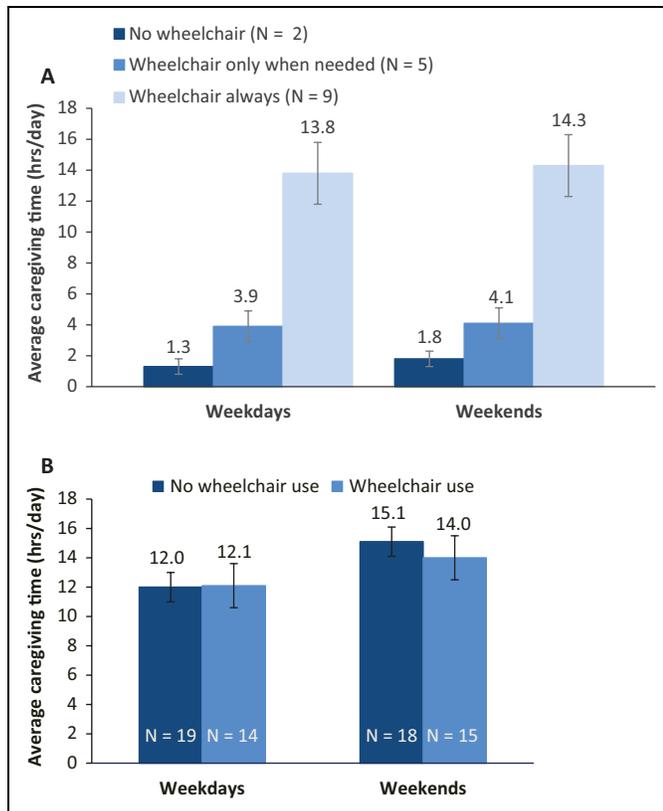
Caregivers (N = 56)	Measure	Outcome
Split by country, n (%)	Brazil	10 (17.9%)
	Colombia	7 (12.5%)
	Germany	23 (41.1%)
	Spain	7 (12.5%)
	Turkey	9 (16.1%)
	Age, years (N = 54)	Mean
	Median	44
	Range	16-71
Gender, n (%)	Female	46 (82.1%)
	Male	10 (17.9%)
Relationship with patient having Morquio A, n (%)	Mother	46 (82.1%)
	Father	9 (16.1%)
	Mother or Father	1 (1.8%)
	Yes	52 (92.9%)
Caregiver considers himself or herself the primary carer of the patient with Morquio A, n (%)	No	4 (7.1%)
	Number of Morquio A patients cared for, n (%)	1
Patients’ age, years (N = 55)	2	15 (26.8%)
	N patients with age reported on	60
	Mean	14.1
	Median	12.5
Number of non-Morquio A children in family, n (N = 42)	Range	1-46
	Mean	1.6
	Median	1
	Range	1-9

partner. The mean age of the patients cared for was 14.1 years (range 1-46 years); two-thirds of the parents cared for children  $\leq 17$  years (N = 37) and one-third for adult patients (N = 19).

### Caregivers’ Time and Support With ADLs Versus Use of a Wheelchair

Information on the use of a wheelchair was available for 17 of the 19 adults and for all 37 children with Morquio A syndrome. Of the 17 adult patients, 2 never used a wheelchair, 6 used it only when needed, and 9 used it always. Of the 37 children with Morquio A syndrome, 22 never used a wheelchair, 14 used it only when needed, and 1 used it always. Wheelchair use increased with age. There were significant differences in mean age between patients not using a wheelchair (9.96 years) and those using a wheelchair sometimes (16.48 years,  $P < .001$ ) or all the time (20.15 years,  $P < .001$ ).

