Psychobehavioral factors and family functioning in mucopolysaccharidosis

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Abstract

Background:

We aimed to evaluate the impact of mucopolysaccharidoses (MPS) on family functioning and related factors.

Methods and Results:

Twenty-five families of MPS patients were included. The communication domain in adaptive behavior exhibited mean scores below the cut-off points in MPS II (35.6±24.3) and III (35.0±22.6). The total difficulty score was associated with the communication domain score in adaptive behavior (p=0.012). Parents of patients with MPS III and VI reported lower (47.1±2.7) and higher (77.4±21.6) quality-of-life scores, respectively; however, there was no significant among-group difference. The quality-of-life scores were positively associated with cultural/intellectual domain (p=0.003) and adaptive behavior (p<0.001) scores. Regarding family functioning, the greatest effects were observed in the areas of independence, intellectual/cultural, activity/recreation, and expressiveness. The domain scores did not differ according to MPS type, treatment, or neurological involvement. The organization domain significantly differed (p=0.015) between families diagnosed for <2 years and >2 years. Family functioning in the cultural-intellectual domain was negatively associated with caregiver stress.

Conclusion:

The impact of MPS on family functioning extends beyond physical aspects and encompasses social and emotional dimensions. By promoting coping strategies, facilitating support networks, and recognizing the positive aspects of caregiving, the overall impact of MPS on families can be mitigated.

Background

Mucopolysaccharidoses (MPS) are a group of rare inherited metabolic diseases (IMDs) caused by a lysosomal enzyme deficiency that affects the catabolism of glycosaminoglycans (GAGs). This deficiency causes the accumulation of intracellular substances, leading to cell functional alterations. Depending on the deficient enzyme, MPS can be classified into eight types: MPS I, II, III, IV, VI, VII, IX, and X. All MPS types are chronic, progressive, and multisystem diseases.

MPS has an extremely variable prognosis, influenced by age at onset, speed of disease progression, and age at treatment initiation (enzyme replacement therapy or hematopoietic cell transplantation). IMDs adversely affect the psychosocial well-being of parents. Furthermore, the severity and clinical manifestations of IMDs, including cognitive and motor impairment, are associated with the quality of life of caregivers. This could be attributed to the increased need for support among patients to perform activities of daily living. These added responsibilities can directly affect the family's health and well-
being, disrupting work performance and social life. Furthermore, since most MPS types involve an autosomal recessive pattern of inheritance, parents may have two or three children with the disorder before diagnosing their first child. However, the psychosocial burden of MPS on parents in developing countries remains unclear.

Accordingly, this study aimed to evaluate the psychobehavioral effects of MPS on family functioning and related factors.

**Methods**

This cross-sectional, observational, descriptive study was conducted in the Pequeno Príncipe Children's Hospital and approved by our Ethics Committee (protocol number 47925921.5.0000.0097). The parents provided consent to the use of all data and images.

We included participants with increased urinary glycosaminoglycans and laboratory-confirmed reduction in enzymatic activity; specifically, the enzymatic deficiency was defined as a reduction in enzymatic activity of < 10% of the normal laboratory reference value.

Participants were further subgrouped according to MPS type, central nervous system involvement, and treatment performed (no treatment, enzyme replacement therapy [ERT], or hematopoietic cell transplantation).

**Cognitive Function**

Estimated full-scale IQ was assessed using the Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R) and Wechsler Abbreviated Scale of Intelligence (WASI).

The WPPSI-R was administered to children aged between 3 years 6 months and 5 years 11 months. The children received a four-subtest short version of the test comprising two subtests that assess perceptual–motor abilities. Raw scores obtained using the four subtests were converted into scaled scores.

The WASI was administered to children aged > 6 years. It comprised four subtests (two verbal and two performance scales), which included the Vocabulary, Similarities, Block Design, and Matrix Reasoning subtests. Raw scores obtained using the four subtests were converted into scaled scores.

