Diagnosis is in the Eye of the Beholder: Barriers to Early Diagnosis of Mucopolysaccharidosis in Children in India

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Abstract

The present study examined referral pattern and diagnostic practices for mucopolysaccharidosis (MPS) in India in 40 patients with a confirmed diagnosis. Time lag between age of onset of symptoms and consultation with primary physician ranged from 0 to 84 months, between consultation with primary physician and visit to genetic clinic of 0 to 128 months, from visit to genetic clinic and diagnosis of 1 to 111 months, and that between onset of symptoms and diagnosis 1 to 154 months. Major causes for delayed diagnosis were symptoms overlooked by physician (54%), late consultation by care giver (48.6%), late onset of symptoms (43.2%), and resource crunch (32.4%). Diagnosis at referral other than MPS was noted in 45%. Thus, diagnostic delay for MPS is common due to health seeking practices of parents, as well as physicians' clinical practices. Overcoming these barriers would necessitate strengthening awareness and educational activities for physicians and lay public.

Keywords
- lysosomal storage disorders
- glycosaminoglycans
- inborn errors of metabolism

Introduction

Mucopolysaccharidoses (MPS) are a group of seven disorders resulting from deficient activity of 11 lysosomal enzymes involved in glycosaminoglycans (GAGs) degradation.[1] Collectively, MPS are one of the commonest lysosomal storage disorders (LSDs) in India accounting for 22 to 33% of LSDs.[2–4] Common manifestations are short stature, intellectual impairment, large head, coarse facies, corneal clouding, abdominal and inguinal hernias, joint stiffness and deformities, joint laxity (MPS IV), spine deformities, and hepatosplenomegaly.[1]

Early diagnosis of MPS may be hampered by several factors as follows: suboptimal awareness among physicians, variability in age and severity of manifestations, wide spectrum of symptoms, and evolving phenotype.[5] Thus early nonspecific symptoms may not arouse suspicion of MPS and attenuated phenotypes, especially escape early detection.[6] Consequences of late diagnosis are high mortality and disability, multiple affected offsprings due to lack of genetic counseling and prenatal diagnosis, and ineligibility for treatment with hematopoietic stem cell transplant (HSCT) or enzyme replacement therapy (ERT). Benefit of therapy in the early stage of the disease is achieved by reversal of some manifestations or halting disease progress. Availability of established therapies for MPS makes assessment of diagnostic practices necessary. This would ensure that timely diagnosis makes patients eligible for therapy in India. It is therefore critical to examine prevalent diagnostic practices for MPS to identify barriers that need to be overcome for early diagnosis.

The primary objective of the present study was to determine diagnostic practices that hamper early and/or correct diagnosis of MPS in India. A secondary objective was to determine the referral pattern for MPS.

Patients and Methods

This was a single center, observational study at a genetic clinic of a tertiary care public hospital in Mumbai, India, from March 2016 through October 2017. Medical records from January 2005 through February 2016 of all patients confirmed to have MPS by demonstration of deficient enzyme

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Table 1 Results of diagnostic evaluation of 128 patients suspected to have mucopolysaccharidosis (MPS)

Confirmed diagnosis of MPS ($n = 40$)		Diagnosis of MPS unconfirmed ($n = 88$)			
Leukocyte enzyme activity	Leukocyte enzyme activity + genotype	Qualitative urinary GAGs	Quantitative + qualitative urinary GAGs	Radiological investigation	Others (ENT, ophthalmology)
33 (82.5%)	7 (17.5%)	6 (6.8%)	34 (38.6%)	72 (82%)	38 (43.2%)

Abbreviations: ENT, ear–nose–tongue; GAG, glycosaminoglycans.

activity and/or genotyping were retrospectively analyzed. Apart from demographic data, parameters recorded were age at onset of first symptom, age at visit to primary physician and referral to the genetic clinic, age at the time of diagnosis, referring physician's diagnosis, reasons for late presentation, and treatment received prior to referral. The time lag between onset of symptoms and diagnosis was computed.