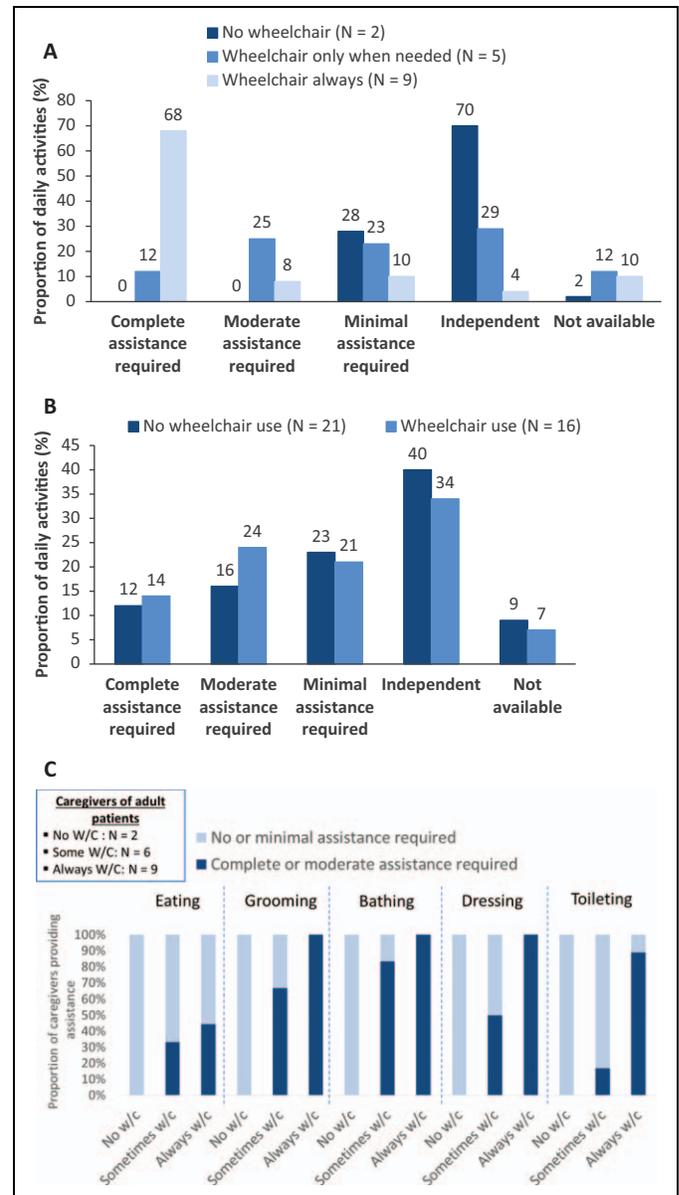
In adults, patients who always used a wheelchair required more care time than the other patients. Indeed, 13.8 hours and 14.3 hours a day of care were given to an adult who always used a wheelchair on weekdays and weekends, respectively, while this time was only 3.9 hours on weekdays and 4.1 hours on weekend days when the wheelchair was used only when needed (Figure 2A). The amount of caregiver time was 1.3 hours on weekdays and 1.8 hours on weekend days for those adult patients who did not use a wheelchair. For children, the



**Figure 2.** Mean number of caregiving hours/day on weekdays and weekends for adults (A) and children (B) with Morquio A syndrome, according to wheelchair use/mobility level.

number of caregiving hours was not affected by wheelchair use (Figure 2B). Caregivers of 2 patients spent more time caregiving than those of 1 patient. However, this difference was not statistically significant.

The proportion of daily activities (as measured by the MPS HAQ) requiring (complete or moderate) assistance from the caregiver was also dependent on wheelchair use/mobility level (Figure 3A and B). The proportion of daily activities that required complete assistance from the caregiver was 68% in those looking after adult patients who always used a wheelchair versus only 12% in those caring for adult patients using their wheelchair only when needed and 0% in those caring for nonwheelchair users (N = 2; Figure 3A). In contrast, although only 4% of the daily activities were performed independently by the adult patients who always used their wheelchair, this was 29% in the “wheelchair only when needed” group and 70% in the nonwheelchair user group. The differences between mobility groups in requirement of assistance with performing daily activities were less apparent for caregivers looking after children with Morquio A syndrome (Figure 3B). When looking at the assistance required for each individual daily activity, the proportion of caregivers providing assistance with each of these activities for adults increased with increasing wheelchair use. All caregivers of adult patients always using a wheelchair needed to provide assistance with grooming, bathing, dressing (Figure 3C), car and tub transfers (Figure 3D), climbing stairs, and using public transportation (Figure 3E). All but 1



