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Clinical Report

Mucopolysaccharidoses in Brazil: What Happens From Birth to Biochemical Diagnosis?

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Mucopolysaccharidoses (MPS) form a group of inherited metabolic disorders characterized by intralysosomal storage of glycosaminoglycans. This study aimed to investigate the path followed by Brazilian patients from birth to diagnosis. An interview was conducted with patient's parents or guardians with subsequent review of patient's medical records. One hundred thirteen patients with MPS were included (MPS I: 18, MPS II: 43, MPS IIIA: 2, MPS IIIB: 3, MPS IIIC: 1, MPS IVA: 15, MPS IVB: 1, MPS VI: 29, MPS VII: 1) from 97 families. Median age at the onset of signs/symptoms was 18 months (MPS I: 18, MPS II: 24, MPS IVA: 8, MPS VI: 8). Skeletal abnormalities (for MPS IVA and MPS VI), joint contractures (for MPS II), and typical facial features (for MPS I) were the most frequently reported first signs/symptoms. Several health professionals were involved in patient's care as of the onset of symptoms until biochemical diagnosis was established. Median age at diagnosis was 76 months (MPS I: 75, MPS II: 95, MPS IVA: 75, MPS VI: 52). Considering the group as a whole, there was a 4.8-year delay between the onset of signs/symptoms and the establishment of the diagnosis. Considering that specific therapies are available for some of these disorders and that early treatment is likely to change more favorably the natural history of the disease, efforts should be made to minimize this delay. We believe that this situation can be improved by measures that both increase awareness of health professionals about MPS and improve access to diagnostic tests. © 2008 Wiley-Liss, Inc.

Key words: mucopolysaccharidoses; lysosomal storage diseases; glycosaminoglycans; inborn errors of metabolism; natural history

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INTRODUCTION

The mucopolysaccharidoses (MPS) form a group of inherited metabolic disorders characterized by intralysosomal storage of glycosaminoglycans (GAGs) secondary to a deficiency in the activity of a specific lysosomal enzyme. This abnormal storage compromises both the architecture and function of cells and organs, and results in a broad spectrum of clinical manifestations that are progressive and multisystemic.

According to international studies, the incidence of the MPS ranges from 1.9 to 4.5/100,000 births [Nelson, 1997; Meikle et al., 1999; Poorthuis et al., 1999; Applegarth et al., 2000; Nelson et al., 2003; Baehner et al., 2005]. The actual incidence of MPS in Brazil is unknown. In a study by Coelho et al. [1997], which reports the diagnosis of inborn errors of metabolism (IEM) in at-risk Brazilian patients,

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lysosomal storage diseases (LSD) were the most frequent group of IEM (59.8% of all diagnoses of IEM), and the MPS represented 54.5% of LSD patients. The MPS Brazil Network, an initiative to improve the diagnosis and management of the MPS diseases in Brazil, identified 161 new MPS patients between April 2004 and September 2006. Another 88 patients, previously diagnosed, are known to be alive. Of these 249 patients, 60 have MPS I, 82 have MPS II, 31 have MPS III (7/31 MPS IIIA, 14/31 MPS IIIB and 10/31 MPS IIIC), 15 have MPS IV (11/15 MPS IVA and 4/15 MPS IVB), 57 have MPS VI, and 4 have MPS VII.

To our knowledge, there are only a few studies that delineate the natural history of MPS, especially when the pre-diagnostic period is considered. Although signs and symptoms are usually noticed early, diagnosis is largely delayed in most instances [Young and Harper, 1982, 1983; Colville and Bax, 1996; Azevedo et al., 2004; Vijay and Wraith, 2005; Schwartz et al., 2007]. Systematic studies of the determinants of this delay have not been conducted.

This study aimed to delineate the path of Brazilian patients with MPS from birth to their biochemical diagnosis, to identify differences in this path between different MPS types, and to identify potential issues to be addressed so that earlier diagnosis of MPS diseases could be made.

