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Overview of Lysosomal Storage Diseases in Kurdistan Region/ Iraq

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Abstract

Background and objectives: The lysosomal lipid storage diseases are diverse disorders each due to an inherited deficiency of a lysosomal hydrolase enzyme leading to the intralysosomal accumulation of the enzyme's particular substrate; each catabolic step, with the exception of the catabolism of lactosylceramide, has a genetically determined metabolic defect and a resultant disease. The objective of this study was to have a better review of these diseases' burden in the region.Methods:A data of 37 patients were collected from 2013 to 2017 in the cities of the region, namely (Sulaimany, Erbil, Duhok, and Kirkuk) retrospectively through establishing a questionnaire distributed to the families of patients in whom the disease was established, and diagnosis was settled, and treatment already initiated to the patients. **Results:** Gaucher and Mucopolysaccharidosis were equally the commonest (17 patients, 45.9%), lysosomal storage diseases were found to be more common in males (59.4%), and more in Kurdish descendants (75.7%). most patients were from Duhok city (43.2%). Consanguinity was positive in (83.8%) of patient's parents. Twenty-four patients (64.9%) of overall lysosomal storage disease were receiving enzyme replacement therapy. Among patients receiving treatment; 20 (83.3%) had showed improvement in their condition, compared to none 0% of patients who did not receive treatment. abdominal distention was the most common first presenting complaint in lysosomal storage diseases (10 patients, 27%). **Conclusions:** Lysosomal storage diseases are more common in consanguine marriage and will respond well to enzyme replacement therapy if regularly provided, it will decrease mortality and morbidity due to the disease.

Keywords; Lysosomal storage diseases; Gaucher disease; Kurdistan region.

Introduction

The lysosomal lipid storage diseases are diverse disorders each due to an inherited deficiency of a lysosomal hydrolase enzyme leading to the intralysosomal accumulation of the enzyme's particular substrate[1]. Inheritance is autosomal recessive except for X-linked recessive Fabry disease, and hunter disease (MPS2), and Danon disease which's X-linked dominant[2, 3].

Table (1): Lysosomal storage disease classification[4].

Mucopolysaccharidosis (mps)	Lipidoses
I-Hurler, Hurler – Scheie, Scheie	GM1 Gangliosidosis
II - Hunter	GM2 Gangliosidosis; Tay – Sachs, Sandhoff
III - Sanfilippo	Fabry disease
IV - Morquio	Gaucher disease
VI - Maroteaux – Lamy	Farber disease
VII - Sly	Nieman-pick disease
	Krabbe disease
	Metachromatic leukodystrophy
	Wolman disease.

Mucopolysaccharidoses are hereditary, progressive diseases caused by mutations of genes coding for lysosomal enzymes needed to degrade glycosaminoglycans (acid mucopolysaccharides). The most common subtype is MPS-III, followed by MPS-I and MPS-II. They could be a cause of hydrops fetalis in newborns[5].

Hurler Disease (MPS I-H): is a severe, progressive disorder with multiple organ and tissue involvement that results in premature death, usually by 10 years of age, if untreated, Hurler-Scheie Disease: Intermediate between Hurler and Scheie diseases, Scheie Disease: MPS I-S is a comparatively mild disorder[1].

Hunter disease: (MPS II) is an X-linked disorder, it manifests almost exclusively in males; it has features similar to those of Hurler disease. Grouped skin papules are present in some patients[1,6]. Mucopolysaccharidosis III; Sanfilippo disease: (MPS III) makes up a genetically heterogeneous but clinically similar group of 4 recognized types[1].

Mucopolysaccharidosis IV: Morquio disease; There is preservation of intelligence[1]. Mucopolysaccharidosis VI; Maroteaux-Lamy: (N-acetylgalactosamine-4-sulfatase deficiency) have somatic features resembling MPS I, but without neurological impairment.

Mucopolysaccharidosis VII; Sly syndrome; (B-glucuronidase deficiency) is a very variable disorder which has hydrops fetalis as its most common presentation. Patients that survive pregnancy have a clinical disease similar to MPS I[8].

