DOI:10.24938/kutfd.675631 Kırıkkale Üniversitesi Tıp Fakültesi Dergisi 2020;22(2):310-313
Original Article *Özgün Araştırma*

LYSOSOMAL STORAGE DISEASES: KIRIKKALE UNIVERSITY EXPERIENCE

Lizozomal Depo Hastalıkları: Kırıkkale Üniversitesi Deneyimi

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ABSTRACT

Objective: Lysosomal storage diseases which were first described in 1880; are important group of metabolic disorders characterized by the deposition of the substrates in lysosomes due to defects of the activity or transport of lysosomal enzymes or a defect in the receptor proteins. LSDs usually show a progressive clinical course and may not be represented with any clinical signs during the neonatal period. The overall prevalence of LSDs is 1 / 7000-8000. The aim of this study was to share the clinical characteristics of our LSDs patients and the experiences of our pediatric metabolic diseases department.

Material and Methods: This retrospective cohort study was conducted at Kırıkkale University Hospital with 56 patients diagnosed as lysosomal storage disease among 315 patients diagnosed with metabolic diseases. Data were collected from outpatient clinic patient files who were diagnosed between 2011-2018.

Results: A total of 315 patients diagnosed with inherited metabolic disease were followed in our clinic and 56 (17.7 %) of them were diagnosed as LSDs. The 56 patients were suffering from the following diseases: 10 patients with Mucopolysaccharidosis, 1 patient with mucolipidosis type 2 (I-cell disease), 41 patients with sphingolipidoses, two patients with cystinosis, one patient with Infantile Pompe Disease and one patient with beta-mannosidosis.

The mean age of the patients with Fabry Disease and the other patients diagnosed with other LSDs were 34.7±14.2 years (minimum 8, maximum 64) and 2.67±3.4 years (minimum 0, maximum 10.5) respectively. All diagnoses were verified by specific enzyme analysis and/or by conducting genetic mutation analysis.

Conclusion: The most common lysosomal storage disease among our patients were Mucopolysaccharidosis and sphingolipidosis. Treatment options, such as enzyme replacement therapy and bone marrow transplantation exist, and 24 of these patients are receiving enzyme replacement therapy.

Keywords: *Lysosomal lipid storage disease, mucopolysaccharidoses, enzyme replacement therapy*

ÖZ

Giriş: İlk olarak 1880 yılında tanımlanan lizozomal depo hastalıkları; lizozomal enzim aktivitesinde veya taşınmasında kusur sebebiyle ya da lizozomal membranların reseptör proteinlerindeki defektlere bağlı olarak substratların lizozomlarda birikmesi ile karakterize önemli bir metabolik hastalık grubudur. lizozomal depo hastalıkları genellikle ilerleyici bir seyir gösterir ve yenidoğan döneminde hiçbir klinik bulgu vermez. Genel popülasyonda lizozomal depo hastalığı prevalansı 1 / 7000-8000'dir. Bu çalışma ile lizozomal depo hastalığı tanılı hastalarımızın klinik özelliklerini ve pediatrik metabolizma departmanımızın bu konudaki deneyimlerini paylaşmayı amaçladık.

Gereç ve yöntemler: Bu retrospektif kohort çalışması Kırıkkale Üniversitesi Hastanesi Çocuk Hastalıkları Metabolizma Bozuklukları polikliniğinde 2011-2018 yılları arasında metabolik hastalık tanısı konulan 315 hasta arasındaki lizozomal depo hastalığı tanısı konulan 56 hasta ile gerçekleştirildi. Hastalara ait veriler poliklinik dosya kayıtları üzerinden toplandı.

Bulgular: Kliniğimizde kalıtsal metabolik hastalık tanısı ile izlenen hastaların sayısı 315'tir. Bu hastaların 56'sı (%17.7) lizozomal depo hastalığı tanısı almıştır. 10 hasta mukopolisakkaridosis, 1 hasta mukolipidoz tip 2 (I-cell hastalığı), 41 hasta sfingolipidoz, 2 hasta sistinoz, 1 hasta infantil Pompe hastalığı ve 1 hasta beta mannosidoz idi. Fabry hastalarının yaş ortalaması 34.7 ±14.2 yıl (min: 8 yıl, maks:64 yıl), diğer lizozomal depo hastalığı olan hastaların yaş ortalaması ise 2.67 ±3.4 yıl (min 0 yıl, maks:10.5 yıl) idi. Tanılar spesifik enzim analizi ve/veya genetik mutasyon analizi ile konuldu.