**Children's Behavioral and Emotional Mental Health**

The Child Behavior Checklist (CBCL) was used to assess behavioral and emotional problems in children during the previous 6 months. It comprised 120 items, which were scored on a three-point scale: 0 (not true), 1 (somewhat or sometimes true), and 2 (very true or often true). It has excellent reliability and has been validated in the Brazilian population. The raw score was converted into T-scores by the Assessment Data Manager software and quantified within the following dimensions: Anxiety/Depression, Withdrawal, Somatic Complaints, Social Problems, Thinking Problems, Attention Problems, Rule-Breaking Behavior,
Aggressive Behavior, Depressive Problems, Anxiety Problems, Somatic Problems, Attention Deficit/Hyperactivity Disorder, Oppositional Defiant Disorder, and Conduct Disorder. Additionally, the instrument can provide a Total Problem Score and the Internalizing and Externalizing Problems scores.

The Strength and Difficulties Questionnaire (SDQ) was used to assess problems related to mental health. The questionnaire comprises 25 items, including 10 items on abilities, 14 items on difficulties, and 1 neutral item. The instrument is divided into five subscales for assessing emotional symptoms (fears, excessive worries, sadness, and hopelessness), conduct problems (irritability, aggression, and antisocial behaviors such as lying), hyperactivity (restlessness, distraction, and inattention), problems with peer relationships (difficulties in relationships with other people, whether children or adults), and prosocial behavior (knowing how to cooperate, help, and share). For each item, the individual could choose false (0 points), more or less true (1 point), and true (2 points). The score of each subscale ranges from 0–10, with a lower score indicating a better mental health status.

**Adaptive Behavior**

The Vineland Adaptive Behavior Scales (Vineland) assessed adaptative behavior. It involves a semi-structured interview using items scored as 0 (never performed), 1 (sometimes or partly performed), or 2 (behavior is usually or habitually performed). Normality was considered when the score was 86 or higher.

**Family Functioning**

The Family Environment Scale (FES) is a self-reported 90-item scale for assessing family functioning across ten different domains. We used the questionnaire version validated for Portuguese. It comprises five subscales, including Cohesion (commitment and family support); Expressiveness (direct communication of feelings); Conflict (express anger and conflict); Independence, Achievement Orientation, Intellectual Cultural Orientation, Active Recreational Orientation, Moral-Religious Emphasis, and Organization (maintenance of the family structure and organization); and Control (trust in rules and procedures to manage family life). The presence of problems is indicated by high scores on the Conflict and Control scales or low scores on the other scales. Table 1 presents the results grouped according to the type of family functioning.

**Table 1.** Classification according to the typology of the family environment.
<table>
<thead>
<tr>
<th>Typology</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Independence orientation</td>
<td>Independence ≥ 69 and independence ≥ achievement/assertiveness</td>
</tr>
<tr>
<td>Achievement orientation/assertiveness</td>
<td>Achievement/assertiveness ≥ 60 and achievement/assertiveness ≥ intellectual/cultural AND moral / religiosity</td>
</tr>
<tr>
<td>Intellectual/cultural orientation</td>
<td>Intellectual/cultural ≥ 60</td>
</tr>
<tr>
<td>Moral and religious orientation</td>
<td>A - Moral/religious structure</td>
</tr>
<tr>
<td></td>
<td>moral / religiosity ≥ 60 and moral / religiosity ≥ intellectual/cultural</td>
</tr>
<tr>
<td></td>
<td>B - Moral/religious dysfunction</td>
</tr>
<tr>
<td></td>
<td>moral / religiosity ≥ 60 and moral / religiosity ≥ intellectual/cultural and organization ≤ 50</td>
</tr>
<tr>
<td>Support Guidance</td>
<td>Cohesion OR expressiveness OR both ≥ 60 and cohesion and expressiveness ≥ conflict</td>
</tr>
<tr>
<td>Conflict orientation</td>
<td>Conflict ≥ 60</td>
</tr>
<tr>
<td>Disorganization orientation</td>
<td>Organization ≤ 50</td>
</tr>
</tbody>
</table>

