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Types and Genetic Evaluation of Lysosomal Storage Diseases in Kurdistan Region

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ABSTRACT

Background and objectives: *Lysosomal storage diseases are a set of single-gene disorders that is attributed to insufficient certain lysosomal hydrolase activity or non-enzymatic proteins vital for typical lysosomal functions. Imperfect lysosomal performance will result in cellular malfunction, sequentially multiple organ impairment and evolution of clinical characteristics. Our study worked towards evaluating the types and molecular analysis of lysosomal storage diseases in the Kurdistan region.* ***Patients and methods:*** *This cross-sectional study concerned 243 patients with suspicion of lysosomal storage diseases. As stated by the clinical properties, a specific enzyme activity was tested as the first step in laboratory evaluation. Ultimately, patients with diminished enzyme activity status were further assessed via genomic analysis to prove a conclusive diagnosis of lysosomal storage diseases.* ***Results:*** *The age group (5-9) years was reported in (22.6%) of cases. Mucopolysaccharidosis was recounted in (40.8%) of lysosomal storage disease cases. Mucopolysaccharidosis type-6- was observed in (51.6%) of subtypes of mucopolysaccharidosis. Infantile-onset type was noted in (88.5%) of Pompe disease cases. The genetic structure "c.864dupt" was remarked in (40.0%) of Fabry cases.* ***Conclusion:*** *The premier lysosomal storage disease was mucopolysaccharidosis, followed by Gaucher disease. Mucopolysaccharidosis type VI had the highest ranking among all subtypes of mucopolysaccharidosis.*

Keywords: Lysosomal storage diseases, Genetic mutation, Mucopolysaccharidosis.

Article Information

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INTRODUCTION

Lysosomal storage diseases (LSD) are a category of hereditary disorders that are marked by defective lysosomal function [(1)]. The hallmark of LSD is the disturbed intra-lysosomal metabolic pathway that principally takes place on account of defects in enzymes, enzyme activator proteins, membrane proteins, or transporters in the lysosome having the result that progressive cumulative accretion of disease- specific stored macromolecules [(2,3)]. Consequently, ongoing continuous building-up of non-break down particles such as lipids, glycolipids, sphingolipids, glycoproteins, sulfatides, and sphingomyelin within the lysosomes, eventually gives rise to cell malfunction and death with subsequent gradual deterioration of tissues and organ systems [(4,5,6)]. It is noteworthy that LSD are genetically passed as an autosomal recessive trait, except for Danon disease, Fabry disease and mucopolysaccharidosis (MPS) type II (Hunter disease) which are x-linked conditions [(7,8)]. Seven categorizations of lysosomal disorders are realized by the deposited substrate: sphingolipidoses (Gaucher disease, Niemann-Pick disease, Fabry disease, gangliosidosis),

mucopolysaccharidosis (I, II, III, IV, V, VI, VII, IX), glycoproteinosis (alpha mannosidosis, mucolipidosis type I), multiple enzyme deficits (mucolipidosis type II/III), lysosome transport deficits (cystinosis), glycogen storage disease (glycogenosis type II) and other lipidoses (Wolman disease) [9]. Generally, insufficiency of lysosomal hydrolases is the cause of LSD specifically caused by mutations in genes codifying lysosomal hydrolases [10]. Even though lysosomal storage diseases are individually rare, the appraised prevalence of LSD is crucial, on condition that they are considered as a group, is 1 in 5000 to 1 in 5,500 [2,11,12]. Over and above that, specific racial groups are more susceptible to having a higher incidence of lysosomal disorders e.g., Ashkenazi Jewish natives are probable to have Tay-Sachs disease, Gaucher disease type -1-, Niemann-Pick disease type -A-, and mucolipidosis [2,4].

