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ORIGINAL ARTICLE

Demographic characteristics and distribution of lysosomal storage disorder subtypes in Eastern China

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Lysosomal storage disorders (LSDs) are a group of >50 different types of inherited metabolic disorders that result from defects in the lysosome. The aim of this study was to investigate the distribution and demographic characteristics of the different subtypes of LSDs in Eastern China. From 2006 to 2012, 376 out of 1331 clinically suspected patients were diagnosed with 17 different subtypes of LSDs at our hospital. Mucopolysaccharidoses (MPS) were the most common group of LSDs (50.5%), followed by sphingolipidoses (25.4%) and Pompe disease (19.8%). Mucolipidosis type II/III accounted for the remaining 4% of diagnosed LSDs. MPS II was the most common form of MPS, comprising 47.4% of all MPS cases diagnosed, followed by MPS IVA (26.8%) and MPS I (16.3%). Gaucher disease and Niemann–Pick disease type A/B were the two most common forms of sphingolipidoses. There was a large variation in the time between disease onset and eventual diagnosis, from 0.3 years in infantile-onset Pompe disease to 30 years in Fabry disease, highlighting timely and accurate diagnosis of LSDs as the main challenge in China.
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INTRODUCTION

Since the discovery of lysosomes by Christian de Duve in 1955,[1] >50 types of lysosomal storage disorders (LSD)s have been identified.[2] LSDs are characterized by the intralysosomal accumulation of undigested macromolecules in different cell types and tissues. The majority of LSDs stem from defects in the various lysosomal hydrolases, while other LSDs result from defects in activator or membrane proteins, or dysfunction in cholesterol and lipid transportation.

Many countries, such as the Netherlands, Australia, Portugal and the Czech Republic, have conducted epidemiological studies to assess their respective national incidence of LSDs, which is estimated to be 12.25–25.00 per 100 000 live births.[3–6] In Taiwan, the incidence of mucopolysaccharidoses (MPS), a subgroup of LSDs, has been estimated to be 2.04 per 100 000 live births.[7] While the individual subtypes of LSDs may be rare, one in 5000–7000 neonates are diagnosed with an LSD.[3,5] Epidemiological data are not only useful in determining the risk of disease and providing genetic counseling for family members, they are also important for assessing the economic burden of these diseases and the need for neonatal screening.

In spite of the low prevalence of LSD, China has a high number of LSD patients due to its large overall population of 1.3 billion people. While case studies,[8] clinical research[9–11] and genetic analyses[12–14] from Shanghai, Beijing and Guangzhou have been reported, these studies were limited to individual LSD subtypes and were conducted in small patient populations. Epidemiological data on LSD as a whole are lacking in China and nationwide estimation of LSD incidence and prevalence is yet to be undertaken in mainland China.

The aim of our study was to describe the subtype distribution and demographic characteristics of the various LSDs that were diagnosed by enzymatic assays in Eastern China.

SUBJECTS AND METHODS

Patients who attended the Department of Pediatric Endocrinology and Genetic Metabolism of Shanghai Xinhua Hospital from August 2006 to December 2012 and were clinically suspected of having LSD based on physical symptoms were tested for the respective LSDs. Patients with coarse facial features, growth retardation, skeletal deformities, enlargement of liver and spleen, mental retardation and joint abnormalities were screened for MPS (types I, II, IIIA, IIIB, IIIC, IIID, IVA, IVB, VI and VII) and mucolipidosis type II/III using enzymatic assays ($n=428$). Patients who presented with massive hepatosplenomegaly were tested for Gaucher disease and Niemann–Pick disease type A/B ($n=212$). Patients with regression or retardation of mental and motor ability were tested for other sphingolipidoses ($n=260$) including Krabbe disease, metachromatic leukodystrophy, GM1 and GM2 gangliosidoses. Juvenile and adult patients with a history of acroparesthesia, with or without proteinuria, were tested for Fabry disease ($n=3$). Patients who presented with hypotonia, hypertrophic cardiomyopathy, dyspnea and elevated levels of serum creatinine kinase were tested for Pompe disease ($n=428$).

