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ORIGINAL ARTICLE

The Face of Lysosomal Storage Disorders in India: A Need for Early Diagnosis

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Abstract
Objectives To study the temporal pattern of lysosomal storage disorders (LSD) from onset of symptoms to the final diagnosis and to study the type and the frequency of the disease.
Methods Retrospective analysis of the case record forms of the patients attending the Genetic Clinic over a period of 12 y (January 2002- December 2013) was undertaken. Only the data of the patients who had confirmatory enzyme analysis or mutation study for LSD was further analysed. The age at onset, suspicion of the illness, first clinical presentation to a tertiary Genetic centre, and the age at the final diagnosis of these confirmed cases was noted.
Results A total of 5,858 patients were referred to the Genetic clinic in this period. The diagnosis of LSD was suspected in 532 patients (9.08 % of all referrals) and it could be confirmed in 119 cases (2.03 % of all referrals). Maximum patients were diagnosed with Gaucher disease (31.93 %) followed by Mucopolysaccharidoses (20.16 %). Mutation analysis was available in 21 patients (17.64 % of the diagnosed cases). The median time interval between onset and suspicion was 6 mo. The median interval between onset and presentation to the authors' Genetic clinic was 12 mo. The median interval between the onset of the disease and its confirmation was 14 mo. The median interval between presentation to the Genetic centre and diagnosis was barely 1 mo.
Conclusions The incidence of LSD at authors' centre was 2.03 %, though it was suspected in 9.08 % of patients. The delay in diagnosis was hugely due to the late suspicion and thereby the late referral to a tertiary centre.

Keywords Lysosomal storage disorders · Delayed referral

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Introduction

India has, in the past few years, witnessed an increase in the burden of genetic diseases, including lysosomal storage disorders (LSD) [1]. These disorders are progressive and most of them are multisystemic [2]. The availability of promising therapeutic options has put the onus of early diagnosis on the Pediatrician. Instituting therapy at an early stage can limit the organ damage and the disability, thus boosting the quality of life of these patients [2].

However, like other inborn errors of metabolism, there could be barriers for the early diagnosis of LSD in a resource poor set up like India [3]. In order to overcome such obstacles, it is imperative to have an audit of the existing diagnostic practices to document the timeline to reach a diagnosis. This would aid in identifying the factors that contribute to delayed diagnosis, pinpoint the stage in the diagnostic journeys where the obstacles occur and help formulate strategies to overcome these obstacles. Thus the present study aimed at documenting the time period in obtaining a diagnosis of LSD and identifying factors that delay the diagnosis. The secondary objective was to study the type and the frequency of LSD at authors' centre.

Material and Methods

The study was initiated after approval of the protocol and the design by the Institutional Ethics Committee. Cases registered at the Genetic Clinic of a tertiary referral centre in Mumbai, over a period of 12 y from 1st January 2002 to 31st December 2013 were analysed retrospectively. Case records of patients who were evaluated for LSD were retrieved and analysed. The number of patients suspected to have LSD and the number of patients having a confirmed diagnosis of LSD (based on enzyme or mutation analysis) were noted. The time profile

of the confirmed cases was noted in the form of age at onset, suspicion, clinical presentation to the Genetic Clinic and the final diagnosis. The age of onset was defined as the age when the first clinical symptom was noticed by the informants. The age of suspicion was the age at which the first suspicion of an illness was made, either by the parent or by the physician. The age at final diagnosis was defined as the age at which the confirmatory enzyme/ mutation study was obtained. The mutation reports were also noted, when available.

Results

During the study period a total of 5,858 patients were referred to the Genetic Clinic. Diagnosis of LSD was suspected in 532 patients (9.08 % of the total referrals). Of these 532 patients in whom the diagnosis was suspected, 335 (62.96 %) were lost to follow up, incompletely investigated or had died. Of the remaining 197 patients, the diagnosis of LSD was ruled out in 78 patients and could be confirmed in 119 cases (33.80 % of the suspected cases, 2.03 % of the total referrals). Of these 119 patients, only 47 (40.33 %) were from Mumbai; while the rest 71 (59.66 %) had to travel from different parts of India to avail of services at the authors' Genetic Clinic. Maximum patients were diagnosed with Gaucher disease (31.93 %) followed by Mucopolysaccharidoses (20.16 %) (Table 1). Mutation analysis was available in 21 patients (17.64 % of the total diagnosed cases) (Table 2). Of the 21 patients for whom mutation analysis was available, 17 (80.95 %) of the mutations were patients with Gaucher Disease.