Regarding the nosology of LSD, they are contemplated as multispectral disorders that are exhibited as wide-ranging progressive clinical presentations demonstrated as visceral, ocular, hematological, skeletal, cardiological, and neurological signs [13]. The emergence of these comprehensive broad-spectrum clinical manifestations is determined by the stored substrate type (glycosaminoglycans in mucopolysaccharidoses, glycosphingolipids in glycosphingolipidoses, etc.), rate of accumulation, and site of deposition [4,14]. Nearly all LSD are classified in the sense of regard to specific genotypes and the age of onset of the clinical manifestations to severe early infantile and milder late-onset (adult type) phenotypes [15]. Particular organ system dysfunction is typical of a certain enzyme deficiency disorder, by way of illustration the kidney in Fabry disease and cystinosis, the heart in Pompe disease and the mononuclear phagocyte system in Gaucher disease [4]. The headmost tread in the diagnosis of LSD is the clinical suspicion which is followed by enzyme activity assays by two methods: the Fluorometry method and the Tandem Mass Spectrometry method. Affirmation for precise diagnosis is accomplished by genetic testing as the final step [16]. The keystone therapeutic regimen of treatment for LSD is enzyme replacement therapy which is accessible for some LSD and under development for other types of LSD. Alternative remedies entail substrate reduction therapy and pharmacological chaperones together with future treatment as gene therapy [17].

PATIENTS AND METHODS

This study was achieved through the period 2018 to 2024 in Raparine Teaching Hospital specifically in Kurdistan Rare Diseases Center as cross-sectional study. Information was assembled through a well- outlined questionnaire from the patients and or their caregivers, the main focuses were age, age at diagnosis, ethnicity and family history of LSD and consanguinity. Weight, height and body mass index were measured and schemed on growth charts. The LSD included in this study were: MPS I, II, III, IV, VI, Acid sphingomyelinase deficiency (ASMD), Gaucher disease, Pompe disease, Fabry disease and nephrogenic cystinosis. In conformity with the pattern of clinical status of the patients, pertinent enzyme assay was performed for the doubtable LSD (MPS, ASMD, Gaucher disease, Pompe disease or Fabry disease). The enzyme assay was appraised utilizing dried blood spotting (DBS) cards by using a venous blood sample by employing the Tandem mass spectrometry method. In case the enzyme intensity level was below the average range (the normal ranges are shown in table 1) afterward genetic testing (by next-generation sequencing (NGS)) was achieved to validate the decisive diagnosis of LSD taking advantage of the same blood specimen.

Table (1): LSD with specific enzyme and cut-off values.

Lysosomal storage disease	Specific enzyme	Unite	Cut-off value
MPS I	Alpha L - Iduronidase	µmol/L/h	>1.5
MPS II	Iduronat-2-sulfatase	µmol/L/h	>2.5
MPS III	N-acetyl-a-glucosaminidase	µmol/L/h	>0.5
MPS IV	N-Acetylgalactosamin-6-s	µmol/L/h	>0.2
MPS VI	β-glucuronidase	µmol/L/h	>5.0
ASMD	Acid Sphingomyelinase	µmol/L/h	>1.2
Gaucher disease	β-Glucocerebrosidase	µmol/L/h	>1.5
Pompe disease	Alpha- 1,4 Glucosidase	µmol/L/h	>2.0
Fabry disease	Alpha-Galactosidase	µmol/L/h	>2.8

Moreover, the cases of nephropathic cystinosis were evaluated and diagnosed by adult or pediatric nephrologists and general pediatricians under clinical dubiety, biochemical investigations (including: arterial blood gasses analysis, serum electrolytes, renal function test with urine test for albumin, sugar and electrolytes) and slit-lamp examination to detect cystine-deposited crystals in cornea thereupon the cases were referred to the center.

Statistical analysis

Data were entered and analyzed by the Statistical Package for Social Sciences (SPSS, version 26). The categorical variables were summarized in the form of frequencies and percentages. Numerical variables were summarized by calculating the mean and standard deviation.

