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Original Article

Clinical, Biochemical and Molecular Characteristics of Fifteen Patients with Mucopolysaccharidosis Type II in Western Turkey

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ABSTRACT

Aim: Mucopolysaccharidosis Type II (MPS II, Hunter syndrome, OMIM 309900) is a rare X-linked lysosomal storage disease due to a deficiency of the iduronate-2-sulfatase (IDS) enzyme, which is one of the degradative enzymes of mucopolysaccharides. The purpose of this study is to present the clinical, biochemical and molecular characteristics of fifteen patients with MPS II in western Turkey.

Materials and Methods: A retrospective study was carried out on fifteen patients with MPS II who were followed up by Ege University Faculty of Medicine, Unit of Pediatric Metabolic Diseases and Nutrition between October 2004 and September 2017.

Results: The age range of the patients enrolled in the study was between 11 months and 318 months at the time of diagnosis. The most common symptom was coarse face. On physical examination, all of the patients presented with coarse face, macrocephaly and organomegaly. Except for one patient, all other were severe phenotype. IDS activity was significantly decreased in all patients in whom enzyme analysis was performed. In this study, one novel mutation was described.

Conclusion: This is the first study on the clinical and molecular characterization of Turkish MPS II patients. The majority of the patients had neurologic involvement with different degrees of severity. The molecular analysis revealed one novel mutation.

Key words: Mucopolysaccharidosis Type II, Hunter syndrome, lysosomal storage disease, Turkey

Introduction

Mucopolysaccharidosis Type II (MPS II, Hunter syndrome, OMIM 309900) is one of the seven types of MPS I, II, III, IV, VI, VII, IX. This is a rare X-linked lysosomal storage disease due to a deficiency of the iduronate-2-sulfatase (IDS) enzyme, which is first degradative enzyme of mucopolysaccharides [now preferentially termed glycosaminoglycans, (GAGs)] dermatan sulfate and heparan sulfate. GAGs are essential constituents of connective tissue including cornea, cartilage, cardiac valve and vessel walls (Table I) (1). Partially digested dermatan sulfate and heparan sulfate accumulates and leads to multisystemic alterations including the skeleton, internal organs and central nervous system. The clinical characteristics of MPS II are macrocephaly, coarse face, hepatosplenomegaly, hernia, stiff joints, recurrent upper airway infections or otitis media, hearing loss, cardiac valve disease and/or cardiomyopathy and neurologic impairment. The *IDS* gene is located on Xq28 and contains 9 exons. The gold standard for diagnosis of MPS II in a male proband is reduced levels of IDS enzyme activity in fibroblasts, plasma or white cells and then diagnosis can be confirmed by means of *IDS* gene analysis. On exceptional occasions, heterozygous females present symptoms of MPS II. X inactivation, which

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is inactivation of normal paternally inherited X chromosome and expression of the maternally inherited X chromosome, can be the explanation for this issue (2,3). The *IDS* gene has three categories of alteration; large gene deletions, rearrangements and small gene deletions. More than 550 different mutations have been identified in the *IDS* gene to date, according to the Human Genome Mutation Database (HGMD® Professional 2016.2, www.hgmd.cf.ac.uk). Most of these are point mutations. IDS gene analysis is beneficial in diagnosing patients with unusual phenotypes and identifying genotype-phenotype correlations and it is also the only reliable way to define female carriers of the disease, which is a crucial factor in family planning (4). MPS II has multisystemic manifestations with variety in both the age of disease onset and rate of progression. Non-specific signs and symptoms that are similar to common childhood diseases and a lack of disease awareness cause delayed diagnosis (5). Although corneal clouding is not a typical feature of MPS II, it should not be forgotten. Two forms of the disease have been described. The most common form is often labelled as "early progressive" and manifests primarily with a combination of progressive cognitive deterioration and other multisystemic involvement. This form usually leads to death by the end of the second decade. The more infrequent form is often labelled as "slowly progressive", without or with a minimally affected central nervous system (6). The disease onset for the severe form is 12-18 months of age and for the attenuated form is 2-4 years of age (7).