**Caregiver Burden**

Caregiver burden was used to assess the version of the Zarit Burden Interview (ZBI) that has been translated and adapted to Portuguese. The ZBI comprises 22 items rated on a 5-point Likert scale that ranges from 0 (never) to 4 (nearly always), with the total score ranging from 0–88. This tool assesses objective and subjective burdens among informal caregivers concerning health, social life, personal life, finances, emotions, and relationship types.

**Quality of Life**

We used the family impact module of the Pediatric Quality of Life Inventory to assess the impact of the disease and treatment on family functioning and the child's adaptation to chronic diseases.

**Coping Techniques**
The self-administered COPE Brief\textsuperscript{17} was used to investigate how individuals responded to stressful situations. It comprises 14 subscales for assessing coping techniques (self-distraction, active coping, denial, substance use, use of emotional support, use of instrumental support, behavioral disengagement, venting, positive reframing, planning, humor, acceptance, religion, and self-censorship).

**Statistical Analysis**

Statistical analyses were performed using the Statistical Package for Social Sciences for Windows, version 22.0 (IBM Corp, Armonk, NY, USA). Descriptive analyses were used to obtain summary measures depending on the nature of the variables. Further, inferential analysis was performed using study-relevant statistical tests (Chi-Square, Fisher's exact test, and Student's t-test). Statistical significance was set at $p < 0.05$.

**Results**

Among 54 patients diagnosed with MPS since 2005, 18 died before the commencement of neuropsychological assessments, eight refused to participate in the study, and five could not be contacted. Accordingly, 25 patients with MPS and their families were included, including four, eleven, two, three, and five patients with MPS I, MPS II, MPS III, MPS IVa, and MPS VI, respectively. The mean age was 13 years (standard deviation [SD]: 7.7 years) (Table 2). Enzyme replacement therapy was performed in 50%, 81.8%, 100%, and 100% of patients with MPS I, MPS II, MPS IVa, and MPS VI, respectively. Additionally, 50% and 18.2% of patients with MPS I and MPS II, respectively, underwent hematopoietic cell transplantation. None of the patients with MPS III received any specific treatment.

Table 2 summarizes the scores for the cognitive functioning and the strengths and difficulties subscales, as well as the total score of difficulties. Patients with MPS III exhibited relatively greater difficulties in emotional areas, conduct, hyperactivity, and peer problems. The total score of difficulties was associated with the presence of neuronopathy ($p = 0.006$); however, no relationships were identified for the subscales.

**Table 2.** Characteristics of the population studied according to the type of MPS$^a$, psychometric characteristics, and family burden.
### Variables