**Figure 3.** Amount of assistance required from caregivers for performing daily activities (as measured by the MPS Health Assessment Questionnaire) by adults (A) and children (B) with Morquio A syndrome, according to wheelchair use/mobility level. Proportion of caregivers providing assistance to adult patients for self-care activities (C), transfer (D), and mobility (E) according to wheelchair use/mobility level. W/C indicates wheelchair.

provided assistance with toileting and chair transfers. The proportion of caregivers of children providing assistance with mainly more independent self-care activities (grooming, dressing, and toileting) and car transfers was also higher when children used a wheelchair. However, the difference with nonwheelchair users was relatively small. The largest differences between caregivers of wheelchair and nonwheelchair users were seen for grooming (proportion providing complete/moderate assistance 73.3% versus 45.5%) and car transfers (66.7% versus 27.3%; data not shown).

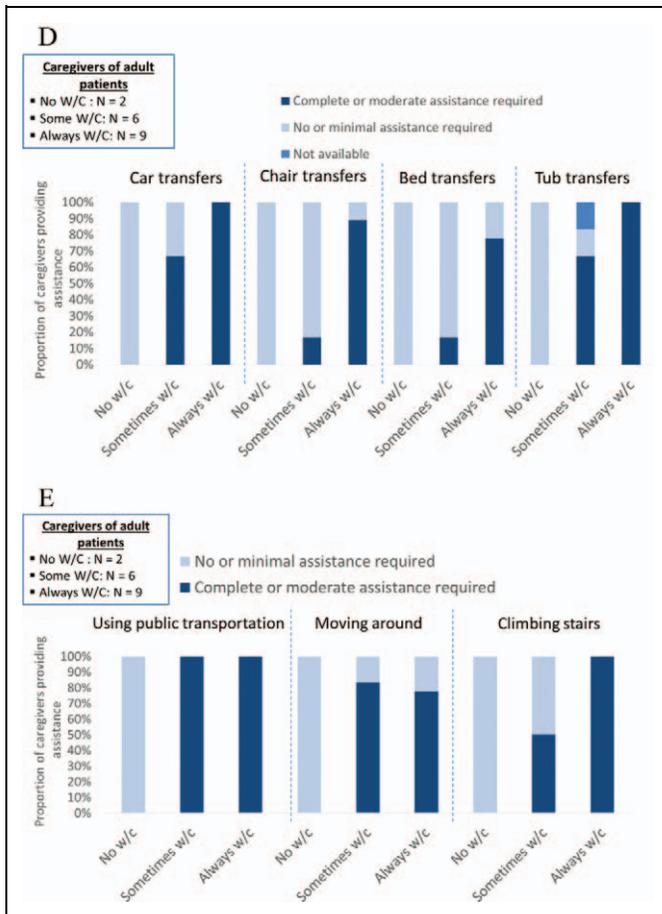


Figure 3. Continued.

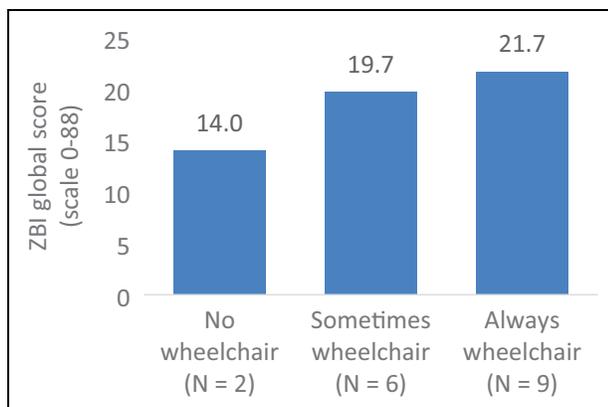


Figure 4. Zarit Burden Interview (ZBI) global score for caregivers of adults with Morquio A syndrome, according to wheelchair use/mobility level.