RESULTS

The mean age (SD) was 7.1 (9.1) years, the median was 4.1, and the age range was 0.1-62.4 years. The predominant affected age group was (5-9) years showing the percentage (22.6%), however the two groups less than one year and more than ten years are nearly equivalent (18.1) and (20.6%) respectively. The four age groups (1-1.9, 2-2.9, 3-3.9, 4-4.9) were within close range (11.5%), (9.9%), (7.4%), and (9.9%) respectively. It is sharply obvious that male and female gender are about to be equal, (50.6%) and (49.4%) respectively. Kurdish tribe was noted in (84.8%) and Arabic in (15.2%). The cases all over Kurdistan governorates were as the followings: Erbil (33.7%), Duhok (38.3 %) and Sulaimani (28.0%). (table 2)

Table (2): Basic characteristics of patients with LSD.

	No.	**%**
Age (years)		
< 1	44	18.1
1-1.9	28	11.5
2-2.9	24	9.9
3-3.9	18	7.4
4-4.9	24	9.9
5-9	55	22.6
≥ 10	50	20.6

	No.	%
Gender		
Male	123	50.6
Female	120	49.4
Ethnicity		
Kurdish	206	84.8
Arabic	37	15.2
Governorate		
Erbil	82	33.7
Duhok	93	38.3
Sulaimani	68	28.0
Total	243	100.0

It is worth bearing in mind that MPS was perceived in around a third of the cases (39.1%), Gaucher disease (17.3%), Pompe disease (10.7%), ASMD (14%), Fabry disease (8.2%), and nephropathic cystinosis (10.7%). ASMD type-A- was described in (35.3%), as well as type-B- in (50%) and type-A/B- in (14.7%). On top of that, subtypes of MPS showed the following results: MPS I and MPS IV (17.9%), MPS II (9.5%), MPS III (3.2%) and peculiarly MPS VI (51.6%). Infantile-onset form of Pompe disease was realized in (88.5%), instead late-onset adult form in (11.5%) of the cases. The lion's share of cases of Gaucher disease was type-1- (97.6%), and only one case (2.4%) with type-2- has been detected. (table 3)

Table (3): Types and subtypes of LSD.

	No.	(%)
Type of LSD		
MPS	95	(39.1)
Gaucher disease	42	(17.3)
Pompe disease	26	(10.7)
ASMD	34	(14.0)
Fabry disease	20	(8.2)
Nephropathic Cystinosis	26	(10.7)
Total	243	(100.0)
Subtypes of ASMD*		
Type- A- (infantile neurovisceral)	12	(35.3)
Type-B- (chronic visceral)	17	(50.0)
Type-A/B- (chronic neurovisceral)	5	(14.7)
Total	34	(100.0)
Subtypes of MPS**		
MPS I	17	(17.9)
MPS II	9	(9.5)
MPS III	3	(3.2)
MPS IV	17	(17.9)

	No.	(%)
MPS VI	49	(51.6)
Total	95	(100.0)
Subtypes of Pompe disease*		
Infantile-onset form	23	(88.5)
Late-onset adult form	3	(11.5)
Total	26	(100.0)
Subtypes of Gaucher disease*		
Non-neuropathic type -1-	41	(97.6)
Acute neuropathic type -2-	1	(2.4)
Chronic neuropathic type -3-	0	(0.00)
Total	42	(100.0)