<table>
<thead>
<tr>
<th>Variables</th>
<th>MPS I (n = 4)</th>
<th>MPS II (n = 11)</th>
<th>MPS III (n = 2)</th>
<th>MPS IVa (n = 3)</th>
<th>MPS VI (n = 5)</th>
<th>p</th>
</tr>
</thead>
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<tr>
<td>Age (Years)</td>
<td>10.7 (5.7)</td>
<td>13.1 (5.4)</td>
<td>9.5 (7.8)</td>
<td>19.0 (12.1)</td>
<td>14.0 (9.0)</td>
<td>0.605</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Intellectual Quotient</td>
<td>81.75 (33.7)</td>
<td>51.0 (17.4)</td>
<td>50 (14.1)</td>
<td>70.7 (12.9)</td>
<td>80.8 (36.4)</td>
<td>0.125</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Capabilities and Difficulties</td>
<td></td>
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<tr>
<td>Mean (SD)</td>
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</tr>
<tr>
<td>Total difficulties</td>
<td>10.0 (2.8)</td>
<td>11.5 (4.4)</td>
<td>25.0 (7.1)</td>
<td>5.7 (6.0)</td>
<td>11.2 (6.3)</td>
<td>0.002*</td>
</tr>
<tr>
<td>Emotional problems</td>
<td>2.0 (1.4)</td>
<td>2.3 (1.8)</td>
<td>6.5 (0.7)</td>
<td>1.7 (2.9)</td>
<td>2.3 (1.5)</td>
<td>0.081</td>
</tr>
<tr>
<td>Conduct problems</td>
<td>1.5 (2.1)</td>
<td>1.7 (1.9)</td>
<td>3.0 (4.2)</td>
<td>0.3 (0.6)</td>
<td>1.3 (1.3)</td>
<td>0.654</td>
</tr>
<tr>
<td>Hyperactivity</td>
<td>3.0 (4.2)</td>
<td>4.8 (3.1)</td>
<td>10.0 (0.0)</td>
<td>0.7 (1.2)</td>
<td>4.0 (0.8)</td>
<td>0.018*</td>
</tr>
<tr>
<td>Peer problems</td>
<td>3.5 (4.9)</td>
<td>2.7 (1.8)</td>
<td>5.5 (2.1)</td>
<td>3.0 (3.0)</td>
<td>0.75 (0.96)</td>
<td>0.210</td>
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<tr>
<td>Prosocial</td>
<td>7.5 (3.5)</td>
<td>5.4 (3.4)</td>
<td>7.0 (0.0)</td>
<td>5.3 (5.0)</td>
<td>8.5 (1.9)</td>
<td>0.545</td>
</tr>
<tr>
<td>Impact</td>
<td>4.0</td>
<td>3.2 (2.8)</td>
<td>0</td>
<td>2.5 (3.5)</td>
<td>0.25 (0.5)</td>
<td>0.234</td>
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<tr>
<td>Adaptive behavior</td>
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<td></td>
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<tr>
<td>Mean (SD)</td>
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<td></td>
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<tr>
<td>Communication</td>
<td>89.5 (9.2)</td>
<td>35.6 (24.3)</td>
<td>35.0 (22.6)</td>
<td>94.7 (16.5)</td>
<td>72.8 (33.4)</td>
<td>0.009*</td>
</tr>
<tr>
<td>Daily Living Skills</td>
<td>81.0 (14.1)</td>
<td>38.3 (27.1)</td>
<td>42.0 (31.1)</td>
<td>78.3 (20.0)</td>
<td>76.0 (44.5)</td>
<td>0.142</td>
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<tr>
<td>Socialization</td>
<td>84.5 (2.1)</td>
<td>49.7 (26.0)</td>
<td>53.0 (15.6)</td>
<td>86.3 (26.1)</td>
<td>78.6 (36.3)</td>
<td>0.183</td>
</tr>
<tr>
<td>Motor Skills</td>
<td>82.5 (0.7)</td>
<td>42.1 (24.1)</td>
<td>45.5 (21.9)</td>
<td>82.7 (24.7)</td>
<td>76.0 (37.1)</td>
<td>0.093</td>
</tr>
<tr>
<td>Problems Score</td>
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<td></td>
<td></td>
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<tr>
<td>Mean (SD)</td>
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</tr>
<tr>
<td>Total</td>
<td>56.0 (5.7)</td>
<td>56.9 (6.9)</td>
<td>63.5 (17.7)</td>
<td>47.7 (7.6)</td>
<td>54.8 (6.7)</td>
<td>0.297</td>
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<tr>
<td>Externalizing</td>
<td>55.0 (1.4)</td>
<td>49.5 (9.3)</td>
<td>56.0 (18.4)</td>
<td>43.3 (0.6)</td>
<td>51.5 (7.1)</td>
<td>0.523</td>
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<td>Quality of life</td>
<td>Family Burden</td>
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<tr>
<td></td>
<td>63.0 (9.9)</td>
<td>63.4 (26.0)</td>
<td>27.5 (4.9)</td>
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<tr>
<td></td>
<td>55.4 (5.2)</td>
<td>69.4 (15.5)</td>
<td>20.7 (1.3)</td>
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<td></td>
<td>65.5 (10.6)</td>
<td>47.1 (2.7)</td>
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<td>67.7 (31.0)</td>
<td>14.0 (8.0)</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>56.0 (8.5)</td>
<td>77.4 (21.6)</td>
<td>24.4 (14.2)</td>
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<tr>
<td></td>
<td>0.176</td>
<td>0.506</td>
<td>0.395</td>
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</tbody>
</table>