METHODS

In the present study, MPS patient's parents or guardians were surveyed by means of a structured questionnaire applied by the same interviewer. After the interview, a review of medical records was performed to assure the reliability of the information and to add new data. In case of discrepancy, the data obtained in the patient's medical records was considered.

All patients had their diagnosis of MPS confirmed by enzyme assays and/or DNA analysis. Patients were from either (1) the Medical Genetics Service of Hospital de Clínicas Porto Alegre, South Brazil (MGS-HCPA), which is a national reference center for the diagnosis and treatment of MPS, or (2) six other Brazilian medical genetics services (five in the southeast region and one in the northeast region). For patients from the MGS-HCPA, interviews were conducted between May 2005 and November 2006, during routine medical evaluations. Patients from other services were interviewed between September 2005 and March 2006.

The interview focused on the period from birth to biochemical diagnosis and included the following variables: MPS type; age; origin; family history; birth data (gestational age, weight and length at birth); developmental milestones; early clinical manifestations; age at the onset of symptoms; professionals involved in patient's care until biochemical diagnosis was established (professional consulted when first early clinical manifestations were noticed, professional who first suspected of MPS, and professional who established the diagnosis of MPS); number of and reasons for hospitalizations and surgeries; and age at biochemical diagnosis.

Data were grouped in a Microsoft Excel® spreadsheet, and analyses were performed with SPSS 15.0 for Windows software. Categorical variables were summarized by frequencies and percentages. Continuous variables with normal distribution were summarized by mean and standard deviation, while those with asymmetric distribution were summarized by median and interquartile intervals. A subgroup analysis was performed of MPS types that represented more than 10% of the sample.

This study was approved by the local Ethics Committee. Before each interview an Informed Consent Form was signed by patients or their parents/legal guardians.

RESULTS

Total Sample

One hundred thirteen Brazilian patients with MPS from 96 unrelated families were enrolled in this study (Table I). Of them, 64 came from the MGS-HCPA (10/64 MPS I, 28/64 MPS II, 1/64 MPS IIIB, 7/64 MPS

TABLE I. Characterization of MPS Patients Regarding MPS Type, Gender, and Age at Interview

MPS type	Total of patients	Gender (male/female)	Age at interview (years) (mean ± SD)
MPS I	18	10/8	13.6 ± 9.7
MPS II	43	43/0	12.7 ± 9.0
MPS IIIA	2	2/0	11/11[a]
MPS IIIB	3	0/3	5/13/18[a]
MPS IIIC	1	1/0	14[a]
MPS IVA	15	10/5	11.9 ± 2.9
MPS IVB	1	1/0	14[a]
MPS VI	29	16/13	9.9 ± 4.9
MPS VII	1	0/1	7[a]
Total	113	83/30	11.9 ± 7.4

MPS: mucopolysaccharidoses.

[a]It is shown the age for each patient for these MPS types.

IVA, and 18/64 MPS VI) and 49 from other Brazilian services (8/49 MPS I, 15/49 MPS II, 2/49 MPS IIIA, 2/49 MPS IIIB, 1/49 MPS IIIC, 8/49 MPS IVA, 1/49 MPS IVB, 11/49 MPS VI, and 1/49 MPS VII). Since MPS I, MPS II, MPS IVA and MPS VI represent each group, more than 10% of the cohort, data on these patients were analyzed separately. Table I shows mean age of patients at interview. Figure 1 shows age at the onset of signs and symptoms and age at diagnosis. No statistically significant differences were found between ages at diagnosis of the groups, except between MPS II and MPS VI that was the only statistically significant difference found (Kruskall–Wallis test, $P < 0.05$).