Gaucher disease is a multisystemic lipidosis characterized by hematologic abnormalities, organomegaly, and skeletal involvement. It is the most common lysosomal storage disease. There are 3 clinical subtypes. All are autosomal recessive traits[1]. GD type I (non-neuropathic) are the most common and least severe form of the disease. Patients in this group usually bruise easily (due to low levels of platelets) and experience fatigue due to low numbers of red blood cells. Depending on disease onset and severity, type I patients may live well into adulthood. The range and severity of symptoms can vary dramatically between patients[1, 9]. Gaucher disease type 2 is much less common, Gaucher disease type 3, Patients often live into their early teen years and adulthood. Diagnoses should be confirmed by determination of the acid β- glucosidase activity in isolated leukocytes or cultured fibroblasts[1, 10].

Neimann-Pick Disease (NPD) is a fatal disorder of infancy characterized by failure to thrive, hepatosplenomegaly, and a rapidly progressive neurodegenerative course that leads to death by 2-3 years of age. Type B disease is a non-neuronopathic form observed in children and adults. Type C disease is a neuronopathic form that results from defective cholesterol transport[1] . Type C NPD is the most common; patients often present with prolonged neonatal jaundice, they may survive into adulthood[1, 11]. Currently there is no specific treatment for NPD; Bone marrow transplant has been tried for type B[1, 12]. The objective of this study was to have a better review of these LSDs' burden among inpatients in Kurdistan region/Iraq, diagnosis was reached to a number of LSDs namely diseases were Gaucher disease, Mucopolysaccharidosis, and Niemann-Pick disease.

Patients and Methods

Data from 37 patients were collected from 2013 to 2017 in the cities Sulaimany, Erbil, Duhok, and Kirkuk retrospectively, provided by Sanofi Genzyme company, through establishing a questionnaire distributed to the families of patients in whom the disease was established, and diagnosis was settled and treatment already initiated to the patients, parameters included were: age, gender, and consanguinity amongst parents…etc

Patient diagnosis was established through blood enzyme analysis and/or genetic analysis, as enzyme assay is not available in the country dried blood samples were obtained from suspected patients and sent to specialized laboratories in Hamburg/Germany (Universitatsklinaikum-Hamburg-Eppendorf). Further investigations of patients whose enzyme assay were inconclusive were made through gene analysis performed in ARCHMED life laboratories in Vienna/Austria to a second blood sample, these measures were taken after high suspicion of patient's signs and symptoms which lead to biopsy taking from liver tissues and bone marrow samples for histopathology examination. The patients were diagnosed by various physicians in their regions, and genetic analysis were done only for 19/37 patients. All patients included in this study were consented. Patients information was collected through a printed questionnaire or information obtained

through phone calls and online data exchange, patients previous medical records, particularly clinical observations of primary physicians were carefully reviewed, then data was stored and interpreted with Microsoft excel. The study was approved from the ethical committee of college of medicine/ university of Sulaimany.

Results

Data analysis of 37 patients with Lysosomal storage diseases found that; Different subtypes of LSDs came in different ratios most common of which was Gaucher disease (17 patients, 45.9%). Equally common was found to be Mucopolysaccharidosis (17 patients, 45.9%) of which: type 1 (hurler disease) 7 patients, type 2 (hunter disease) 2 patients, and type 6 (Marteaux-Lamy) 8 patients. and lastly Niemann-Pick disease was the least common, only 3 patients (8.1%). Age of patients involved in the study ranged from 18 months-35 years, with the mean age of 17 years, with most frequent age of 2-4 years. For Gaucher the age ranged from 18 months to 19 years, with the mean age of 9 years, and the most frequent age of 3-4 years, while for Mucopolysaccharidosis the age ranged from 18 months – 29 years, with the mean age of 14 years, and most frequent age of 6-9 years, but for Niemann-Pick the age was 3-35 years, with the mean age of 16 years, and the most frequent age of 3 years. According to this study all Lysosomal storage diseases are found to be more common in male patients at a ratio of 59.4%; 22 patients (59.4%) were male, 15 patients (40.6%) were female. In Gaucher disease 10 patients (58.8%) were males, 7 patients (41.2%) were females, in Mucopolysaccharidosis 9 patients (52.9%) were males, and 8 patients (47.1%) were females. For Niemann-Pick disease; all patients were male. Lysosomal storage diseases were found to be different among different ethnic groups as data shows, in the scope of geographical region that patients were analyzed data shows that, over all, the disease is more prevalent in patients from Kurdish descendant at a rate of 75.7% (28 patients) as compared to other nationalities within the same geographical locations namely patients from Arabic descendant 9 patients (24.3%). in Gaucher disease; 12 patients (70.5%) were Kurds, 5 patients 29.5% were Arabs. In Mucopolysaccharidosis; 13 patients (76.5%) were Kurds, 4 patients (23.5%) were Arabs. While in Niemann-Pick disease; all patients were Kurds. Consanguinity was positive in 31 patients (83.8%), for overall lysosomal storage diseases, 13 patients (76.5%) of Gaucher disease, 15 patients, (88.2%) of Mucopolysaccharidosis, and (100%) of Niemann-Pick patients. Family history was positive in 17 (45.9%) of the overall lysosomal storage disease patients, 8 (47%) of Gaucher, 8 (47%) of Mucopolysaccharidosis, and 1 (33.3%) of Niemann-Pick patients as shown in Table 2.