Table 1 Distribution of the 119 confirmed cases of LSDs at a tertiary centre from January 2002- December 2013

Disorder	Number of cases (*N*=119)
Gaucher disease	38 (31.93)
Mucopolysaccharidoses	24 (20.16)
GM1 Gangliosidosis	10 (8.40)
Tay Sach's disease	9 (7.56)
Sandhoff's disease	9 (7.56)
Niemann Pick disease	9 (7.56)
Metachromatic Leukodystrophy	8 (6.72)
Krabbe disease	5 (4.20)
Neuronal Ceroid Lipofuscinosis	3 (2.52)
Mucolipidosis II	2 (1.68)
Pompe disease	1 (0.84)
Farber disease	1 (0.84)
TOTAL	119

Figures in parentheses indicate percentages

Overall, the median age of onset of the disease was 8 mo (range 0.5–254 mo). The median age for clinical suspicion was 18 mo (range 2–257 mo), whereas the median ages for presentation and confirmation of diagnosis were 27 and 30 mo respectively (range 3.5–274 mo and 4–269 mo, respectively) (Table 3).

The median time interval between onset and suspicion was as long as 6 mo with the longest interval being about 12.5 y. The median interval between the onset and presentation to the Genetic Clinic was 12 mo, with the longest interval being nearly 17.5 y. The median interval between the onset of the disease and its confirmation was 14 mo. This data shows that there was a median interval of over a year after the disease onset, before a child was diagnosed with a confirmatory test (Table 3).

However this delay was largely due to the late suspicion and thereby the late referral to a tertiary centre, rather than the diagnostic work up thereafter. This is reflected by the fact that the median interval between presentation to a specialist Genetic Clinic and diagnosis was barely 1 mo (range 0–11 mo).

Discussion

There exist multiple hurdles in the early diagnosis of lysosomal storage disorders. These hurdles could be due to the patients themselves (like lack of follow up, lack of awareness, delay in seeking medical help), primary care physicians (like delayed suspicion and referral) and the health care system (like dearth of tertiary genetic referral centres, lack of universal health insurance policy and adequate diagnostic facilities at affordable costs). In the present study, a total of 5,858 patients were referred to the Genetic Clinic. Diagnosis of lysosomal storage disorders could be confirmed in only 119 cases (2.03 % of the total referrals), while the dropout rate was as high as 62.96 %. The prohibitive costs of the investigations, dearth of diagnostic facilities [4, 5], illiteracy and the lack of incentives for diagnosis (since treatment is not always possible); could be the contributory factors for this high dropout rate. Thus, current prevalence figures may underestimate the actual frequency of these disorders. The fact that almost 60 % of the patients had to travel from outstations to avail of the services at authors' centre, highlights the additional cost borne by the families. The financial constraints involved in travel, accommodation, repeated hospital visits add to the woes of the patient. Health care funding in the Indian scenario is mainly made directly out-of-pocket by nearly 71.13 % of the patients. The absence of a universal health insurance makes the scenario even grimmer [6].

In the current study, maximum patients were diagnosed with Gaucher disease (31.93 %) followed by Mucopolysaccharidoses (MPS) (20.16 %). In a recent study

Table 2 List of mutations detected in patients with LSD presenting to authors' centre

Serial number	Diagnosis	Mutation
1–7.	Gaucher disease (7)	Homozygous *L444P*
8.[a]	Gaucher disease (1)	Homozygous *G355D*
9.[a]	Gaucher disease (1)	Homozygous *R359Q*
10.[a]	Gaucher disease (1)	Homozygous *S356F*
11.	Gaucher disease (1)	Homozygous *S125R*
12.	Gaucher disease (1)	Homozygous *F123 I/(c754A)*
13.	Gaucher disease (1)	Homozygous *R448W*
14.	Gaucher disease (1)	*Rec Ex2* (c.44 T>C+46A>G+IVS2+ Ig> a: R170C (C.625 C>T, exon 6)
15.	Gaucher disease (1)	*L444P/A456P/R496C/55 bpdel*
16.	Gaucher disease (1)	*L444P, R643C*
17.	Niemann-Pick disease (1)	Homozygous *R543X*
18.	Pompe disease (1)	*c.1003G> A (p.G335R)*
19.	Maroteaux-Lamy syndrome (MPS VI) (1)	Homozygous *W450C*
20.	Metachromatic leukodystrophy (1)	Compound heterozygous for *G34E* and *P136L*
21. [b]	Farber disease (1)	Homozygous *IVS6+ 4A> G*