⁎ *Gaucher, ASMD and Pompe diseases were classified under clinical properties.*

⁎⁎ *Categorization of MPS subtypes as specified by certain enzyme deficient.*

To flip through Tab.4, it is undoubted that there are distinct numerous mutations of LSD, c.1267C>T and c.416T>C;c.848C>T (14.7%) were the main two mutations among patients with ASMD followed by c.84 8C>T (11.8%), c.1805G>A, c.416T>C and c.1652T>C (8.8%), 1556A>G and c.1486+5G>A (5.9%), along with c.490G>T;c.742G>A, c.967A>C, c.1492C>T and c.1376A>G (2.9%). Moreover, the molecular analysis of Fabry disease showed c.864dupt (40%), c.865dupt (20%), c.859T>C (15%), c.784G>T (10%) together with c.937G>T, c.865_866insT and c.967C>T (5%). It is visible in this table that c.1448T>C (23.8%) was the principal genotype affecting patients with Gaucher disease, then again c.1226A>G and c.1246G>A (9.5%), c.1246G>A;(c.1448T>C,c.1483G>C;c.1497G>C) (4.8%), c.1193G>T, c.1228C>G, c.1205A>G and c.1205A>G;c.1342G>C (2.4). Concerning the genetic analysis of Pompe disease, c.258dupC (30.8%) was the predominant mutation, other mutations include: c.258dup and c.2237G>A (11.5%), c.-32-13T>G;896T>C and c.1848C>A (7.7%), c.1392_1393delinsTT, c.1802C>T, c.118C>T;670C>T, c.1210G>A, c.2608C>T and c.898T>C (3.8%).

Table (4): Molecular analysis of LSD.

	No.	(%)
Mutations of ASMD		
N/A	3	(8.8)
c.1267C>T	5	(14.7)
c.1805G>A	3	(8.8)
c.416T>C	3	(8.8)
c.490G>T;c.742G>A	1	(2.9)
c.1652T>C	3	(8.8)
1556A>G	2	(5.9)
c.967A>C	1	(2.9)
c.1492C>T	1	(2.9)

	No.	(%)
c.416T>C;c.848C>T	5	(14.7)
c.1486+5G>A	2	(5.9)
c.848C>T	4	(11.8)
c.1376A>G	1	(2.9)
Total	34	(100.0)
Mutations of Fabry		
c.937G>T	1	(5.0)
c.865dupt	4	(20.0)
c.865_866insT	1	(5.0)
c.864dupt	8	(40.0)
c.784G>T	2	(10.0)
c.859T>C	3	(15.0)
c.967C>T	1	(5.0)
Total	20	(100.0)
Mutations of Gaucher		
N/A	18	(42.9)
c.1448T>C	10	(23.8)
c.1193G>T	1	(2.4)
c.1228C>G	1	(2.4)
c.1226A>G	4	(9.5)
c.1205A>G	1	(2.4)
c.1246G>A	4	(9.5)
c.1246G>A;(c.1448T>C,c.1483G>C;c.1497G>C)	2	(4.8)
c.1205A>G;c.1342G>C	1	(2.4)
Total	42	(100.0)
Mutations of Pompe		
N/A	2	(7.7)
c.258dup	3	(11.5)
c.1392_1393delinsTT	1	(3.8)
c.-32-13T>G;896T>C	2	(7.7)
c.1848C>A	2	(7.7)
c.1802C>T	1	(3.8)
c.258dupC	8	(30.8)
c.118C>T;670C>T	1	(3.8)
c.2237G>A	3	(11.5)
c.1210G>A	1	(3.8)
c.2608C>T	1	(3.8)
c.898T>C	1	(3.8)
Total	26	(100.0)

Mutations of MPS I were as follows; c.908T>C and c.713T>A (17.6%), c.1154C>T, c.613T>C;c.1090_1100dup, c.1A>C, c.1466G>A and c.del16_24 delCCCGCGCCinsICGCA (5.9%). Regarding MPS II, four mutations were identified with the

same percentage (11.1%): c.944G>A, c.1406C>T, c.1403G>A and c.1150_1162del. As well as MPS III has been observed with two mutations: c.1811C>T (33.3%) and c.1241A>G (66.7%). It is crystal clear that the mass mutation among patients with MPS IV was c.421T>A (23.5%), followed by: c.860C>T (17.6%), c.139G>A;c.244T>C and c.1196delA (11.8%), along with c.1341_1349del, Deletion of exons 13 and 14, c.410T>C and c.433C>T (5.9%). Genetic profiling of the MPS VI disclosed the following mutations: c.962T>A (24.5%), c.710C>A and c.753C>A (8.2%), c.944G>A and c.1143_1_1143invGT (6.1%), c.323G>T;c.962T>C and c.585T>A (4.1%), together with c.323G>T, c.959G>A, c.953A>T, c.585T>A;c.1143_1_1143invGT and c.288C>A;c.962T>C (2.0%). (Tab.5)

Table (5): Genetic constitutions of subtypes of MPS.