Table (2): Demographic data of the patients.

No. of Patients		All LSD[1]		Gaucher Disease		MPS[2]		Niemann-Pick Disease	
		37		17		17		3	
		No.	%	No.	%	No.	%	No.	%
Sex	Male	22	59.4	10	58.8	9	52.9	3	100
	Female	15	40.6	7	41.2	8	47.1	0	0
Race	Kurds	28	75.7	12	70.5	13	76.5	3	100
	Arabs	9	24.3	5	29.5	4	23.5	0	0
Consanguity	Positive	31	83.8	13	76.5	15	88.2	3	100
	Negative	6	16.3	4	23.5	2	11.8	0	0
Family history	Positive	17	45.9	8	47.0	8	47.0	1	33.3
	Negative	20	54.1	9	53.0	9	53.0	2	66.7
Range		18 months-35 years		18 months–19 years		18 months–29 years		3-35 years	
Mean		17 years		9 years		14 years		16 years	
Most frequent		2-4 years		3-4 years		6-9 years		3 years	

[1] LSD = Lysosomal Storage Disease
[2] MPS = Mucopolysaccharidosis

In our study; most patients with LSDs were found to be located in Duhok city,19 patients (51%), 8 patients (22%) from Sulaimany, similarly, 8 patients (22%) from Erbil, while only 2 patients (5%) were from Kirkuk, Table3.

Table (3): Geographical distribution of the patients.

Governorate	Total LSD[1]		Gaucher Disease		MPS[2]		NPD[3]	
	No.	%	No.	%	No.	%	No.	%
Duhok	19	51	11	60	6	30	2	10
Sulaymani	8	22	2	25	5	62.5	1	12.5
Erbil	8	22	4	50	4	50	0	0
Kirkuk	2	5	0	0	2	100	0	0

[1] LSD = Lysosomal storage disease

[2] MPS = Mucopolysaccharidosis

[3] NPD = Niemann-Pick Disease

Twenty- four patients (64.9%) of overall lysosomal storage disease were receiving enzyme replacement therapy, 16 (94.1%) of Gaucher patients, 8 (47%) of Mucopolysaccharidosis patients, but none of the Niemann-Pick patients were receiving the enzyme therapy. Among patients receiving treatment; 20 (83.3%) had showed improvement in their condition, 1 patient, (4.2%) showed no improvement, 3 patients (12.5%) of lysosomal storage disease on enzyme replacement therapy died. This compared to 12 patients, (92.3%) of patients who did not receive the enzyme replacement therapy did not show any improvement, only 1 (7.7%) of the patients died without the enzyme replacement therapy, Table 4.

Table (4): Treatment and Outcome.