Parental consanguinity was reported by 20/96 families (20.8%). Sibling recurrence of MPS was found in 22/96 families (2/16 MPS I; 9/37 MPS II; 1/6 MPS III; 3/12 MPS IVA; 0/1 MPS IV-B; 7/23 MPS VI; 0/1 MPS VII). In two of these families the diagnosis of the recurrent case was made before first symptoms were noticed: one MPS VI patient was diagnosed at the age of 5 months, and one MPS IIIB patient was diagnosed at the age of 20 months. Sixty of the 113 patients (53.1%) were born by caesarean, and 53/113 (46.9%) by vaginal delivery. Eight (8/113) patients had preterm birth, and two (2/113) had post-term births. Considering all births at term, mean weight at birth was 3,409 g (2,200–5,100 g, SD 594). Mean length at birth was 50.3 cm (41–57 cm, SD 2.7).

Information regarding neuropsychomotor development was obtained for 102/113 (90.3%) patients. Developmental delay was reported in 44/102 (43.1%). As expected, all MPS III patients presented with cognitive impairment.

The most frequently mentioned initial signs and symptoms are shown in Figure 2. Considering all patients, the mean number of medical specialists who saw patients since the onset of symptomatology until biochemical diagnosis was established was 4.7 (range = 1–11). A total of 22 medical specialties were involved in the care of patients, and information on the medical professionals who played a role prior to diagnosis is shown in Table II. In 94.8% of the patients, the biochemical diagnosis of MPS was reached by a clinical geneticist. Other professionals who diagnosed MPS were pediatricians (3/113 or 2.6%) and neurologists (3/113 or 2.6%). The information on the specialty of physicians who referred for evaluation by a geneticist was available for 110/113 patients; most referrals were made by pediatricians (n = 35/110), followed by neurologists (n = 16/110) and orthopedists (n = 15/110). In 14/110 patients, geneticists were the first medical specialist to be seen - these families sought a geneticist due to previous family history of MPS.

Of the 113 patients, 67 (59.3%) had undergone at least one surgical procedure before diagnosis was established (Table III), and 46 (40.1%) were hospitalized at least once in the period between birth and diagnosis. The main reasons for hospitalizations were respiratory problems in 32/46 patients and gastrointestinal disturbances in 11/46 patients. Other causes for hospitalization were the following: clinical investigation (4/46), heart problems (2/46), seizures (2/46), gum bleeding after dental extraction (1/46), oropharynx infection (1/46), postoperative complications (2/46), and ear infection (1/46). For these 46 patients, the number of hospitalizations ranged from 1 to 10, and the mean number of hospitalizations until diagnosis was established was 3.98 (total of hospitalizations = 183).

MPS I (n = 18 Patients)

MPS I patients came from 16 unrelated families. Parental consanguinity was reported by 3/16 (18.7%) families. Of the 18 patients, three presented with the severe form of the disease, 13 with the attenuated