### Caregiver Burden

The ZBI revealed an increasing burden (ZBI global score) on caregivers of adult patients with increasing wheelchair use (Figure 4).

The questionnaires assessing the impact of caring on clinical and mental health showed that caregivers frequently have back

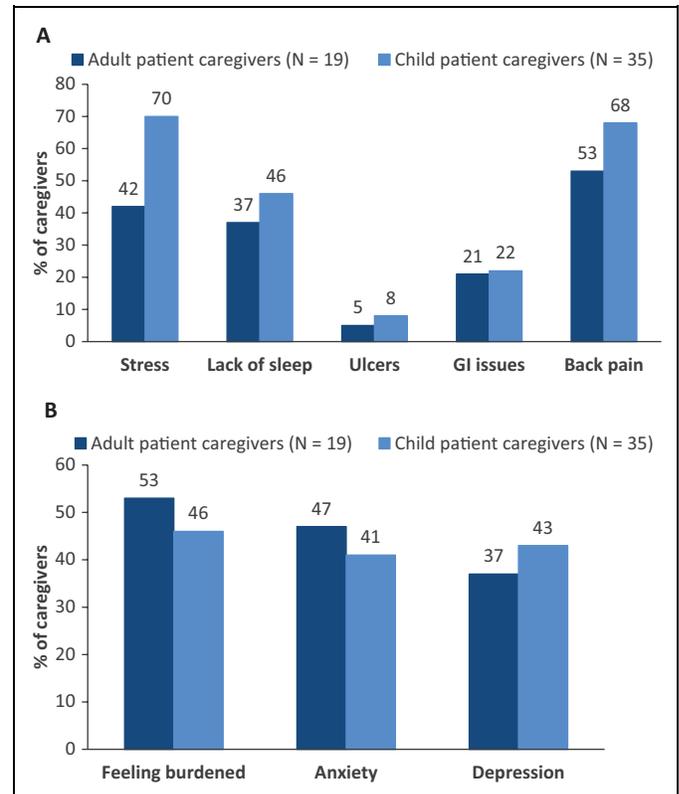


Figure 5. Impact of carrying and caring for adults and children with Morquio A syndrome on caregivers' clinical symptoms (A) and mental health (B). GI indicates gastrointestinal.

pain due to carrying of patients (Figure 5A). In addition, caregivers often reported gastrointestinal problems or ulcers (in 26%-30% of caregivers; Figure 5A). The latter may be due to the higher level of stress reported by the caregivers looking after adult patients (in 42% of caregivers) and, in particular, children (in 70% of caregivers; Figure 5A). Caregivers of patients with Morquio A syndrome also reported having lack of sleep (37%-46% of caregivers; Figure 5A). The mental health of the caregivers was also affected; anxiety was reported by 41% to 47% of caregivers, depression by 37% to 43%, and 46% to 53% of caregivers felt burdened (Figure 5B). Moreover, 26% and 16% of caregivers of adult and child patients, respectively, reported receiving therapy for their emotional and psychological health that included the use of medications (11% and 8%, respectively) due to caring of patient with Morquio A syndrome.