Figures in parentheses indicate the absolute number of patients diagnosed with the respective mutation

[a] Published: Reference number 10

[b] Published: Reference number 9

carried out in Western India, the case distribution of LSD during the time interval of 2002–2012, revealed MPS topping the list (22 %) followed by Gaucher disease (16 %) [4]. In another study elucidating the spectrum of LSD in Northern India over a period of 3 y, the commonest diagnosis was MPS followed by Gaucher disease [5]. The present centre is one of the few centres in the country to offer enzyme replacement therapy for Gaucher disease. Thus there is a possibility of a referral bias for the suspected cases of Gaucher disease to authors' centre, thereby resulting in relatively more cases of the same. Besides, the confirmatory diagnosis of MPS often requires the testing of multiple enzymes, due to the overlapping nature of the clinical presentation of the different subtypes of MPS [2, 7]. This could result in greater financial constraint, causing a higher drop-out rate and ultimately resulting in relatively fewer patients diagnosed.

Table 3 Time profile of the 119 confirmed cases of LSD presenting at authors' centre from January 2002- December 2013

Time parameter*	Median value (mo)	Range (mo)
Onset (O)	8	0.5–254
Suspicion (S)	18	2–257
Presentation (P)	27	3.5–274
Diagnosis (D)	30	4–269
Interval between onset and suspicion (S-O)	6	0–149
Interval between onset and presentation (P-O)	12	0–208
Interval between onset and diagnosis (D-O)	14	1–162
Interval between presentation and diagnosis (D-P)	1	0–11

*Definitions of the time parameters

O- Age of the first clinical symptom; S- Age at first suspicion of an illness; P- Age at presentation to the Genetic centre; D- Age at which the confirmatory enzyme/ mutation study was obtained

An Indian study on LSD reported mutations in only seven families of the 68 confirmed patients [5], reflecting the underutilization of genotyping in the comprehensive evaluation of LSD. The advantages of conducting genotype analysis for patients with LSD are multifarious. Other than confirming the diagnosis, it also has a role in detecting carriers in the family since enzyme analysis does not always reliably detect heterozygous carriers [8]. It also increases the accuracy of prenatal diagnosis [8]. In certain LSDs like Gaucher disease, genotype analysis also has a role in phenotype prediction [8]. In the current study, three of the 21 confirmed mutations for LSD were novel, while four have been published [9, 10]. The novel mutations were homozygous *R543X* mutation in a patient with Niemann-Pick disease, homozygous *W450C* mutation in a patient with Maroteaux-Lamy syndrome (MPS VI) and the homozygous mutation *IVS6+ 4A> G* in the patient with Farber disease [9].

With improving socioeconomic conditions, the incidence of primarily "environmental" disease is declining in most developing countries, largely because of better basic public health measures and the introduction of vaccination programs for childhood infectious diseases. As a result, genetic disorders now account for an increasing proportion of morbidity and death [11]. The incidence of LSD varies from 1 in 1,500 to 1 in 7,000 live births [2]. With 26 million births occurring in India every year, the extrapolated burden of LSD would be nearly 3,700 to 17,000 affected babies born every year. Therefore, these disorders can no longer be perceived to be

rare. This calls for heightened awareness about the diseases among Pediatricians for suspecting diseases and for timely referral [4].