Mucolipidosis type II/III was diagnosed by demonstration of a 10-fold elevation in the activities of α-mannosidase and β-hexosaminidase in serum.[15] Patients with suspected Pompe disease were screened by first assessing the activity of acidic α-glucosidase in dried blood spot on filter paper, followed by a confirmatory test in leukocytes for patients with a high probability of a positive diagnosis.[16] For patients suspected of other LSDs, the corresponding enzyme activities in leukocytes were measured for confirmatory diagnosis.[10,14,17,18] With the exception of mucolipidosis type II/III, which was diagnosed by elevated serum enzyme activity, all other LSDs were diagnosed by the absence or

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reduction of the respective enzyme activities, and the presence of classical clinical signs and symptoms. Most diagnoses were further confirmed by gene testing, which was not included in this report. All data were analyzed by the SPSS17.0 software package (SPSS Inc., Chicago, IL, USA). Informed consent was obtained from all patients or their guardians before blood samples were collected for enzymatic analysis.

RESULTS

Patient demographics

Of the 1331 participants who were clinically suspected of having an LSD, 376 (28.2%) were diagnosed with 17 different subtypes of LSDs (Table 1). The cohort of diagnosed patients included slightly more males (64.6%), but gender distribution was balanced between males and females (53.5% and 46.5%, respectively) after excluding patients with X-linked recessive diseases (MPS II and Fabry disease). The majority of patients (88%) were below the age of 18 years (Table 1). Individuals at or over the age of 18 years were regarded as adults. Patients with the adult form of Pompe disease ($n=21$) constituted nearly half of all adult cases, while Gaucher disease patients ($n=14$) constituted one-third. There were only four adult MPS patients diagnosed.

Patients in our study were from 21 provinces and municipalities in China, with 85.8% ($n=322$) from Eastern China, which includes Shanghai, Jiangsu, Zhejiang, Anhui, Fujian, Jiangxi and Shandong. A small proportion of patients were from Northern China ($n=2$), Northeast China ($n=3$), Southwest China ($n=8$), Northwest China ($n=9$), Southern China ($n=11$) and Central China ($n=21$) (Figure 1).

Eleven percent (42/376) of patients had a family history of the same LSD subtype, including 19 with MPS, 13 with sphingolipidoses, nine with Pompe disease and one with mucolipidosis type II/III (Table 1).

Distribution of LSD subtypes

Seventeen different subtypes of LSDs were diagnosed. Out of 428 suspected patients, 47.9% ($n=205$) had a confirmed diagnosis of MPS or mucolipidosis type II/III. MPS (50.5%) was the most common group of LSDs, followed by sphingolipidoses (25.8%) and Pompe disease (19.7%) (Figure 2). Mucolipidosis type II/III comprised 4% of all diagnosed cases. No patients were diagnosed with α-mannosidosis, α-fucosidosis, Schindler disease or MPS type IIIC/D in our study.

In the MPS group, MPS II represented nearly half of all MPS cases diagnosed (47.4%) and a quarter of all diagnosed LSD cases, followed by MPS IVA (26.8%), I (16.3%), VI (4.2%), IIIA/B (3.7%) and VII (1.1%) (Table 2). Only one patient was diagnosed with MPS IVB. In the MPS group, three types (I, II and IVA) constituted more than 90% of all MPS patients.

Out of 212 suspected patients, 70 (33%) were diagnosed with Gaucher disease and Niemann–Pick disease in the sphingolipidoses subgroup. For other sphingolipidoses, 27 (10.3%) out of 263 suspected patients were confirmed to be positive. Thus, Gaucher disease (39.2%) and Niemann–Pick disease (33.0%) were the two most frequent disorders in the sphingolipidoses subgroup, followed by metachromatic leukodystrophy (MLD) and Krabbe disease. GM1 gangliosidosis, GM2 gangliosidosis and Fabry disease were comparatively rare (Table 3).

Out of 428 suspected patients, 74 were diagnosed with Pompe disease. The two forms of Pompe disease, infantile onset and late onset, were equally represented (Table 4).