Results

Over 11 years, 1,180 out of 4,638 referrals to the genetic clinic were clinically suspected to have LSDs. Of these 1,180 patients, 128 (10.8%) were suspected to have MPS. At our center, evaluation for suspected MPS includes radiological examination and screening by quantification of urinary GAG and urine GAG electrophoresis. Those with abnormal screening results are advised confirmation of diagnosis by enzyme activity. Option for type-specific genotyping is offered upon confirmation of diagnosis. Nature of diagnostic evaluation is presented in ►**Table 1**. Amongst those with a confirmed diagnosis of LSDs (114 patients), MPS accounted for 35% of cases making it the most frequent LSD at our Center. The distribution of subtypes of MPS in our study is presented in ►**Table 2**.

Age distribution of the 40 patients (male:female ratio = 2.6:1) is shown in ►**Table 3**. Parental consanguinity was present in 16 patients (40%; third-degree consanguinity in 14). There was a history of an additional family member with MPS in 11 cases (27.5%); apart from the index case one family had three additional affected members and each of the other two families had two additional affected members.

Table 2 Distribution of mucopolysaccharidosis (MPS) subtypes and corresponding enzyme activity ($n = 40$)

Type of MPS	No. of patients	Range of enzyme activity (nmol/h/mg protein)	Laboratory reference range (nmol/h/mg protein)
I IH/IHS/IS	4 (10) 2/1/1	α-L-iduronidase 1–14	20–108
II	9 (22.5)	Iduronate-2-sulfatase	
	6	0–2.3	15–57
	1	0	494–1113
	1	0.05	17–46
	1	4.5	167–475
III A	7 (17.5) 2	Heparan–N-sulfatase 0.17–0.6	1.3–6.8
B	4	α-N-acetylglucosaminidase 0–1.2	6–20.5
C	1	Acetyl CoA: glucosaminide acetyltransferase 0.5	11.1–48
IVA	16 (40)	N-acetylgalactoseamine-6-sulphate sulphatase	
	7	0–2.9	23–283
	1	12	24–205
	2	0–7	23–152
	4	2.3–8.6	40–70
	2	0–2.1	3.9–21
VI	4 (10)	N-acetyl galactosamine-4-sulfatase	
	1	12.6	115–226
	2	6.6–6.8	8.4–45.2
	1	0.12	0.6–8.5

Abbreviations: IH, Hurler; IHS, Hurler-Scheie; IS, Scheie.
Note: Figures in parentheses represent percentage.

Table 3 Age distribution and age at onset, visit to physician, referral, and diagnosis ($n = 40$)

Age	Onset of symptoms	Visit to primary physician	Referral to genetic clinic	Presentation to genetic clinic	Age at confirmation of diagnosis
Median (mo)	21	24	45	52.5	63.5
Range (mo)	0.03–84	0.03–132	2–132	2–144	3–162
Age (y)					
<1	16 (40)[a]	11 (27.5)	3 (7.5)	2 (5)	3 (7.5)
1–5	23 (57.5)	24 (60)	26 (65)	21 (52.5)	17 (42.5)
>5–10	1 (2.5)	4 (10)	9 (22.5)	16 (40)	17 (42.5)
>10	0	1 (2.5)	2 (5)	1 (2.5)	3 (7.5)

Note: Figures in parentheses represent percentage.
[a]Figures represent number of patients.

Four patients had an affected undiagnosed sibling and three patients had a history of death of an undiagnosed sibling with similar features.

Analysis of the ages at onset, visit to a physician for symptoms, referral to genetic clinic, and confirming diagnosis is presented in ►**Table 3**. Number of patients who had onset of symptoms, visit to physician, referral to genetic clinic, presentation to genetic clinic, and confirmation of diagnosis with respect to various ages is also presented in ►**Table 3**. Two infants presenting at 5 (MPS IV) and 2 months of age (MPS VI) were referred in view of coarse facies and affected older siblings in both and kyphosis in the patient with MPS IV. The median time lag (in months) between age of onset of symptoms and consultation with primary physician was 0 (range: 0–84) and 7 (range: 0–128) between consultation with primary physician and visit to genetic clinic. Median time period (in months) from visit to genetic clinic and diagnosis was 6 (range: 1–111). A median time lag of 35.8 months (range: 1–154) was noted between onset of symptoms to diagnosis.