*MPS: mucopolysaccharidoses

*Asterisks indicate statistical significance

The communication domain in adaptive behavior exhibited mean scores below the cut-off points in patients with MPS II (35.6 ± 24.3) and MPS III (35.0 ± 22.6), with a significant among-group difference (p = 0.009). The total difficulty score was associated with the communication domain score in adaptive behavior (p = 0.012). Both patients with high and very high scores in the conduct problems domain showed communicative impairment.

Additionally, 9.1%, 4.5%, and 9.1% of patients exhibited behavioral or emotional problems, externalizing symptoms, and internalizing problems, respectively. Participants undergoing ERT had fewer behavioral or emotional problems than those who underwent other treatments (p = 0.019). However, the presence of behavioral or emotional problems did not significantly differ according to nervous system involvement (p = 0.195), age (p = 0.097), or time from diagnosis (p = 1.000).

Parents of patients with MPS III and MPS VI reported relatively lower (47.1 ± 2.7) and higher (77.4 ± 21.6) quality-of-life scores, respectively; however, there was no significant among-group difference (p = 0.506) (Table 2). Regarding the impact on family functioning, the quality-of-life scores were positively associated with the cultural/intellectual domain score (p = 0.003); however, they were not associated with the other domains of family functioning or coping techniques used. Regarding adaptive behavior, the mean quality-of-life score was 63.14 ± 17.7 in patients with low and normal adaptive behavior (p < 0.001).

There was no difference between the quality of life reported by family members according to the type of MPS (Table 2). In addition, self-reported quality of life scores was obtained from only eight participants. The scores did not significantly differ among patients with MPS I (72), MPS II (72.5 ± 12.0), MPS VI (74.2 ± 3.3), and MPS IVa (83.5 ± 20.5 [p = 0.780]).

Regarding family functioning and its domains, the adverse effects of MPS were observed in the domains of independence (mean: 45.3 ± 8.9), intellectual/cultural (mean: 46.7 ± 9.4), activity/recreation (mean: 49.9 ± 9.8), and expressiveness (mean: 49.1 ± 6.7). However, no differences existed in any family functioning domains according to the MPS type, treatment type, or neurological involvement. Nevertheless, the organization domain significantly differed (p = 0.015) between families diagnosed for < 2 years (mean: 54.6 ± 7.6) and > 2 years (mean: 62.7 ± 4.5). Furthermore, there was a greater impact on
the moral-religiosity domain in families with recurrent cases (mean: 49.0±9.1) than in families with isolated cases (mean: 57.2 ± 5.8) (p = 0.027). Similarly, there was a lower impact on the expressiveness domain in families with recurrence (mean: 55.4 ± 8.0) than in families without recurrence (mean: 46.7 ± 0.54) (p = 0.013).

According to typology, families with a conflict orientation had non-significantly (p = 0.520) higher scores on the caregiver stress scales (mean: 33.0 ± 19.8) than those without a conflict orientation (mean: 19.88 ± 6.0). Moreover, families with an intellectual/cultural orientation had a longer illness duration (mean: 15.00 ± 5.6) and better Problem-Focused Coping techniques (mean: 2.7 ± 0.19) than families without an intellectual/cultural orientation (mean: 7.3, SD: 3.7 and 1.9, SD: 0.56; respectively). These differences were statistically significant (p = 0.008; p = 0.033, respectively).