Two main therapies have been reported for MPS II patients: The first one is idursulfase as an enzyme replacement therapy (ERT) which is a recombinant form of human IDS. This was approved in 2006 in individuals with the slowly progressing form of the disease. ERT has been shown to improve somatic symptoms, but the results with regard to cognitive functioning have been poor as idursulfase does not cross the blood-brain barrier (8). Hematopoietic stem-cell transplantation (HSCT) is reported as the other therapy. To date, only a few studies have examined the long-term outcomes of HSCT in patients with MPS II (9,10). HSCT can preserve neurocognition when performed early in the course of the disease. The need for early identification makes Hunter disease a candidate for new-born screening (NBS). Additionally, if NBS becomes widespread for MPS II, much milder presentations will be identified (11). Since there are no studies in Turkey on MPS II patients, the objective of this study is to present the genetic and clinical characteristics of patients in Western Turkey with Hunter syndrome.

Materials and Methods

A retrospective study was carried out on 15 patients with MPS II (from 13 families) and who were followed up by the Ege University Faculty of Medicine, Unit of Pediatric Metabolic Diseases and Nutrition, between October 2004 and September 2017. The data of patients including demographic, clinical, biochemical, radiological and mutation analyses were collected from their medical records. Diagnosis of MPS II was carried out by a detection of decreased levels of IDS enzyme activity in fibroblasts, plasma or white cells or by molecular genetic analysis. None of the patients were screened at birth for MPS II.

Statistical Analysis

The quantitative patient characteristics are summarized by means and standard deviations (SD). The qualitative characteristics such as general appearance and organ complications are presented as a frequency distribution.

Results

We collected data from 15 patients belonging to 13 families followed up by the Ege University Faculty of Medicine, Unit of Pediatric Metabolic Diseases and Nutrition. There were four patients in this study from two separate families. All patients were male. The patients age was between 11 months and 318 months at the time of diagnosis with a mean of 62 months and a median of 52 months. The youngest age at the diagnosis was eleven months and the oldest was 318 months. At the time of the study, the mean age of the living patients was 88.1 (SD 53.8) months. According to the birth weight data, two patients were "macrosomic", which literally means "big bodied", (defined by the American College of Obstetricians and Gynaecologists, as birth-weight >4000 g or >4500 g irrespective of gestational age). Another two patients were large for gestational age (LGA) (defined as a weight, length or head circumference that lies above the 90th percentile for gestational age). The clinical characterizations of the patients are summarized in

Table I. Pathological glycosaminoglycans in different mucopolysaccharidosis

	Normal	Mucopolysaccharidosis							Typical clinical findings, affected organ systems
		I	II	III	IV	VI	VII	IX	
Chondroitin sulphate	+				(+)		+	++	
Dermatan sulphate		++	++			++	n-+		Skeleton + internal organs
Heparan sulphate		+	+	+			n-+		Intellectual disability
Keratan sulphate					+				Skeleton

++: Prominent feature, +: Often present, (+): Sometimes present

Table II. The height of the patients was variable depending on their age (between +1.88 SD and -7.5 SD); under five years, 5-10 years and >10 years, the mean heights were +0.07±1.8 SD, -2.48±2.05 SD and -3.84±2.58 SD respectively. Figure 1 presents the main symptoms of the study group; the most common symptom was coarse face (100%), and the others, in order of prevalence, were developmental delay (93%), joint stiffness (60%), recurrent upper airway infections (47%), hernia (33%), convulsion (27%) and recurrent ear infections (20%). Coarse face, macrocephaly and organomegaly were the main findings detected by physical examination (Figure