MPS was correctly suspected by referring physician in just 22 cases (55%). MPS was not suspected before referral in the other 18 (45%) cases where the referring diagnosis was unspecified genetic disorder and rickets (MPS IV) in four cases (10%) each, skeletal dysplasia (MPS IV) and attention deficit hyperactivity disorder (ADHD); MPS III) in three cases each (7.5%), hypothyroidism (MPS I and MPS II) in two cases (5%), and achondroplasia (MPS IV) and glycogen storage disorder (MPS III) in one patient (2.5%).

Causes for delayed diagnosis ascertained in 37 patients were symptoms overlooked by physician (20), late medical consultation by care giver (18), and resource limitation (monetary, time, professional commitment, residence in remote areas, and unstable general condition) (12). Parents were erroneously reassured by the physician in seven cases (19%), parents overlooked symptoms in six cases (16.2%), and in four cases (11%), parents did not visit the genetic clinic despite referral. Apart from these, late onset of symptoms was observed in 16 (43.2%) of patients. Need for uncommon surgeries at an unusually young age (median age of 4 months [range: 4 days–54 months]) failed to evoke suspicion of MPS in five cases (12.5%) undergoing seven surgeries (ligation of patent ductus arteriosus [MPS IVA], inguinal hernia repair [MPS I], cervical vertebral C1–C2 fixation [MPS IV A], genu valgum correction [MPS IVA], correction of congenital talipes equinovarus [MPS I], and adenoidectomy [MPS I]].

Discussion

The present study and available published data indicate that MPS is the most common LSD in India.[2–4] Therefore among the rare diseases in India, proportion of treatment beneficiaries with MPS may be substantial under Government of India's proposed National policy for treatment of rare diseases. Therapy with ERT is prohibitively expensive and patient selection is critical to ensure optimum benefits. Some of the critical determinants of long-term therapeutic outcome are age at commencing therapy and early initiation of therapy before irreversible organ damage sets in.[7] Both these factors in turn depend on age of diagnosis. In this context, it is important to examine diagnostic practices for MPS in India.

Our study including all types of MPS documents a median delay of 35.8 months from onset of symptoms to diagnosis. For global comparison, few studies have addressed delays and barriers for diagnosis of MPS. In the Asia Pacific region, the mean ages in months at onset of symptoms, presentation, and diagnosis for MPS IVA were 77.1, 78.9, and 113.8, respectively.[8] Another study from Mexico documented a delay of 16 months from suspicion to diagnosis of MPS IV A.[9] In the Netherlands, Kuiper et al reported median diagnostic delay from visit to physician to final diagnosis: 9 months (range: 1–147 months) for MPS I, 39 months (range: 2–438 months) after visit to general practitioner, and 33 months (range: 1–365 months) after visit to medical specialist for MPS III.[10] Bruni et al noted an average delay of 3 years for diagnosis of attenuated MPS I in Europe, Latin America, and North America.[6] Thus diagnostic delays vary by subtype of MPS, severity of phenotype, and type of physician. These barriers could also be country specific depending on sociodemographic factors and availability and quality of health infrastructure.

Several factors contributing to delayed diagnosis were identified in our study, namely, delayed referral/visit to the genetic clinic and delay in diagnosis after genetic consultation. Additionally, MPS was not suspected by the physician

and an alternative clinical diagnosis was considered in 45% of cases or parents were incorrectly reassured. A survey of diagnostic practices for MPS I in Europe, Latin America, and North America disclosed that with the exception of geneticists or metabolic disease specialists, most physicians or specialists refer patients as a genetic disease or without suspicion of MPS, manage without diagnosis, reassure, manage, or monitor symptoms or make incorrect diagnosis.[6] This reflects low level of awareness among physicians worldwide. Apart from consulting general practitioners or pediatricians, patients with MPS visit several specialists like rheumatologists, orthopaedic surgeon, ENT (ear–nose–tongue) surgeon, neurologist, and endocrinologist on numerous occasions.[6,8,9] In our study, five patients had undergone surgeries without the surgeon suspecting MPS. These specialists may not be familiar with manifestations of MPS, thus the true nature of the disease is missed. Additionally, earliest manifestations of MPS like hearing loss, respiratory symptoms, and otitis media are nonspecific, whereas distinguishing features such as kyphosis, corneal clouding, cardiac disease, joint disease, and large head appear later.[11] Coarse facies is not a typical feature of MPS type IV, it is relatively mild in MPS III and skeletal or joint abnormalities in MPS III are subtle.[12,13] Overt corneal clouding is absent in MPS III and IV.[12,13] Symptoms, such as autism, behavioral and sleep abnormalities, and ADHD (typical of MPS type III), would not lead to suspicion of MPS. Thus, diagnosis may not be suspected early when familiar distinguishing features of MPS are not evident in type-III and -IV disease.