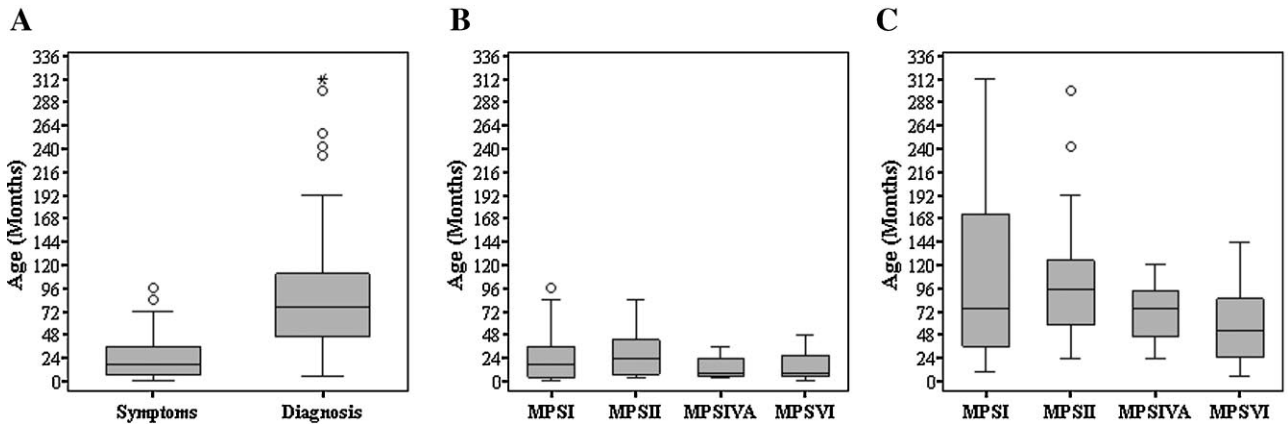

FIG. 1. Age at the onset of signs/symptoms and age at biochemical diagnosis (in months). **A**: Including all MPS patients (111/113) at age of the onset of signs and symptoms; two patients were asymptomatic at diagnosis. **B**: Age at the onset of signs and symptoms for MPS I (n = 18/111), MPS II (n = 43/111), MPS IVA (n = 15/111), and MPS VI (n = 28/111). **C**: Age at biochemical diagnosis for MPS I (n = 18/113), MPS II (n = 43/113), MPS IVA (n = 15/113), and MPS VI (n = 29/113).

form, and disease severity was undetermined in two patients. As to neuropsychomotor development before diagnosis was established, 7/18 (38.9%) patients showed at least one abnormal finding, such as speech delay (n = 6) and delayed sphincter control (n = 2). Information regarding the age at the onset of symptomatology, first symptomatology, physicians involved in patient's care and surgeries performed until diagnosis is shown in Figures 1 and 2 and in Tables II and III, respectively.

MPS II (n = 43 patients)

MPS II patients came from 37 unrelated families. Parental consanguinity was reported in one family. Of the 43 patients, 11 presented the severe form of the disease, 19 the attenuated form, and disease severity was undetermined in 13 patients. Data regarding neuropsychomotor development before diagnosis was established was available for 40/43 patients as follows: 22/40 (55.0%) presented with at least one abnormal finding such as speech delay (n = 16/22), delayed sphincter control (n = 8/22), and delay in walking without support (n = 4/22). Information regarding the age at the onset of symptomatology, first symptomatology, physicians involved in patient's care and surgeries performed until diagnosis is shown in Figures 1 and 2 and in Tables II and III, respectively.

MPS IVA (15 Patients)

MPS IVA patients came from 13 unrelated families. Parental consanguinity was reported by 4/13 (30.7%) families. Four of the 15 (26.7%) patients presented with delayed neuropsychomotor development before diagnosis was established (delay in walking without support = 4/4; speech delay = 1/4). Information regarding the age at the onset of symptomatology, first symptomatology, physicians involved in patient's care and surgeries performed until diagnosis is shown in Figures 1 and 2 and in Tables II and III, respectively.

MPS VI (29 Patients)

MPS VI patients came from 23 unrelated families. Parental consanguinity was reported by 9/23 (39.1%) families. Nine patients (31.0%) presented with delayed neuropsychomotor development before diagnosis was established (delay in walking without support = 4/9; speech delay = 6/9). Information regarding the age at the onset of symptomatology, first symptomatology, physicians involved in patient's care and surgeries performed until diagnosis is shown in Figures 1 and 2 and in Tables II and III, respectively.

TABLE II. Physicians Who Were Involved in the Care of MPS Patients (at the Onset of Signs and Symptoms and at Suspicion of MPS)