Sonuç: Hastalarımızda en yaygın lizozomal depo hastalığı mukopolisakkaridoz ve sfingolipidoz idi. Tedavi seçenekleri arasında enzim replasman tedavisi ve kemik iliği transplantasyonu yer alır. Hastalarımızdan 24'ü enzim replasman tedavisi almaktadır.

Anahtar Kelimeler: *Lizozomal lipid depo hastalığı, mukopolisakkaridozlar, enzim replasman tedavisi*

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Received / Geliş Tarihi: 16.01.2020 **Accepted** / Kabul Tarihi: 21.12.2020
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KÜ Tıp Fak Derg 2020;22(3):310-313
Doi:10.24938/kutfd.675631

INTRODUCTION

Lysosomal storage diseases (LSDs) are an important group of inherited metabolic diseases (IMDs) characterized by storage of substrates in lysosomes due to defects in enzyme activity, defects in receptor proteins of lysosomal membranes and transport defects (1). In LSDs, there is a damage in degradation and removal mechanisms of the substrates, such as sphingolipid, glycosaminoglycan, glycoprotein, and glycogen where these substrates are stored in the endosome and/or lysosome as a complex (1). They are generally named by the type of substance accumulated and more than 60 LSDs are known (2). The most common seen pathologies of these groups are mucopolysaccharidosis (MPS), which arised as a result of the accumulation of glucosaminoglycans in the lysosomes, and sphingolipidoses, which are formed by the accumulation of glycosphingolipids after the combination of ceramide and sugar radicals. LSDs take place in the rare diseases group with a cumulative frequency of 1/7000-8000 (3). Each of the lysosomal storage disease is presented with different clinical findings depending on the type of product stored and the distribution in the organism. The emergence of different clinical types of the same disease can be explained by molecular heterogeneity (4). Diagnosis of lysosomal diseases can be made by determination of enzyme deficiency in tissues, blood cells and fibroblast cultures or by molecular diagnostic methods. Prenatal diagnosis and identification of carriers are possible for many LSDs (4).

Most of the LSDs do not have an effective treatment. Hematopoietic stem cell transplantation is a very successful treatment option at first stage in some of lysosomal diseases (5). Recombinant enzyme products. are currently used in the treatment of Fabry disease, Gaucher disease, Pompe disease and MPS type I-II-IV-VI. It has been observed that with the introduction of recombinant enzyme products, the morbidity decreased significantly, especially in patients with mild clinical conditions (6).

Hunter's disease (MPS type II) and Fabry's disease (Mucolipidosis) are inherited X-linked, while other lysosomal diseases show autosomal recessive inheritance. Therefore, with high incidence of inbreeding in closed societies such as Turkey, the incidence of these diseases is high (7). In this study, we aimed to share the clinical characteristics of LSD patients followed up in our clinic.

MATERIALS AND METHODS

In 2011, Kırıkkale University Faculty of Medicine Pediatric Metabolic Diseases Department and Laboratory has been founded and started giving service for the whole region. Our clinic has been shown as a reference center for inherited metabolic disorders. With the completion of the institutionalization, significant gains have been achieved in the quality of service provided to students before and after graduation. Between 2011-2018, a total of 2430 patients were followed up for nutritional and metabolic disorders in our clinic. Anthropometric measurements, initial complaints, physical examination findings, diagnostic methods, treatment and follow-up of patients were reviewed retrospectively.

RESULTS

Of the 2430 patients, 315 (12.9%) were diagnosed with inherited metabolic disease, and 56 were diagnosed with lysosomal storage disease. The incidence of LSDs among all IMDs is 56/315 (17.7%) (Table 1):

- 10 patients had MPS (MPS type 1S: 1, MPS type 2: 3, MPS type 3: 1, MPS type 4: 3, MPS type 6: 2),
- 1 patient had mucolipidosis type 2 (I-cell disease),
- 41 patients had sphingolipidosis (Fabry: 33, Niemann Pick: 4, Gaucher: 1 Krabbe: 1, Sandhoff's disease: 2, GM1-gangliosidosis: 1),

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- 2 patients had cystinosis
- 1 patient had Infantile Pompe Disease
- 1 patient had oligosaccharidosis (beta mannosidosis)