In an attempt to identify causes for late diagnosis in MPS IVA, Bhattacharya et al documented several factors such as atypical symptoms in 28%, subtle symptoms in 22%, symptoms resembling other diseases, and false negative urine GAG testing results.[8] Some of the incorrect diagnosis in their study were craniosynostosis, Leg–Calve–Perthe disease, Leri–Weil syndrome, Marfan's syndrome, and psuedoachondroplasia.[8] Colmenares-Bonilla and Esquitin-Garduño also documented an alternative diagnosis at referral in 10 out of 50 cases of MPS IVA.[9] Most frequent misdiagnosis were skeletal dysplasia (4/10), achondroplasia (2/10), and one case each as Ehlers–Danlos and Soto's syndromes.[9] MPS I may be mistaken for rheumatoid arthritis, autoimmune or connective tissue disorders, or rickets,[6,14] and MPS III is incorrectly diagnosed as ADHD, autism, idiopathic developmental delay, and speech delay.[13] In our study, 50% of patients with MPS IV were misdiagnosed as rickets, skeletal dysplasia, and achondroplasia. Thus, due to the nature of bony defects and short stature, MPS IV is particularly prone to delayed diagnosis and misdiagnosis often as skeletal dysplasia.[12] In such cases, geneticists or metabolic specialists ultimately make the correct diagnosis.[6,8,9] This underscores the importance of a genetic referral for patients suspected to have a skeletal dysplasia. As a corollary, physicians should meticulously examine for systemic signs in suspected skeletal dysplasia and perform testing for MPS when multiorgan involvement is detected.

Apart from documenting delayed or incorrect diagnosis, our study reveals that an overwhelming majority of cases suspected to have MPS were unconfirmed as diagnostic testing was incomplete. Enzyme estimation from peripheral blood leukocytes or dried blood spots is expensive. This is relevant as almost all health-related expenditure in India is out of pocket[15] and hence testing for MPS is often unaffordable. Also, availability of testing is restricted to metropolitan cities in India. It could also be speculated that affected children succumb before evaluation is complete, or there is no motivation for parents to spend on expensive diagnostic tests especially when a disease has no cure or therapy is inaccessible and/or unaffordable.

What's New

This study documented a median diagnostic delay of 35.8 months for mucopolysaccharidosis from symptom onset and identifies caregiver and physician related barriers contributing to the diagnostic delay for the first time in India.

Limitations

The present study had some limitations. Being a rare disease with small number of patients, a prospective study could not be planned resulting in lack of uniformity in nature of recorded data. Data extracted retrospectively from medical records were sometimes incomplete though every attempt was made to obtain missing information during follow-up visits. Recall bias in parent reporting would influence accuracy for time points like age of onset of first symptom and age at first consultation.

Conclusion

In conclusion, our study documented a median delay of 35.8 months for diagnosis of MPS in India. Contributory factors were caregiver (medical attention seeking behavior, ignoring or overlooking symptoms, and limited resources for diagnostic testing) and physician related, chiefly lack of familiarity with manifestations of MPS, and incorrect diagnosis. One strategy to promote awareness and early recognition of MPS is to strengthen educational activities by conducting awareness campaigns, organizing lectures at various scientific and academic forums, dissemination of educational material, and media exposure of events organized by patient support groups.

Ethical Approval

This study was reviewed and approved by the Institution's ethics committee.

Authors' Contributions

M.M. conceptualized the study, designed the protocol, supervised data collection and analysis, and wrote the manuscript. M.G. collected and analyzed the data.

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Conflict of Interest

None declared.

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