	Physician who first saw the patient in the beginning of the signs and symptoms						Physician who first suspected of MPS in these patients					
Medical specialist	MPS (n = 111)	MPS I (n = 18)	MPS II (n = 43)	MPS IVA (n = 15)	MPS VI (n = 28)	MPS (n = 111)	MPS I (n = 18)	MPS II (n = 43)	MPS IVA (n = 15)	MPS VI (n = 28)
General physician	8.1% (n = 9)	11.1% (n = 2)	7.0% (n = 3)	13.3% (n = 2)	7.1% (n = 2)	0	0	0	0	0
Geneticist	6.3% (n = 7)	11.1% (n = 2)	4.6% (n = 2)	6.7% (n = 1)	7.1% (n = 2)	69.4% (n = 77)	61.1% (n = 11)	60.5% (n = 26)	86.7% (n = 13)	75.0% (n = 21)
Neurologist	2.7% (n = 3)	0	4.6% (n = 2)	0	0	9.0% (n = 10)	11.1% (n = 2)	14.0% (n = 6)	0	7.1% (n = 2)
Orthopedist	12.6% (n = 14)	0	9.3% (n = 4)	46.7% (n = 7)	7.1% (n = 2)	2.7% (n = 3)	0	4.6% (n = 2)	0	0
Pediatrician	64.0% (n = 71)	72.2% (n = 13)	65.2% (n = 28)	33.3% (n = 5)	75.0% (n = 21)	9.9% (n = 11)	16.7% (n = 3)	11.7% (n = 5)	0	10.7% (n = 3)
Others	6.3% (n = 7)	5.6% (n = 1)	9.3% (n = 4)	0	3.6% (n = 1)	9.0% (n = 10)	11.1% (n = 2)	9.2% (n = 4)	13.3% (n = 2)	7.2% (n = 2)

MPS: mucopolysaccharidosis. MPS III (n = 6), MPS IV-B (n = 1) and MPS VII (n = 1) patients were not included in the table due to small sample size (see Methods Section).

TABLE III. Surgical Procedures Performed on MPS Patients From Birth to Biochemical Diagnosis (n = 67/113)

Surgical procedure	MPS[a] (n = 67/113)	MPS I (n = 13/67)	MPS II (n = 30/67)	MPS IVA (n = 4/67)	MPS VI (n = 16/67)
Inguinal herniorrhaphy	24	6	11	1	6
Umbilical herniorrhaphy	25	6	11	–	8
Adenoidectomy	33	6	18	–	7
tonsillectomy	16	3	9	–	2
Ear tubes placement	13	2	7	–	3
Orthopedic surgery[b]	4	1	1	2	1
Others[c]	11	1	6	1	2
Total	126	25	63	4	29

[a]MPS: mucopolysaccharidoses; considering the total sample, 67/113(59.2%) patients were submitted to some type of surgical procedure before biochemical diagnosis was established. MPS III (n = 3 patients) and VII (n = 1 patient) are not shown in the table because they did not reach a minimum of 10% of the sample (see Methods Section).
[b]Club foot correction (n = 2), spine surgery (n = 2).
[c]Ventricular peritoneal shunt placement (n = 2), phimosis correction (n = 2), gastrostomy (n = 1), tracheostomy (n = 1), lung lobectomy (n = 1) carpal tunnel syndrome (n = 1), hiatal hernia correction (n = 1), urether stenosis correction (n = 1), arachnoids cyst excision (n = 1).

DISCUSSION

Ninety-seven Brazilian MPS families were interviewed in an attempt to understand the patient's path from birth to diagnosis in Brazil. Parental consanguinity rate for the total sample (20.6%) was much higher than the expected for the Brazilian population, which is 1.6% [Liascovich et al., 2001], but it was similar to that described by Azevedo et al. [2004] in a study with South-American patients with MPS VI. The consanguinity rate found for MPS II patients (2.7%) was quite similar to that reported by Liascovich et al. [2001]; this was expected since MPS II is the only X-linked MPS.

The total number of patients born through caesarean (46.9%) was higher than that for the Brazilian population in general, which is 30.9% [Faúndes and Cecatti, 1991]. Premature birth was 7.1%, approximately the same level expected for the Brazilian population, which ranges from 6% to 10% [Morrison and Rennie, 1997]. The average weight and length at birth were similar to the expected for the general Brazilian population [Nóbrega, 1985]. Thus, the higher number of caesareans was not explained by the usual factors (prematurity, macrosomia), and this difference is yet to be explained.