Age at symptom onset and diagnosis

The median (range) age at symptom onset of all LSDs was 1.9 years (0–42) and the median age at diagnosis was 4.8 years (0.25–49), with an interval between onset and diagnosis of 3.0 years (Table 1).

Table 1 Age at disease onset and diagnosis of patients with lysosomal storage disorders

Disease	*Median age at symptom onset (range), years*	*Median age at diagnosis (range), years*	*Interval, years*	*Number of patients*	*Number of adult patients*	*Positive family history, %*
Total	1.87 (0–42.00)	4.83 (0.25–49.00)	2.96	376	44	11.10
MPS (all types)	2.00 (0–12.00)	5.00 (0.83–29.00)	3.00	190	4	10.00
MPS I	1.25 (0–5.00)	3.50 (0.83–17.00)	2.25	31	0	0
MPS II	2.00 (0–8.00)	5.00 (1.20–27.00)	3.00	90	2	13.33
MPS IIIA/B	2.50 (0–5.50)	5.04 (0.91–8.00)	2.54	7	0	14.30
MPS IVA	2.00 (0.25–7.00)	6.30 (2.00–29.00)	4.30	51	2	0
MPS IVB	12.00	14.00	2.00	1	0	0
MPS VI	0.90 (0–8.00)	6.04 (1.50–11.50)	5.14	8	0	75.00
MPS VII	0.75 (0.50–1.00)	2.21 (0.92–3.50)	1.46	2	0	0.00
Mucolipidosis type II/III	0.25 (0–1.00)	1.50 (0.41–5.00)	1.25	15	0	6.66
Pompe disease (all types)	0.41 (0–42.00)	0.83 (0.25–49.00)	0.42	74	21	12.20
Pompe disease (infantile onset)	0.20 (0–0.75)	0.50 (0.25–2.00)	0.30	34	0	11.80
Pompe disease (late onset)	15.00 (1–42.00)	21.00 (5.50–49.00)	6.00	40	21	12.50
Sphingolipidoses (all types)	2.00 (0–40.00)	3.50 (0.33–47.00)	1.50	97	19	13.40
Fabry disease	8.50 (8.00–9.00)	38.50 (38.00–39.00)	30.00	2	2	100.00
Gaucher disease	2.50 (0–39.00)	7.75 (0.33–47.00)	5.25	38	14	3.16
Krabbe disease	1.50 (0.08–20.00)	2.75 (1.08–24.00)	1.25	8	1	0
GM1	0.33 (0.25–0.33)	0.91 (0.83–1.00)	0.58	3	0	0
GM2 (Tay–Sachs disease)	0.50	1.00	0.50	1	0	0
GM2 (Sandhoff disease)	0.66	1.20	0.50	1	0	0
MLD	1.75 (1.50–6.50)	2.66 (2.00–7.92)	0.90	12	0	8.33
Niemann–Pick A/B	1.00 (0–40.00)	2.80 (0.83–46.00)	1.80	32	2	15.63

Abbreviations: MPS, mucopolysaccharidoses; MLD, metachromatic leukodystrophy.
GM1 GM1 gangliosidosis, *GM2* GM2 gangliosidosis.

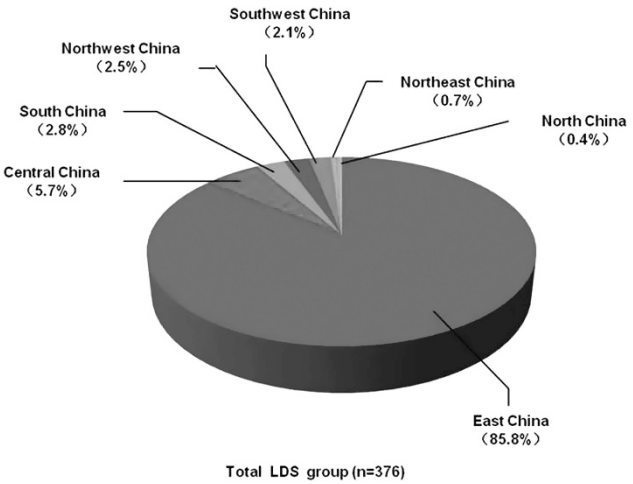

Figure 1 Geographical distribution of patients with lysosomal storage disorders diagnosed at our center. The majority of LSDs patients in this cohort were from Eastern China (85.8%). LSDs, lysosomal storage disorder. A full color version of this figure is available at the *Journal of Human Genetics* journal online.