Many caregivers (47.4% of those caring for adults and 64.9% of those caring for children with Morquio A syndrome) felt that the needs of the patient they cared for came before theirs, with 42.9% indicating that they had no time for themselves (Table 2). This also considerably affected the relationship with their partner and other family members: 51.8% had limited time to spend with their direct family, and 46.4% and 30.4% experienced strained relationships with their partner and other family members, respectively (Table 2). Taking care of a patient with Morquio A syndrome also led to a limited social life in terms of relationships with friends and the ability to leave home for

**Table 2.** Impact of Morquio A Disease Experienced by Caregivers.

Impact experienced by caregivers (N = 56)		n (%)
On family life	Limited time spent with spouse or other family members	29 (51.8)
	Strained relationship with partner	26 (46.4)
	Relationship with other family members suffered	17 (30.4)
	Siblings cannot live a "normal" life	12 (21.4)
On social life	Limited/no time to spend with friends	22 (39.3)
	Friendships have suffered	14 (25.0)
	No time for self	24 (42.9)
	Cannot leave home due to caring responsibilities	20 (35.7)
	Received therapy	6 (10.7)
On family finances	No impact	11 (19.6)
	Slight impact	8 (14.2)
	Moderate impact	12 (21.4)
	Significant impact	25 (44.6)
Financial contributions	Move to a more accessible property	13 (27.7)
	Adapt the home	16 (34.0)
	Adaptable car	6 (12.8)
	Wheelchair	8 (17.0)

social activities (Table 2). Moreover, the level of unemployment among caregivers was high. Only 53% of caregivers of adult patients and 46% of caregivers of children were working, and among them only 21% and 11%, respectively, worked full time. Of the 29 (52%) unemployed caregivers, 55% reported that this was due to caring. In the working caregivers, 48% worked restricted hours, 44% had turned down opportunities, and 55% used most vacations for care duties. This had a significant impact on family incomes in 44.6% of caregivers, whereas these families had to face large expenses related to the care for a patient with Morquio A. This was associated with moving or adapting their house (for around 30% of caregivers) or buying an adapted car or a wheelchair (for around 15% of caregivers; Table 2).

## Discussion and Conclusions

With an increasingly aging population in all developed countries, the fundamental role of the caregiver for society, both from a functional and an economical perspective, is stressed more and more. Unlike physicians and nurses, caregivers provide long-term care to elderly people and individuals with a variety of chronic conditions such as dementia, cancer,<sup>16</sup> juvenile rheumatoid arthritis, multiple sclerosis,<sup>17</sup> Duchenne muscular dystrophy,<sup>18</sup> and MPS.<sup>19</sup> However, it is increasingly recognized that caring for a patient is an emotional challenge and causes a significant burden on the life of the caregiver.<sup>16,19,20</sup>

Morquio A syndrome is a progressive disorder that causes a gradual reduction in the patient's functional capacity, mobility, and autonomy. It leads to increasing disability, decreasing mobility, and increasing need for walking aids and wheelchairs, with around 45% to 55% of children<sup>6,13</sup> and 85% to 88% of adult patients requiring a wheelchair.<sup>13</sup> This limits their

independence considerably. It also implies that patients with Morquio A syndrome have an increasing need for assistance with ADLs during their life. This assistance is provided by informal caregivers, which most of the time are their parents. Of the caregivers included in this study, 82% were female. Most caregivers considered themselves as the primary caregiver, but more than 80% of the caregivers indicated that they were satisfied or very satisfied with the level of support they received from their partner. Together, these findings suggest that mothers tend to be more involved in caring for their child with Morquio A syndrome than fathers but that both partners have an important role.

Although our survey included a limited number of caregivers (which should be put into perspective of the ultra-rare nature of the disease) and data are missing for some variables, it confirmed that patients with Morquio A syndrome require a lot of caregiving time and support with daily activities from caregivers. Moreover, it showed that adult patients with Morquio A syndrome who do not use a wheelchair, or use it only when needed, keep their autonomy and consequently require less time for assistance with daily activities than patients using a wheelchair always. In line with these findings, the PRO study showed that employment rates of adult patients varied with the patients' mobility/wheelchair use, i.e. 100% for those always using a wheelchair, 46% for those using it sometimes and 22% for those using it always<sup>13</sup>. Wheelchair use did not affect the number of hours of care given to child patients. This may be explained by the fact that caregiving cannot be distinguished from that provided by parenting, in particular in domains where children are more dependent on their parents such as transfers and mobility. Moreover, most children were not always using a wheelchair and therefore might have kept some level of independence. However, when they become adult, more patients appear to become reliant on a wheelchair and need caregiving support practically all waking hours of the day. In our survey, adult patients required complete assistance from the caregiver for 68% of daily activities. Practically all adult patients who used a wheelchair always required assistance from a caregiver for all daily activities evaluated, whether related to self-care (with the exception of eating), transfer, or mobility. The high impact of wheelchair use on caregivers of adult patients in the present patient group was also reflected by the increasing burden (ZBI global score) with increasing wheelchair use, although less dramatic. The relatively small impact of wheelchair use on the ZBI global score probably indicates that the ZBI, which has been developed for caregivers of older patients, is not a very sensitive assessment tool for caregivers of patients with Morquio A syndrome.