The broad spectrum and overlapping nature of phenotypes in different LSDs can make their recognition difficult [2]. The task is made even more challenging by the fact that the clinical manifestations and their severity can vary markedly within a single disorder or its subtype [2]. The fact that atypical presentations of LSD are common, makes the diagnosis a formidable challenge [2]. Many symptoms of LSD could mimic common childhood illnesses [2]. For example Fabry's disease often presents with misleading symptoms like severe right lower quadrant abdominal pain (misdiagnosed as acute appendicitis), unexplained pain in the extremities (misdiagnosed as growing pains) and the angiokeratomas (misdiagnosed as petechiae) [12]. Other examples where LSD can mimic other childhood illnesses include recurrent otitis media in Hunter syndrome and behavioral problems in MPS III [2]. Pompe disease is often misdiagnosed as hypothyroidism, myocarditis or acute flaccid paralysis due to poliomyelitis [13]. In such a scenario, the patients would be investigated and the alternative diagnosis of LSD would be considered late; thereby exhausting the patient funds, delaying referral to experts and contributing to the diagnostic lag. In the current study of 119 patients too, there were instances of overlooked diagnosis of LSDs. Patients with Gaucher disease were invariably suspected to have a hemoglobinopathy. Similarly, there are records showing that children with MPS IV were initially treated as rickets. Another child having MPS III was repeatedly following up in the Child Psychiatry department since he was diagnosed as having Attention Deficit Hyperactivity Disorder (ADHD).

When the time to reach diagnosis was compared from a retrospective study conducted by Glass et al. at the Hospital for Sick Children in Toronto [14], the mean age of consultation for confirmed cases of genetic metabolic disorder was 4.1 y. However 81 % of the cases were diagnosed within 1 mo of presentation to the metabolic specialist. In this respect the data was similar to the index study (1 mo for final diagnosis after referral to a specialised centre). The most important factor, which could be attributed to the early diagnosis in the Toronto study, was awareness of the referring physician and initiation of diagnostic workup prior to referral. The disparity with the present study is striking where the mean time required for the final diagnosis to be reached after the first clinical symptom was 14 mo. In the study from Toronto, at least 45 % of the referring physicians had initiated the diagnostic investigations for the presence of a metabolic disorder. Another fact apparent from the study was that not only did they suspect the presence of a metabolic disorder, but the initial diagnostic investigations sent were also appropriate. Therefore the most important modality for early diagnosis appears to be heightened physician awareness [14]. Lack of this factor could be one of the reasons for a delay of almost a year to confirm the diagnosis of lysosomal storage disorders in India. Physicians may not be aware of the most appropriate test, thereby losing out on precious time and resources [5]. As an example, there is undue reliance on techniques like bone marrow for diagnosis of Gaucher disease and Niemann-Pick disease; when enzyme analyses and genotyping are available and are in fact, the diagnostic tests of choice. Recent consensus guidelines, in fact discourage the use of bone marrow for the diagnosis of Gaucher disease, since these patients could bleed during the procedure due to the underlying thrombocytopenia and coagulopathy [8]. Other examples include over reliance on tests like urine spot (which is known to cause false positives and false negatives) for the diagnosis of MPS, when more robust, sensitive and specific tests are available.

In a resource limited set up like ours, the availability of Genetic centres with expertise are confined mainly to the metropolitan cities. Taking positive example from countries like Australia, Portugal and Czech Republic [4], India too should set up special working groups on LSDs that increase the awareness amongst the medical fraternity. Encouragingly enough, in India, very recently Indian Council of Medical Research (ICMR) has set up a special task force on LSDs which will focus on the magnitude of these disorders in the different parts of the country, increase awareness amongst clinicians by organising regional training programme, and establish common mutation spectrum for different LSDs [4].

As a result of the delayed diagnosis, the parents of the affected child lose out on timely genetic counseling, and the advantage of prenatal diagnosis. This puts the couple on the risk of having another affected child, thereby increasing the load of these diseases even further. In the index study, 26 patients (21.84 %) had history or biochemical investigations pointing towards an affected sibling. The absence of curative therapy for all disorders and state of art rehabilitation and support services, only adds to the financial, psychological and the social burden of the family, and the nation as a whole.

The need of the hour is to facilitate early and accurate diagnosis of these conditions and to offer timely prenatal care. The most critical issue in this respect would be to sensitize and educate the Pediatricians about the diverse clinical features of LSDs and the suitable investigations if these disorders are suspected. Increasing the awareness about these conditions in the general public is also desirable so that the parents too can pick up subtle features earlier in the course and avoid a delay in seeking medical advice. Genuine political and social commitment in concert with the above measures would hopefully help change the face of these disorders in a resource poor set up like ours.

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