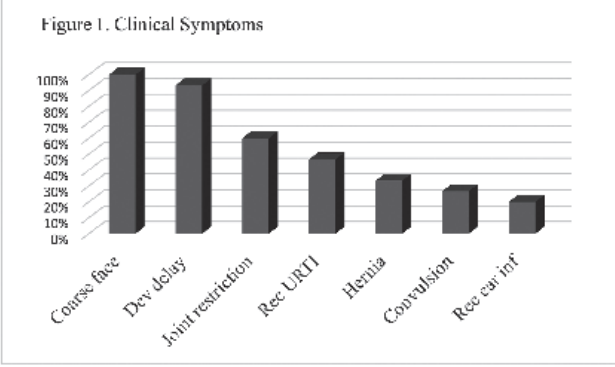

Figure 1. Clinical symptoms
Dev: Development, URTI: Upper respiratory tract infection, Rec: Recurrent, Inf: Infection

Table III. Iduronate-2 sulfatase activity

Patient	Enzyme activity	Normal range	Unit of measure	Sample type
H2	0	494-1113	nmol/mL/4 h	Plasma
H3	0.37	494-1113	nmol/mL	Plasma
H4	0.5	32-65	nmol/4 h/mg protein	Plasma
H6	0	35-110	nmol/4 h/mg protein	Fibroblast
H7	0.62	28.2±9.75	nmol/4 h/mg protein	Plasma
H8	0	494-1113	nmol/mL/4 h	Plasma
H8S	0	494-1113	nmol/mL/4 h	Plasma
H10	0	494-1113	nmol/mL/4 h	Plasma
H10S	0	494-1113	nmol/mL/4 h	Plasma
H13	0	494-1113	nmol/mL/4 h	Plasma
		Control		
H5	0	PC: 0.91 - NC: 0.74	nmol/mg/mL	Plasma
H9	0.06	NC1: 32.33 - NC2: 31.37	nmol/4 h/mg protein	Plasma
H11	0.71	NC1: 42.4 - NC2: 47.4	nmol/4 h/mg protein	Plasma

H: Hunter, NC: Normal control, PC: Positive control, S: Sibling

Table II. Clinical characteristics of mucopolysaccharidosis Type II patients

Patient	Last visit (m)	Starting therapy (m)	Diagnosis (m)	Current (m)	Valvulopathy	Cardiomyopathy	Hearing loss	Carpal tunnel	Hydrocephaly	Intellectual disability	SDS for height (last visit)
H1	140	No	12	Ex	+	+			+	+	
H2	127	No	53	Ex					+	+	-0.98
H3	353	354	318	Ex	+	-	+	+	-	-	-4.98
H4	160	95	64	Ex (159)	+	+	+	+	+	+	-5.36
H5	180	99	52	Ex (180)	+	+	+	+	-	+	-3.11
H6	179	82	24	Alive (178)	+	-	+	+	-	+	-7.50
H7	112	66	57	Ex (119)	+	-	+	+	-	+	-3.42
H8	80	No	68	Ex	+	+		+	+	+	-4.92
H8S	39	72	50	Alive (126)	+	+		-	-	+	-2.50
H9	134	53	52	Alive (133)	+	-	+	+	+	+	-1.10
H10	55	33	30	Alive (54)	-	-	-	-	-	+	-0.08
H10S	89	66	69	Alive (88)	+	-	+	+	+	+	-0.58
H11	37	24	20	Alive (36)	+	-	+	-	-	+	1.00
H12	21	13	11	Alive (21)	-	+	+	-	+	+	1.88
H13	70	1	62	Alive (69)					-	+	-1.00