Families with a guidance and support orientation had a non-significantly (p = 0.063) longer diagnostic time (mean: 12.0 ± 4.5) than those without this typology (mean: 7.3 ± 4.4) (Figure 1).

For all patients, the mean caregiver stress score was 21.6 ± 8.5. Moreover, 44%, 40%, and 4% of the family members reported no/mild, moderate, and severe burdens, respectively. Caregiver stress did not significantly differ according to the type of MPS (p = 0.395), treatment type (p = 0.731), or neurological involvement (p = 0.554).

Family functioning in the cultural-intellectual domain was negatively associated with lower caregiver stress, with families with low and moderate/severe burden scoring 51.2 ± 9.1 and 42.2 ± 8.1, respectively (p = 0.025). Similarly, caregiver burden was negatively associated with quality of life (p = 0.002).

The most reported coping techniques were Problem-Focused Coping techniques (average: 2.02 ± 0.6), followed by Emotion-Focused Coping (1.68±0.43) and Avoidant Coping (0.26±0.26). The reported coping techniques did not significantly differ according to the type of MPS (p = 0.431, p = 0.267, and p = 0.692, respectively), type of treatment (p = 0.173, p = 0.093, and p = 0.107, respectively), or neurological involvement (p = 0.882, p = 0.061, and p = 0.479, respectively).

Discussion

The neurocognitive impact of MPS widely varies from minor attention and executive function difficulties to severe intellectual disability. Similarly, we observed a wide range of cognitive impacts in patients with MPS II, ranging from mild effects to drastically low IQ scores, which indicates brain involvement and functional impairments despite them being considered as "non-neuronopathic. Contrastingly, patients with MPS IV and MPS VI did not show progression of neurocognitive abnormalities, with most of them showing normal function. This is consistent with previous reports of relatively preserved cognitive functioning in these patients compared with those with other MPS types. Taken together, our findings emphasize the heterogeneity in the cognitive impacts of MPS and the need to perform individualized assessments and interventions.
Notably, we observed difficulties in cognitive functioning and adaptive behavior across several domains. Patients with MPS II and MPS III exhibited relatively lower scores in the communication domain of adaptive behavior. Indeed, speech, language, and communication impairments have been reported in patients with MPS, especially MPS II and III.\textsuperscript{18–19} These impairments manifest as delayed language and speech development, limited vocabulary, speech absence, and impaired communication skills. Moreover, these communication deficits adversely affect their activities of daily life, especially the expression of needs and desires.\textsuperscript{20–21} Additionally, the total difficulty score was associated with adaptive performance in communication. The impact of these communication difficulties extends beyond the linguistic domain; instead, it limits social interactions, educational opportunities, and participation in various activities. Specifically, patients may experience frustration, social isolation, and difficulty forming meaningful relationships.\textsuperscript{22} Over time, adaptative behavior may allow these children to cope with interpersonal issues, even with persistent or worsening physical problems.\textsuperscript{20,23} Therefore, adequate adaptive capacities can improve the psychosocial quality of life, consistent with the previous report by Shapiro.\textsuperscript{23}

Interventions targeting speech, language, and communication skills are crucial in supporting individuals with MPS to enhance their quality of life and promote their overall well-being.\textsuperscript{24} Specifically, prompt interventions, including speech therapy and augmentative and alternative communication strategies, can extensively improve communication outcomes and overall functioning.\textsuperscript{25} Additionally, multidisciplinary approaches that address the broader needs of individuals with MPS, including educational support and social skills training, can further enhance their communication abilities and optimize their participation in various aspects of life.