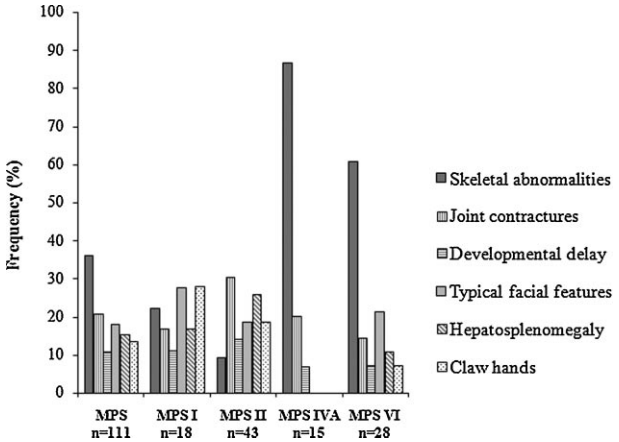

FIG. 2. Mucopolysaccharidoses: first signs and symptoms (n = 111/113). The first signs and symptoms are shown for MPS types that represent more than 10% of the total sample (see Methods Section). MPS III (n = 6), MPS IVB (n = 1) e MPS VII (n = 1) patients were excluded from the subgroup analysis due to low n (see Methods Section). Two patients were diagnosed before the onset of signs and symptoms (one with MPS IIIB and one with MPS VI).

Considering MPS I, II, IVA and VI, MPS II was the main group that presented developmental delay before diagnosis was established. In a study by Young and Harper [1983] including severe MPS II patients from Great Britain, developmental delay was observed in most patients, mainly regarding sphincter control and speech acquisition; this was also found in this cohort. A study of South-American MPS II patients [Schwartz et al., 2007] showed that early clinical manifestations of patients with the severe form were usually language and motor development delay. MPS I was the second group with most reports of developmental delay before diagnosis was established, mostly regarding speech, and this is in accordance with the literature [Conway et al., 2005; Dusing et al., 2006]. MPS IVA and MPS VI were the groups with fewer reports of delayed development, as expected, since these subtypes of MPS usually do not show cognitive impairment [Neufeld and Muenzer, 2001]. Therefore, the presence of developmental delay associated with other findings in the medical history should always raise the suspicion of an inborn error of metabolism such as MPS [Cleary and Green, 2005].

The MPS II group presented the most heterogeneous clinical manifestations and clinical presentations. As to the MPS IVA and MPS VI types, initial signs and symptoms were more homogeneous and were mainly skeletal abnormalities. These two groups also showed the youngest age at the onset of symptoms; this can be explained by the fact that this kind of clinical manifestation is more easily noticed and considered as abnormal by parents and health professionals.

In a study of British patients by Colville and Bax [1996], the signs and symptoms first noticed in patients with MPS I were the typical facial features, hirsutism, and protuberant abdomen. In MPS II, hearing problems, language and developmental

delay were initially found. In MPS IV patients, initial findings were skeletal abnormalities, and this is in agreement with our observations. In a British report by Vijay and Wraith [2005], which included patients with the attenuated form of MPS I, the main early clinical manifestations were joint stiffness, corneal opacity, ear, nose and throat manifestations, and umbilical hernia. In a study of British patients with the severe form of MPS II, Young and Harper [1983] found that the first sign noticed was developmental delay. However, in a study of milder MPS II patients from Great Britain, the first symptom noticed was the facial gestalt [Young and Harper, 1982]. Joint contractures, macrocephaly, distinctive facial features, and increased abdominal volume/hepatosplenomegaly were the most frequent early clinical manifestations found by Schwartz et al. [2007] in a study of MPS II South-American patients.

The pediatrician was the most frequently sought specialist at the onset of clinical manifestations of MPS disease, except for MPS IVA. The orthopedist was the first physician consulted for MPS IVA, and this reflects the main early clinical manifestation (skeletal abnormalities) in this group. However, the same behavior was not seen in the MPS VI group, which reported skeletal abnormalities as the most frequent initial feature as well. In most cases, the first professional to raise the hypothesis of MPS was the clinical geneticist and, in almost all patients, the diagnosis was reached under the guidance of this specialist. This probably reflects the lack of knowledge of Brazilian health professionals about MPS as well as the characteristics of the health system operation in the country. Studying patients with the attenuated form of MPS I, Vijay and Wraith [2005] found that 48.1% were diagnosed by a pediatrician, 33.3% by other specialists, 14.8% by the screening of affected families, and only 3.7% by a geneticist.