	No.	(%)
Mutations of MPS1		
N/A	6	(35.3)
c.908T>C	3	(17.6)
c.1154C>T	1	(5.9)
c.613T>C;c.1090_1100dup	1	(5.9)
c.713T>A	3	(17.6)
c.1A>C	1	(5.9)
c.1466G>A	1	(5.9)
c.del16_24delCCCGCGCCinsICGCA	1	(5.9)
Total	17	(100.0)
Mutations of MPS II		
N/A	5	(55.6)
c.944G>A	1	(11.1)
c.1406C>T	1	(11.1)
c.1403G>A	1	(11.1)
c.1150_1162del	1	(11.1)
Total	9	(100.0)
Mutations of MPS III		
c.1811C>T	1	(33.3)
c.1241A>G	2	(66.7)
Total	3	(100.0)
Mutations of MPS IV		
N/A	2	(11.8)
c.1341_1349del	1	(5.9)
c.139G>A;c.244T>C	2	(11.8)
Deletion of exons 13 and 14	1	(5.9)
c.410T>C	1	(5.9)
c.433C>T	1	(5.9)
c.421T>A	4	(23.5)
c.1196delA	2	(11.8)
c.860C>T	3	(17.6)
Total	17	(100.0)

	No.	(%)
Mutations of MPS VI		
N/A	14	(28.6)
c.962T>A	12	(24.5)
c.323G>T;c.962T>C	2	(4.1)
c.323G>T	1	(2.0)
c.944G>A	3	(6.1)
c.710C>A	4	(8.2)
c.753C>A	4	(8.2)
c.1143_1_1143invGT	3	(6.1)
c.959G>A	1	(2.0)
c.953A>T	1	(2.0)
c.585T>A	2	(4.1)
c.585T>A;c.1143_1_1143invGT	1	(2.0)
c.288C>A;c.962T>C	1	(2.0)
Total	49	(100.0)

DISCUSSION

This study put into words the types and genetic valuables of lysosomal storage diseases in the Kurdistan region. Our study revealed broad diversity in the age at diagnosis, varying from early infancy to adulthood, the most common age group was (5-9) years, this is made clear by the period needed for the signs and symptoms to come into view, and an appreciable number of cases below one year, which is clarified by investigating the cases (before clinical features exhibition) when other family members were diagnosed with LSD. This diversity agrees with the Egyptian study [18]. Notwithstanding the notorious fact that LSD standardly affect the childhood period, our study submitted proof that the initial presentation could be in adulthood, as Pompe and Fabry diseases were the two most LSD exhibited in adult patients (about 25 cases), these findings were indistinguishable from the detections of Chin et al [19]. The gender categories are evenly affected in this study, which is parallel to the Chinese study [20]. The master parentage in our region is Kurdish thus almost all the cases were Kurdish. In our region, kin marriages are traditional, and on account of that, there is a higher possibility of hereditary diseases. This paper put out MPS as the most predominant LSD in our region followed by Gaucher disease, in accord with the Egyptian study [18] but averse to Chin et al [19] which stated Fabry disease followed by Pompe disease. Nephropathic cystinosis constitutes a tenth of the cases of LSD, which is in the vicinity of the Egyptian study that showed cystinosis in 13.7%.