Our findings indicated a relationship between behavior disturbance and cognition in patients with MPS; specifically, IQ scores were negatively associated with a risk of behavioral issues. Consistent with previous reports, we found that scores for adaptive behaviors were lower in patients with MPS II and MPS III than those in the general population, irrespective of treatment.\textsuperscript{20,26} There has been insufficient research on behavioral, attentional, and executive function abnormalities in patients with MPS IV and MPS VI, which negatively affect the quality of life.\textsuperscript{18} However, our findings demonstrated the presence of emotional and peer problems in the MPS Iva group, albeit to a lesser extent than those in the MPS III group. Various behavioral problems have been reported in patients with MPS IVa, including anxiety/depression, attention difficulties, and somatic complaints.\textsuperscript{27} These findings demonstrated the need to address cognitive and behavioral aspects when managing patients with MPS.

A Brazilian study reported a mean quality of life score of 48.06 in 11 mothers of children with MPS.\textsuperscript{5} In our study, except for MPS III, the other MPS groups had values higher than the aforementioned one, even in the presence of cognitive impairment. Contrastingly, they were lower than that reported by an Irish study (93.81) on patients with MPS, predominantly those with mild forms of the disease. The better quality of life observed in this Irish study could be attributed to a high level of social support.\textsuperscript{28} These inconsistencies in the reported impact of MPS on the quality of life may be attributed to several factors, including variability in the disease manifestations, treatment availability, and social support systems across different regions and healthcare systems. These factors can considerably affect the perception of
quality of life by individuals with MPS and their families. Furthermore, these inconsistencies can be attributed to the small sample sizes and potential cultural differences in the studied populations.

In our study, scores related to family functioning were lower in patients with MPS than in the healthy Brazilian population, especially in the domains of independence, intellectual/cultural, activity/recreation, and expressiveness. Children with MPS greatly rely on family members for assistance and support, which places a remarkable burden on the family and affects their overall functioning.

Furthermore, caring for children with MPS can adversely affect the parents' working lives. Specifically, parents may be unemployed or forced to reduce their working hours to provide care for their children with MPS. Balancing caregiving responsibilities with work obligations can be challenging and cause financial strain and changes in career trajectories. These findings highlight the substantial impact of MPS on the family unit and the need for comprehensive support systems.

Inconsistent with previous reports, we observed no correlation between the severity of MPS and its impact on families, which could be attributed to coping characteristics, including recognizing positive aspects of the caring process, reevaluating life goals, and receiving support from other affected families.

MPS's progressive and complex nature places notable demands on families and caregivers. The clinical manifestations of MPS can limit activities of daily living; moreover, the chronic and progressive disease nature can result in functional disability and a decrease in quality of life. Various MPS forms are related to behavioral problems that require coping strategies, time, and physical presence from caregivers, directly contributing to social isolation among families. This may explain the relatively greater impact in the independence domain. Generally, the severity of MPS symptoms is negatively associated with family functioning.

Family organization is an important aspect of family functioning. It encompasses several factors, such as order, structure, financial planning, adherence to rules, and responsibilities. These factors contribute towards maintaining stability and managing the demands of caring for a child with MPS. Notably, although MPS is a progressive disease, there was an improvement in organization and positive family environment with an increase in the disease duration. This suggests that families may develop adaptive strategies and become more adept at managing various lives as they gain experience and familiarity with the disease. Specifically, families may develop routines, implement effective planning strategies, and establish clear roles and responsibilities within the family unit, which can contribute to improved organization.

Expressiveness within the family refers to the extent to which family members are encouraged to express their feelings and thoughts openly. Moral-religiosity refers to the emphasis placed on ethical and religious values and issues within the family. In our study, familial recurrence had a greater impact on moral religiosity, which could be attributed to the fact that numerous questionnaire items predominantly
focused on religious aspects without explicitly considering spirituality. The observed impact on religion could be influenced by the increased demands placed on family members caring for multiple affected relatives, which may cause them to emphasize religious practices and values as a means of coping.