A great number of patients underwent surgical procedures before their MPS diagnosis was established. This fact is quite relevant since perioperative mortality risk in MPS patients is estimated at around 20% [King et al., 1984]. If patients do not carry the diagnosis of MPS yet, surgical procedures are performed with the medical staff being unaware of the possible complications associated to the disease, such as airway maintenance issues and the risk of anesthesia [Belani et al., 1993]. Despite the substantial number of patients who underwent umbilical and inguinal herniorrhaphy, adenoidectomy and tonsillectomy, hernia and upper airway obstructive problems were not reported as initial manifestations. Main causes for hospitalizations were respiratory problems and gastrointestinal disturbances, but these findings were not associated with early clinical manifestations in most patients.

The age at the onset of symptoms in this cohort was higher for MPS I (18 months) and for MPS II (24 months) and lower for MPS IVA (8 months) when compared to the Colville and Bax [1996] study. These authors found that the age at diagnosis was 13, 21, and 19 months for MPS I, MPS II and MPS IV, respectively. However, that report did not specify how many patients showed the severe or attenuated forms of MPS I and MPS II. It also did not show how many patients with MPS IV were from subgroups A or B. As to age at diagnosis, all groups in our sample showed a greater delay at diagnosis (MPS I: 75 months; MPS II: 95 months; MPS IVA: 75 months) when compared to the data of Colville and Bax [1996] (MPS I: 30 months; MPS II: 51 months; MPS IV: 56 months).

In the study of Vijay and Wraith [2005] on the attenuated form of MPS I, the age at the onset of symptoms (34.8 months) and the age at diagnosis (110.4 months) were greater than those found in our work. This can be explained by the fact that our sample had patients with the severe form of the disease.

Studying patients with the attenuated form of MPS II, Young and Harper [1982] reported the age at the onset of signs and symptoms as being 4.3 years. In a study with patients with the severe form of MPS II, these same authors [Young and Harper, 1983] reported the age at the onset of signs and symptoms as being 2.5 years. Schwartz et al. [2007] reported median age at the onset of symptoms as being 1.5 years, and median age at biochemical diagnosis as being 6 years. Considering patients with the attenuated form, median age at the onset of symptoms and diagnosis was 3.2 and 14 years, respectively. As to patients with the severe form, the median age at the onset of symptoms and diagnosis was, respectively, 2 and 7 years.

A work with South-American MPS VI patients [Azevedo et al., 2004] found that 48% showed the beginning of the symptoms before the age of 6 months and the remaining 52% between the age of 6 and 36 months. The mean age at diagnosis was 48 months. In comparison, in this cohort, the median age at the onset of symptoms was 8 months, and the age at confirmation of diagnosis was 52 months.

In summary, in this cohort drawn from Brazilian medical centers the diagnosis of MPS was reached approximately 4.8 years after the onset of the first signs and symptoms. The group with most delay in the diagnosis was that with MPS II. This finding is likely due to the broader clinical heterogeneity of the disease. On the other hand, the group which showed the shortest time interval between the onset of clinical manifestations and the diagnosis was that with MPS IVA (3.6 years), which shows more homogeneous clinical manifestations.

Significant delays were encountered in the establishment of an MPS diagnosis in Brazil. This situation could be changed by improving the awareness of health professionals about the MPS diseases and by facilitating access to diagnostic tests. Information can

be provided by brochures, lectures, and the inclusion of lysosomal diseases and MPS in the curricula of schools that prepare health professionals. The earlier diagnosis of MPS patients is important to provide better genetic counseling, to enable a better management of complications, and to improve the outcome of specific treatments (like hematopoietic stem cell transplantation and enzyme replacement therapy) that are available for some of these conditions.

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