The fact that they needed to provide assistance with all kinds of activities dramatically reduced the time the caregivers had for themselves or for others including their partner, other family members, and friends, which can considerably affect these relationships. Besides the impact on their family and social life, caring for patients with Morquio A syndrome induced pain, stress (with potentially related gastrointestinal problems and ulcers), and sleeplessness. Although the prevalence of back pain is around 18% in the normal population,<sup>21</sup> in this survey 53% to 68% of caregivers reported back pain. Similarly, the

incidence of stress reported by caregivers was much higher than in the normal population (around 4%). Caregivers of children experienced stress more frequently (70%) than those caring for adult patients (42%). This could be related to apprehension of caregivers about the impact of the disease on their children. Analysis of the PRO data exploring the psychological burden of Morquio A syndrome showed that patients seem to adapt and become more determined and less apprehensive as their disease progresses (BioMarin 2014, unpublished data). This adaptation could translate into reduced caregiver burden. The anxiety and depression rates reported by caregivers of patients with Morquio A syndrome (of around 40%) were also considerably increased compared to the normal population in these countries, with prevalence rates ranging between 8% and 12%.<sup>22</sup> Not surprisingly, 16% to 26% of caregivers in the survey reported requiring therapy to better cope with this burden on their emotional and psychological health.

The survey confirmed that caring for patients with chronic disability makes it very difficult for caregivers to find and/or keep a job. In this survey, 52% of caregivers were unemployed compared to August 2013 unemployment rates of 5.3%, 9.3%, 5.5%, 25%, and 8.5% in Brazil, Colombia, Germany, Spain, and Turkey, respectively.<sup>23</sup> Consequently, most of the carers did not work, or worked part time, and their free time and vacation was dedicated to the patient. Therefore, it can be expected that caring for a patient with Morquio A syndrome substantially affects the family income, especially because caring for a patient with Morquio A syndrome is associated with many extra expenses, such as changing or adapting the house and buying an adapted car or a wheelchair.

The caregiver outcomes of this survey support the PRO part,<sup>13</sup> which showed that (continuous) wheelchair use does not only increase the burden of the caregiver but also dramatically decreases the patient's QoL.<sup>13</sup> The HRQoL in patients was assessed through the validated EQ-5D-5L questionnaire with utility values ranging between 1 (*perfect health*) and 0 (*death*). In adult patients always using a wheelchair, the HRQoL utility value (of 0.057) approached a feeling of being dead and was only slightly better than the level reported for patients with multiple sclerosis who are bedridden or are completely immobile (-0.049). It is therefore not surprising that also their caregivers feel extremely burdened, stressed, and depressed.

In conclusion, Morquio A disease places a huge burden on the caregivers of individuals with this disease and considerably affects their QoL, health, family and social life, employment, and finances. Wheelchair use, particularly when it has to be always used, has a profound negative impact on caregiving time and level of caregiver support required by patients with Morquio A syndrome. Small improvements in the patient's mobility (eg, when the wheelchair only has to be used part of the time) may lead to a considerable reduction in the level of caregiver support and in the burden of caregiving.

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### Supplemental Material

The online [appendices/data supplements/etc] are available at <http://iem.sagepub.com/supplemental>.

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