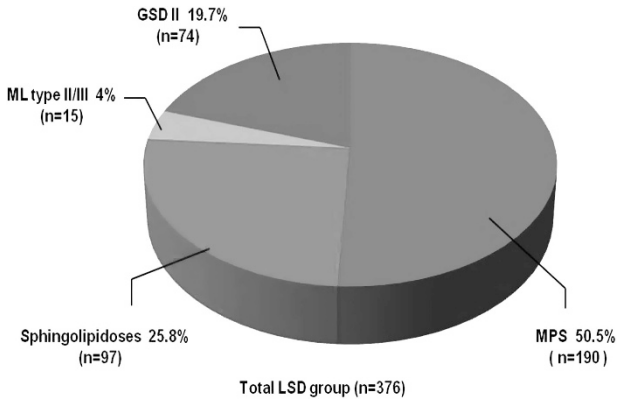

Figure 2 Frequencies of subtypes of lysosomal storage disorders diagnosed at our center. In this cohort of LSD patients, MPS which comprises half the number of patients, was the most common LSD, followed by sphingolipidoses, Pompe disease and mucolipidosis type II/III. LSD, lysosomal storage disorder; MPS, mucopolysaccharidose. A full color version of this figure is available at the *Journal of Human Genetics* journal online.

Table 2 Relative frequencies of mucopolysaccharidoses in different populations

	Our center		*The Netherlands*		*Australia*		*Portugal*		*Germany*		*Brazil*		*Northern Ireland*		*Taiwan*	
Disease	*N (male/female)*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*
MPS I	31 (16/15)	16.3	82	25.0	38	23.4	20	22.0	93	19.6	54	25.6	14	41.2	7	5.4
MPS II	90 (89/1)	47.4	52	15.8	26	16.0	22	24.2	86	18.1	24	11.4	6	17.6	68	52.3
MPS IIIA/B	7 (3/4)	3.7	156	47.4	58	35.8	23	25.3	211	44.5	42	19.9	3	8.8	25	19.2
MPS IVA	52 (25/27)	27.4	27	8.2	21	13.0	10	11.0	53	11.2	25	11.8	11	32.4	21	16.1
MPS VI	8 (4/4)	4.2	6	1.8	17	10.5	15	16.5	31	6.5	39	18.5	0	0	9	6.9
MPS VII	2 (1/1)	1.0	6	1.8	2	1.2	1	1.1	0	0	4	1.9	0	0	0	0
All types	190 (138/52)	100	329	100	162	100	91	100	474	100	211	100	34	100	130	100

Abbreviations: MPS, mucopolysaccharidosis.

For MPS, the median age at symptom onset was 2.0 years (0–12) and the median age at diagnosis was 5.0 years (0.83–29), with an interval between onset and diagnosis of 3.0 years (Table 1). MPS types IVA and VI had a comparatively longer interval between onset and diagnosis of 4.3 and 5.1 years, respectively. The median age at onset of sphingolipidoses was 2.0 years (0–40) and the median age at diagnosis was 3.5 years (0.33–47), giving an interval between the two of 1.5 years. Only two patients in this cohort were diagnosed with Fabry disease and diagnosis was delayed for both patients by >30 years. Median age at onset of symptoms of severe infantile-onset Pompe disease was 0.20 years (0–0.75), with diagnosis established within a short interval (0.30 years) at 0.50 years of age (0.25–2.0). In late-onset Pompe disease, the median ages at symptom onset and diagnosis were 15 (1.0–42) and 21 years (5.5–49), respectively, with an interval of 6.0 years.

DISCUSSION

Our hospital is currently the only center that provides lysosomal enzyme testing in Eastern China, with the exception of one kidney center for adults that provides enzyme testing for Fabry disease.[19] Most clinically suspected cases from the provinces or municipalities of Shanghai, Zhejiang, Jiangsu, Anhui and Jiangxi in Eastern China are referred to our center for a confirmatory diagnosis. Our data are thus highly reflective of the status of LSDs in Eastern China.