The mean age of application for patients diagnosed with Fabry Disease was 34.7 ±14.2 years (minimum 8, maximum 64). The mean age of the patients with other LSDs was 2.67 ±3.4 years (minimum 0 years, maximum 10.5 years). Twenty-seven of our patients (50.9%) were female and 26 (49.1%) were male. Mean height percentiles ranged from 10 to 25th percentile (pc), weight percentages ranged from 25 to 50th pc and Body Mass Index (BMI) ranged from 50 to 75th pc. Among all, 10 (18.8%) patient's height for age, 11 (20.7%) patient's weight for age and 7 (13.2%) patient's BMI were under 3rd percentile. Generally, the first complaints were atypical facial appearance. In 21 (39.7%) patients atypical facial features, hepatosplenomegaly in 16 (30.2%) of the patients, changes in bone structure (dysostosis multiplex) in 15 (28.3%) patients were observed. Nineteen (35.8%) patients had a history of mental retardation and neuromotor developmental retardation. All diagnoses were confirmed by performing specific enzyme analyzes and / or genetic mutation analyzes.

In our clinic, a total of 24 LSD patients (MPS Type 1S (1 patient), Type 2 (2 patients), Type 4 (3 patients), Type 6 (2 patients), Gaucher (1 patient), Fabry (16 patients)) are receiving enzyme replacement therapy. One patient, who was diagnosed with MPS Type 2, discontinued treatment after 7 months of enzyme replacement therapy due to incompatibility (Patients with MPS type 1S, MPS type 2 and MPS type 3 were excluded due to inappropriate follow-up). Of the 33 patients diagnosed with Fabry disease, 16 had organ involvement findings and received enzyme replacement therapy while the other 17 patients were closely followed up with a multidisciplinary approach.

Table 1: The incidence of lysosomal storage diseases in the Department of Pediatric Metabolic Diseases

Lysosomal Storage Disease	n (%)
Mucopolysaccharidosis	10 (17.8)
Sphingolipidosis	41 (73.2)
Mucolipidosis	1 (1.7)
Cystinosis	2 (3.5)
Pompe Disease	1 (1.7)
Beta mannosidosis	1 (1.7)

DISCUSSION

In our population, the two most common groups in LSDs were sphingolipidoses and mucopolysaccharidoses in accordance with the literature. Despite the fact that the substance accumulation usually starts in the prenatal period, clinical findings are observed in infancy or later in age groups. Many of these diseases are progressive with the impact of severe skeletal deformities, hepatosplenomegaly, heart and respiratory failure, and involvement of many other systems. With age, pathological symptoms increase, patients' quality of life deteriorates, permanent sequelae occur. For this reason, it is important to diagnose and to initiate early treatment before causing irreversible damage.

Depending on the distribution of the stored product in the species and organism, each of the LSDs is confronted with different clinical findings. Mutagenesis of different clinical types in the same disease can be explained by molecular heterogeneity (4). The diagnosis of lysosomal diseases can be made by determining enzyme deficiency in tissues, blood cells or fibroblast cultures, or by molecular diagnostic methods. Prenatal diagnosis and identification of carriers are possible for many (5).

Most LSDs do not have effective treatment. Hematopoietic stem cell transplantation is a treatment option made in the first stage and shown to be successful in some of the lysosomal diseases (6). For the treatment of Fabry disease, Gaucher's disease, MPS

types I-II-IV and VI enzyme replacement therapy is currently used. Along with the use of recombinant enzyme products, especially among patients with mild clinical status, morbidity has decreased markedly (7).

While Hunter's disease (MPS type II) and Fabry's disease (Spingolipidosis) show X-linked recessive inheritance, other lysosomal diseases show an autosomal recessive transition. For this reason, the incidence is increasing in closed societies (8). Excluding Fabry patients, mean age at admission was 18.7 months. It seems to be relatively late diagnosed age. As, early treatment is important before the irrevocable sequels occurred, increasing the awareness of not only pediatricians but also almost all clinicians is inevitable.

We rigorously follow our patients in Kırıkkale University Faculty of Medicine Hospital, Department of Pediatric Metabolic Diseases, according to our research and education program in order to enable our assistants to increase their knowledge on this disease group and lead them to refer their patients to a metabolic diseases specialist as soon as possible.

Acknowledgements:

We received no funding for this study. All named authors meet the ICMJE criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval to the version to be published.

We declare no conflict of interest. This article does not contain any new studies with human or animal subjects performed by any of the authors.

Ethics Committe Aproval: Kırıkkale University Ethics Committe of Noninvasive Clinical Research, date: 038.01.2020; number: 2019.12.22.

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