1). Apart from H3, all of the patients presented neurologic involvement, mild to severe intellectual disability. H3 had no intellectual disability. Among follow up and living patients, five patients are able to walk without support and two patients are wheelchair-bound. Convulsion was noted in four patients 4/15 (26%). Cardiac involvement manifested at variable grades of valvulopathy (11/13-84%) and left ventricular hypertrophy (6/13-46%). In 11 patients with valvulopathy; mitral valve involvement was 90% (10/11), aortic valve involvement 63% and tricuspid valve involvement was 36% (4/11). On bone survey, dysostosis multiplex was noted in 12/12 patients. Hydrocephaly was noted in 7/15 patients on cranial imaging, and three of the seven patients with hydrocephaly had a shunt procedure. Carpal Tunnel syndrome was observed in eight patients on electromyography (8/12-66%). Three patients had broad Mongolian spot on physical examination. Three patients never received ERT and none of patients had no HSCT. ERT was started at the age of 83±76 months (limits: 11-319). Urinary GAG was elevated in all patients and increased dermatan sulfate and heparan sulfate was seen in GAG electrophoresis of 9 patients. IDS activity was significantly diminished in all patients in whom enzyme analysis was performed (Table III). Minor genetic defects were identified by molecular analysis (Table IV) in all patients in whom IDS gene analysis was performed, one of them was nonsense and the others were missense. One novel mutation was described.

Discussion

This is the first study on the clinical and gene mutation characterizations of Turkish MPS II patients. According to the birth weight data, two patients were macrosomic and another two patients were LGA. Previous studies have analysed birth parameters in patients with MPS II and mean birth weight has been reported to be slightly higher in MPS II patients than in those of the general population (15-19). Recently, a new large study from The Hunter Outcome Survey (HOS) also shows that birth weight is not associated with disease severity, in contrast to other previous studies (20). The age of admission or referral to a metabolic centre may be delayed. The need for early identification of mild presentations makes Hunter disease a candidate for NBS (11). The second most common symptom was developmental delay (93%), parallel to this data 14/15 patients had the severe form of the disease, which is consistent with recent studies (21-23). A total of 13/15 patients were assessed with echocardiography and cardiac involvement was detected in 12 of these patients. This data is compatible with the reports from HOS wherein the prevalence of cardiac presentation is high and valvular disease is the most common involvement (24-27). Three patients had broad Mongolian spot on physical examination. A clinical link between Mongolian spots and MPS II and other lysosomal storage diseases has already been reported in the literature (28-30). Mongolian spots may be one of the key factors in the early diagnosis of MPS II. IDS activity was significantly diminished in all patients in whom enzyme analysis was performed. Residual enzyme activity showed no predictive value (31).

Study Limitations

Limitations of the present study are that the enzyme levels were not measured for all of the patients and the molecular analysis of all patients were not taken into consideration.

Conclusions

This is the first study on the clinical and gene mutation characterization of Turkish MPS II patients. The clinical characteristics of MPS II in this case series were in agreement with what has been reported in that the age of diagnosis is much delayed despite an earlier onset of symptoms. Most of the patients had neurologic findings with different grades of severity. The molecular analysis revealed one novel mutation.

Ethics

Informed Consent: Informed consent was obtained.
Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: H.Y., E.C., H.O., F.Ö., Concept: S.K.U., Design: M.Ç., Data Collection and Processing: E.C., Analysis and Interpretation: H.Y., Literature Search: E.E., Writing: H.Y.

Conflict of Interest: No conflict of interest was declared by the authors.

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Table IV. Mutation analysis of *IDS* gene

Patient	Mutation	Consequence	Location	Phenotype	Status	Reference
H3	c.322T>G	p.Y108D	Exon 3	Mild	Novel	-
H4	c.262C>T	p.R88C	Exon 3	Severe	Published	Rathmann et al., (12)
H6	c.262C>T	p.R88C	Exon 3	Severe	Published	Rathmann et al., (12)
H9	c.672G>A	p.G224E	Exon 5	Severe	Published	Karsten et al., (13)
H11	c.263G>A	p.R88H	Exon 3	Severe	Published	Rathmann et al., (12)
H12	c.162T>G	p.Y54X	Exon 2	Severe	Published	Mutesa et al., (14)

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