Notably, familial recurrence was associated with greater expressiveness within the family. This could be attributed to a better understanding among family members with firsthand experience caring for a person with MPS. Additionally, this shared experience may foster a climate of increased openness and emotional expression within the family. However, further studies are warranted to elucidate the factors underlying the observed patterns in familial recurrence, moral-religiosity, and expressiveness.

The caregiver burden reported by family members of children with MPS was lower than that reported by family members of children with other chronic diseases or Down syndrome. However, it was higher than that reported by family members of healthy Brazilian children. The caregiving responsibilities limit opportunities for leisure activities and social engagement. Moreover, these caregivers often experience parental stress, grief, feelings of loss, guilt, marital strain, and conflicts in their roles. Additionally, the chronicity of the disease contributes to family stress and imposes psychosocial demands on caregivers.

The caregiver burden is negatively associated with the quality of life for the patient, which indicates that the patient's well-being influences the family dynamics. Notably, the caregiver's well-being remarkably influences the overall care provided to the child. Specifically, stress and burden levels among caregivers are negatively associated with their ability to provide optimal care and support to the child with MPS. Moreover, the caregiver burden is negatively associated with the perception of quality of life in pediatric patients. It is difficult to determine the causal relationship between caregiver stress and the child's quality of life since these domains are interconnected and influenced by various factors. Accordingly, to elucidate this relationship, it is important to consider the multifaceted nature of MPS and its impact on the entire family unit.

Our study has some limitations, primarily stemming from the fact that the analysis was conducted at a single center. However, we believe that its impact is substantial given the rarity of the disease and the large national reach of the referral hospital from which our participants were enrolled.

In conclusion, the impact of MPS on family functioning extends beyond physical aspects and encompasses social and emotional dimensions. By promoting coping strategies, facilitating support networks, and recognizing the positive aspects of caregiving, the overall impact of MPS on families can be mitigated.

**Abbreviations**

MPS, Mucopolysaccharidoses

IMDs, inherited metabolic diseases
GAGs, glycosaminoglycans
ERT, enzyme replacement therapy
WPPSI-R, Wechsler Preschool and Primary Scale of Intelligence-Revised
WASI, Wechsler Abbreviated Scale of Intelligence
CBCL, Child Behavior Checklist
SDQ, Strength and Difficulties Questionnaire
FES, Family Environment Scale
ZBI, Zarit Burden Interview

Declarations

Ethics Approval and Consent to Participate

All research aspects were approved by the Ethics Committee on Research Involving Human Subjects at our institution (approval number 47925921.5.0000.0097). Written informed consent was obtained from the patients’ parents for publication of this report.

This work was approved by the research ethics committee of the Pequeno Príncipe Hospital. All methods were carried out in accordance with the guidelines and regulations of the Brazilian National Commission of Health (Commission of Ethics in Human Research-CEP/CONEP).

A statement to confirm that all methods were carried out in accordance with relevant guidelines and regulations

Consent for publication

Written informed consent was obtained from the patients’ parents for publication of this report.

Availability of data and materials

The data supporting this study's findings can be requested from the corresponding author, M. Cordeiro, upon reasonable request based on Data Transfer Agreement.

Competing Interests

All the authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Author Contributions

D.V., a physician, participated in clinical management, conceptualized the study, drafted the initial manuscript, and reviewed and revised the manuscript. This report is, in part, his doctoral thesis.

M.L.S. is also an attending physician for the families of the participants, and she reviewed and revised the manuscript.

T.B. and V.F. helped with the neuropsychological data gathering. T.B. did the statistical analysis.

M.L.C., the principal investigator, coordinated the study, revised the manuscript, and conducted critical reviews of the manuscript for key intellectual content. All authors contributed to the drafting of the manuscript, approved the final version, and agreed to be accountable for all aspects of the work.

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References


Figures

![Box Plot according to family environment domains.](image)

**Figure 1**

Box Plot according to family environment domains.