	Patients receiving enzyme replacement therapy								Patients not receiving enzyme replacement therapy							
	Total		Improvement		No Improvement		Dead		Total		Improvement		No Improvement		Dead	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
L[1]	24	64.9	20	83.3	1	4.2	3	12.5	13	35.1	0	0	12	92.3	1	7.7
G[2]	16	94.1	13	81.3	1	6.3	2	12.5	1	5.9	0	0	1	100	0	0
M[3]	8	47.0	7	87.5	0	0	1	12.5	9	52.9	0	0	8	88.9	1	11.1
N[4]	0	0	0	0	0	0	0	0	3	100	0	0	3	100	0	0

L[1]. Lysosomal storage disease G[2]. Gaucher disease

M[3]. Mucopolysaccharidosis N[4]. Niemann-Pick disease

Over all; abdominal distention and hepatosplenomegaly were the most common first presenting complaint in lysosomal storage diseases as a whole (10 patients, 27%), while jaundice was the least frequent first presenting complaint (1 patient, 2.7 %). It was the same for Gaucher disease as abdominal distention due to hepatosplenomegaly was the most frequent first presentation in 6 patients (35.29%) while sleep apnea with difficulty in respiration, jaundice, anemia, and visual impairment were all reported with the same frequency of only 1 patient for each, making them equally least frequent first presentation, of only (5.88%) occurrence.

While for Mucopolysaccharidosis, short stature and bone abnormalities were the most frequent first presenting complaint, occurring in 8 patients (47%), but anemia, abdominal distention and hepatosplenomegaly, and visual impairment were all presented with the same least frequency of each occurring in a single patient, (5.88%). All patients of Niemann-pick disease were presented with abdominal distention due to hepatosplenomegaly (100%), Table 5.

Table (5): First presenting complaint.

		P1	P2	P3	P4	P5	P6	P7	P8	P9
GD	No.	3	6	1	1	1	1	4	0	0
	%	17.6	35.3	5.9	5.9	5.9	5.9	23.5	0	0
MPS	No.	4	1	2	0	7	1	1	6	8
	%	23.5	5.9	11.8	0	41.2	5.9	5.9	35.3	47
NPD	No.	0	3	0	0	0	0	0	0	0
	%	0	100	0	0	0	0	0	0	0
All LSDs	No.	7	10	3	1	8	2	5	6	8
	%	18.9	27	8.1	2.7	21.6	5.4	13.5	16.2	21.6

GD. Gaucher disease MPS. Mucopolysaccharidosis

NPD. Niemann-Pick disease LSD. Lysosomal storage disease

P1. Failure to Thrive P2. Abdominal Distention &/or Hepatosplenomegaly P3. Difficulty Breathing

P4. Jaundice P5. Delayed Develop Mental Mile Stones P6. Visual Impairment

P7. Anemia P8. Abnormal Facial Features P9. Bone and Stature Problems

Discussion

There are 45 patients of LSD reported in Kurdistan region, as provided by Sanofi Genzyme company, that has been diagnosed with enzyme and genetic study, but we couldn't contact 6 of them, and 2 of them refused to take part in the study, which left us with a smaller sample of patients, which at the end will affect the accuracy of the study. This in addition to the fact that there are many other suspected patients of different LSDs, but they are not yet confirmed by enzyme essay, and /or genetic study, Table 1.