MPS was identified as the most common group of LSDs in our cohort of patients, which differs from epidemiological studies in Western countries such as Australia, The Netherlands and the Czech Republic, where sphingolipidoses has been identified as the most frequent LSD type.[3,5,6] Approximately one in five LSD patients in our cohort was diagnosed with Pompe disease, which is a higher proportion than in Western populations, in whom Pompe disease accounts for 3–17% of all LSDs.[3,5,6] On the other hand, the proportion of mucolipidosis type II/III in our study (4% of all LSDs) was similar to that reported in Europe and Australia.[3,5,6]

MPS II was the most common subtype of MPS, as well as the most common LSD, in Eastern China, accounting for 47.4% of all MPS cases and 23.9% of all LSDs. Similar findings have been reported in Southern China, where MPS II accounts for 38% of all MPS cases diagnosed,[9] and in Taiwan, where MPS II constitutes 52% of all MPS.[7] In contrast, other MPS types are more prevalent in non-Chinese populations. In Brazil and Northern Ireland, MPS I is the most common MPS subtype,[20,21] while MPS III is the most common subtype in Australia, Germany and The Netherlands where only 16–24% of all MPS cases are MPS II,[3,5,22] a substantially lower proportion than in China.

The higher prevalence of MPS II in Chinese populations than in Western populations is possibly due to the higher allele frequency of the iduronate 2-sulfatase (IDS) R468 mutation in East Asia. It was

Table 3 Relative frequencies of sphingolipidoses in different populations

	Our center		*The Netherlands*		*Australia*		*Czech Republic*		*Portugal*	
Disease	*N (male/female)*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*
Fabry disease	2 (2/0)	2.1	27	6.4	36	14.8	49	19.0	4	1.9
Gaucher disease	38 (19/19)	39.2	102	24.0	71	29.1	49	19.0	84	40.6
GM1	3 (3/0)	3.0	20	4.7	10	4.1	13	5.0	9	4.3
GM2 (Tay–Sachs and Sandhoff diseases)	2 (1/1)	2.1	49	11.6	29	11.8	13	5.0	49	23.6
Krabbe disease	8 (5/3)	8.2	70	16.5	21	8.6	15	5.8	11	5.3
MLD	12 (7/5)	12.4	103	24.3	35	14.3	25	9.6	21	10.1
Niemann–Pick A/B	32 (21/11)	33.0	27	6.4	16	6.6	23	8.8	11	5.3
Others	0	0	26	6.7	26	10.7	72	27.8	18	8.7
Total	97 (58/39)	100	424	100	244	100	259	100	207	100

Abbreviation: MID, metachromatic leukodystrophy.
GM1 GM1 gangliosidosis, *GM2* GM2 gangliosidosis.

Table 4 Relative frequencies of Pompe disease in different populations

	Our center		*Czech Republic*		*The Netherlands*	
Disease type	*N (male/female)*	*%*	*N*	*%*	*N*	*%*
Infantile onset	34 (20/14)	45.9	6	50.0	67	42.1
Late onset	40 (20/20)	54.1	6	50.0	92	57.9
Total	74 (40/34)	100	12	100	159	100

found that in a cohort of 38 Chinese MPS II patients, 13.2% had the IDS R468 mutation.[18] In Taiwanese patients, IDS R468 mutations accounted for nearly half (42.9%) of all mutations.[23] In addition, 11.6% of patients were identified with IDS R468 mutations in a group of 43 Japanese individuals with MPS II.[24] In contrast, only <6% (6/103) of patients diagnosed with MPS II in South America had IDS R468 mutations.[25]

Our study also identified MPS IVA as the second most common MPS in Eastern China, where it accounted for 27.4% of all MPS cases (Table 2). This is a slightly lower proportion than that in Northern Ireland, which has the highest incidence of MPS IVA (32%) among Western populations.[3,4,5,20]