Taking notice of the subtypes of ASMD, type -B- was the top-tier one followed by type -A-, this was an antonym for Doerr et al [21] which flaunted type -B- and -A/B- as almost proportionate and not reporting cases with type -A-, nevertheless, it was ascertained by Cox et al [22] showing the same result. Delve deeper into the subtypes of MPS, MPS VI came to know as the foremost one followed by MPS I and IV, in opposition to Ghaffari study et al [23] that identified MPS IV as the chief subtypes followed by MPS I and VI along with Brazilian study [24] by which MPS II was the major subtype, except Al-Sanaa et al [25] which evinced the same matching results. Infantile-onset Pompe disease was the dominant clinical type of Pompe disease in the Kurdistan region, only a few cases were diagnosed with late-onset type, which was absolutely at variance

with Löscher et al [26] that showed a predominance of adult type. This survey told of Type-1- Gaucher disease as the widespread type except for one case of type-2- which is of Syrian roots, this was in dispute with a Taiwanese study [27] (Type-3- was mostly affected). A widely known information is that geography almost entirely frames human genetic variation and so there is a well-built interrelation between human genetic heterogenicity and geographic distribution of hereditary diseases impinged upon environmental factors (for example: environmental factor in our thesis is consanguineous marriage), therefore different races have dissimilar genetic mutations. The rating of genetic variants of ASMD in this inquest informed "c.1267C>T and c.416T>C;c.848C>T" as the rifest, this was refuted by Cox et al [22] that put in the picture "c.1826GCC[1](R608del)" on the top among the three subtypes of ASMD.

The genetic analysis of Fabry disease in this inquiry highlighted "c.864dupt" as the most registered mutation; this is controverted by a Chinese study [28] with exactly different mutations "c.128G > A, c.811G > A, c.950T > C, c.37G > C, c.1241delT". As stated above, "c.1448T>C" was the master molecular error in patients with Gaucher disease, this is consented to by Sheth et al [29] but on the other hand reversed by Dimitriou et al [30] that showed beyond doubt "c.1226A> G" as the most common genetic mutation. It was emphasized in this paper that "c.258dupC" is the utmost customary genetic fault of Pompe disease antagonizing Löscher et al [26] which proved "c.-32-13T > G" instead. Concerning MPS I, two mutations "c.908T>C and c.713T>A" were disclosed most commonly, by this our study antagonizes Voskoboeva et al [31] and Taghikhani et al [32] which both made known "c.208C>T" and "p.Y109H" as the commonest respectively. Mucopolysaccharidosis type II proclaimed carbon-copy incident of all reported mutations, dissimilar to the Chinese study [33] that exhibited c.1122C>T on the top of mutations. The number of MPS III patients was a nadir in this study, so it is inconsistent to compare it with other studies. Over and above that, "c.421T>A" was on the top of the pyramid of the mutations of MPS IV followed by "c.860C>T", on the reverse of Pachajoa et al [34] (p.Gly301Cys was the most common followed by p.Arg386Cys). Our study marked "c.962T>A" as the most conventional genetic gaffe among patients with MPS VI, which is in dissent with D'Avanzo et al [35] and Voskoboeva et al [36] (both showed c.454C > T and c.962T > C as the most common) along with Al-Sannaa [37] et al (reveal c.753C>G as the commonest).

CONCLUSION

Our study proclaimed MPS as the most pervasive among LSD in the Kurdistan region. Simultaneously Gaucher disease was rated in the second set followed by ASMD. Therewithal MPS VI was crowned as the pre-eminent subtype out of all types of MPS. The subdivisions: type-B-chronic visceral, Infantile-onset form and non-neuropathic type -1- were made aware as the most universal among ASMD, Pompe and Gaucher diseases respectively. The supreme genetic alterations in this study were c.1267C>T and c.416T>C;c.848C>T, c.864dupt, c.1448T>C, c.258dupC, c.908T>C and c.713T>A, c.1241A>G, c.421T>A, and c.962T>A among all cases of ASMD, Fabry disease, Gaucher disease, Pompe disease, MPS I, MPS III, MPS IV and MPS VI individually. The inceptive clinical signs and symptoms of LSD might be in adulthood as most of the adult cases in this study were Fabry and Pompe diseases.

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