Gaucher and mucopolysaccharidosis were equally the most common LSD in our study, the high prevalence of Gaucher disease was in accordance with previously reported study (14.4 %), Verma et al[13], Feroze et al[14], Sheth et al[15]. While in Al-Jasim et al[16], GM1 Gangliosidosis was the most prevalent. But MPS was 2nd in frequency in other similar studies like Pinto et al[17], Meikle et al[18], Poupetova et al[19], Verma et al[13], and Sheth et al[15]. Among MPSs in our study Mortoux-Lamy disease was the most prevalent, while in other similar studies like Verma et al[13]. And Sheth et al[15], Hurler disease was most prevalent, which's second in frequency in our work. Among MPSs, Hurler disease was (41.2%) of the MPSs, Hunter disease was (11.7%), and Martoux-Lamy was (47%); this compared to (21%) of MPS1 and 52% MPS6 in Al-Sannaa et al[20]. Male gender was affected more frequently than females, which has probably little to do with X-linked Hunter disease, as we had only 2 patients of hunter disease out of 37 patients. In our study, age for Gaucher disease ranged from 18 months to 19 years, with the mean age of 9 years. And most common age of 3-4 years, while most prevalent age group at presentation was (1 – 5) years in Thejeal et al[21]. The ethnicity predilection is known to be associated with a specific lysosomal disease like Gaucher, Tay-Sachs, Niemann-Pick type A, and ML IV disease in Ashkenazi Jewish descendants, Salla disease and aspartylglucosaminuria in Finnish population; and Gaucher type III disease in people of Swedish descent[22]. In Sheth et al[15], the prevalence of Gaucher disease was found to be higher in Maharashtra region, whereas Tay-Sachs was more in Gujarat province. In this study LSD was found to be more common among Kurdish descendant (75.7%) than those of Arabic descendants but compared to the ratio of Kurdish descendants to Arabic descendants in Kurdistan region's population, the prevalence of the disease could be equal between Kurds and Arabs if even not higher in Arabs. As the region's main population is of those of Kurdish descendants, those of Arabic descendants are a minority in Kurdistan region. Our study is conducted within the borders of Kurdistan reign, but still included certain patients from cities outside the borders of the region like Baghdad and Enbar, although these patients are currently living in there cities outside the borders of the region, but at the time of diagnosis and receiving the treatment they were living in Kurdistan region, as internally displaced people, some of them are still registered in health departments of Kurdistan region and still receive their treatment monthly from Kurdistan region's ministry of health. In our study,

highest population of patients were from Duhok, (51%), while in a study done in Baghdad involving only Gaucher disease, Thejeal et al21, it was found that most patients were from Baghdad itself. This probably is because of more consanguine marriage in Duhok, and less ethnic diversity of the population there, Table 2. Consanguinity was positive in 31 patients (83.8%), for overall lysosomal storage diseases, compared to (72%) in Indian patients with LSD; Sheth et al[15]. And was positive in (76.5%) of our patients of Gaucher disease, compared to (93.3%) in a study done in Baghdad, Thejeal[21]. In fact, burden of consanguine marriage and subsequent family history in siblings; was so obvious in our study that 5 of our patients of Mucopolysaccharidosis from Duhok were from the same family, of consanguine parents, which proves the link between the disease and consanguinity[24], Table 1. Twenty -four patients (64.9%) of overall lysosomal storage diseases were receiving enzyme replacement therapy, 16 (94.1%) of Gaucher patients, 8 (47%) of Mucopolysaccharidosis patients, but none of the Niemann-pick patients were receiving the enzyme therapy. That's because enzyme replacement therapy is only available for patients with Gaucher and MPS1 currently in Iraq. The very high percentage of patients improved after receiving the enzyme replacement compared to no improvement at all in those who do not receive the hormone replacement was in concordance with Thejeal et al[21], and Ibrahim[23]. The more mortality in patients on treatment compared to those who did not receive the treatment is due to many reasons; including the fact that they are of different type of LSD. The treatments the patients are receiving are not regularly available, often on and off. Certain patients reported not receiving the treatment for a period of 6-12 months. In our country LSD enzyme replacement therapy started in May 2013 covered by ministry of health, many patients were diagnosed as having Gaucher and MPS1 disease before that date but they couldn't afford any treatment except few patients received treatment outside Iraq before that date, as for Kurdistan region, treatment were provided in limited amount only for the past 2 years before the study, after 2014, considering the fact that the age of patients involved in the study is widely variable (18 months – 35 years) makes us reach the conclusion that delay in the age of starting the enzyme replacement therapy, (certain patients already reached adulthood when started the enzyme replacement therapy) is another fundamental factor, Table 3. Abdominal distention and hepatosplenomegaly was the most common first presenting complaint of overall LSDs, which was in concordance with Thejeal[21], Table 4.

Conclusions

Lysosomal storage diseases are seriously prevalent disabling diseases in Kurdistan region, that's more common in consanguine marriage, and will respond well to enzyme replacement therapy if regularly provided, it will decrease mortality and morbidity due to the disease.

we recommend; enzyme study, genetic testing, and newborn screening be provided for early detection, and the enzyme replacement needs to be provided regularly and sufficiently, for all.

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