Gaucher disease was found to be the most common type of sphingolipidosis in Eastern China, with 38 (39.2%) of the 97 sphingolipidosis patients at our center affected. This is in line with Western countries: Gaucher disease was found to be the most common sphingolipidosis in Australia, the Czech Republic and Italy.[3,6,26] Also, in China, Gaucher disease is the only disease that can be treated by enzyme replacement therapy, [11] and as such, public awareness of this disease may be greater compared with other LSDs. In contrast with Australia, The Netherlands and Portugal, where Niemann–Pick disease type A/B was reportedly less common than MLD and Krabbe disease,[3–5] 32 (33%) patients were diagnosed with Niemann–Pick disease type A/B at our center, making it the second most common sphingolipidosis in Eastern China. As for GM2 gangliosidosis in the sphingolipidoses group, the proportion of such patients ranged from 5% in the Czech Republic to 23.6% in Portugal (Table 3); in our study that proportion was found to be 2.1%, which is much lower than that observed in Western populations.[3–6]

Delayed diagnoses of LSDs were found to be common in our study. The interval from onset of symptoms to disease diagnosis of ten patients with Hurler syndrome was demonstrated to be 1.8 years, which is far longer than the 0.3-year interval reported in a global disease registry where age at onset was comparable (0.70 versus 0.8 years).[27] This delay in diagnosis may be due to the lack of awareness and experience of clinicians in recognizing the variable phenotypic presentation of this rare group of diseases. Also, most clinics and hospitals in China lack the diagnostic facilities required for measurement of enzyme activities associated with LSDs.

Although most LSDs have maturity-onset subtypes, our study did not identify any adult MLD patients. This is in contrast with reports from the Netherlands, the Czech Republic and Portugal where adult-type MLD accounted for 22.3–33.3% of all MLD patients[4–6]. Many reasons may underlie the absence of adult MLD patients in our cohort. First, symptoms are often atypical and milder in the adult form than in the infantile and juvenile forms. Second, compared with pediatricians, physicians caring for adults may lack awareness of genetic metabolic disorders that are often associated with paediatric patients. In addition, in contrast to Gaucher disease where the presence of Gaucher cells in bone marrow biopsies suggests a positive diagnosis, no such test is available for adult MLD, making adult MLD difficult to diagnose. In this study, 44 out of 250 clinically suspected adults were diagnosed with an LSD, indicating that LSDs, particularly late-onset Pompe, Fabry and Gaucher disease, are starting to be recognized by clinicians other than pediatricians.

In our study, 11% of LSD patients had positive family histories, which reflects the importance of confirmatory testing and genetic counseling. There is great necessity for early diagnosis of LSDs in China. Early diagnosis can alert parents to seek genetic testing and prenatal diagnosis to make informed decisions based on the risk of their children inheriting the disorder. Furthermore, treatments such as enzyme replacement therapy, substrate reduction therapy and haematopoietic stem cell transplantation are available for some LSD subtypes and could be carried out before the onset of irreversible pathological changes, thereby ameliorating disease burden by significantly impacting the disease course.

A limitation of this study was that some patients tested in our center were not from Eastern China. One main reason is that our hospital has a well-known and well-established paediatric department which attracts patients from other regions in China. Nevertheless, these patients accounted for only <15% of the cohort and we believe that

this cohort remains representative of patients in Eastern China. Furthermore, the distribution and demographic characteristics could be underestimated as a result of misdiagnosis or delayed diagnosis, which is common or widespread in small cities and rural areas in China. Finally, as most patients with Fabry disease are adults, they are highly likely referred to the adult kidney center instead, resulting in a lower diagnosed prevalence of Fabry disease in our center.

In conclusion, our study was the first to investigate the distribution and demographic characteristics of the various LSD subtypes in Eastern China. MPS II and Pompe disease are the two most common LSDs in Eastern China. Other common subtypes include MPS IVA, Gaucher disease and Niemann–Pick disease type A/B. In the light of the varied clinical manifestations of LSDs and the great delay in diagnosis, we believe that multidisciplinary collaboration will have a significant role in improving care for patients with LSDs. We look forward to cooperation with the three other LSD diagnostic centers in China to conduct more comprehensive surveys on the prevalence of LSDs in the country to provide more valuable information for genetic counseling and public health.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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