Clinical and Genetic Characteristics of Romanian Patients with Mucopolysaccharidosis Type II

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Abstract Background: Mucopolysaccharidosis type II (MPS II, Hunter syndrome) is a rare X-linked disorder caused by deficiency of iduronate-2-sulfatase (I2S) enzyme, which leads to the accumulation of partially digested glycosaminoglycans (GAGs) in the lysosomes and induces multisystemic alteration (coarse facial features; skeletal dysplasia; hepatosplenomegaly; joint stiffness and contractures; heart, lung, vision, and hearing disability; profound neurological decline).

The purpose of this study is to present the clinical and genetic characteristics of Romanian patients with Hunter syndrome and the genotype–phenotype correlation.

Material and Methods: 15 unrelated patients, with MPS II ranging from mild (4 subjects) to severe phenotype (11 subjects) aged 2 to 20 years, were evaluated clinically, cognitive development, enzyme assay and molecular analysis.

Results: The molecular analysis of the 15 unrelated Romanian MPS II patients has identified 15 different mutations (2 major genetic defects (13%) and 13 minor genetic defects (87%): microdeletions and point mutations (missense, nonsense), seven of them described for the first time—deletion encompassing 3 to exon 7; c823G>T, pD275Y; c.1600A>C (pN534H); c.102_10delAG (p.D5Cfs*11); c.448_471del (p.P150_P157del); c.421delA (p.I141Yfs*72); and c.419-1G>C. The major genetic defects were correlated with a severe course of disease.

Conclusion: This is the first study on the clinical and molecular characterization of the MPS II Romanian patients. This study supports the evidence of the mutational heterogeneity of the I2S gene as well as the difficulty to correlate genotype and phenotype in the patients with MPS II.

Introduction

Mucopolysaccharidosis type II (MPS II, Hunter syndrome) is a rare X-linked disorder caused by alterations in the iduronate-2-sulfatase (I2S) gene (Wraith et al. 2008). This enzyme degrades glycosaminoglycans (GAGs), such as heparan sulfate and dermatan sulfate. The deficiency of the enzyme activity leads to the accumulation of partially digested GAGs in the lysosomes and induces multisystemic alteration. The gene responsible for IDS synthesis is located on chromosome Xq27–q28 and includes nine coding exons. IDS pseudogene is located in a distance of 20 kb of IDS's telomere and includes identical sequence of exon 2 and intron 2 and chimeric sequence of intron 3 and intron 7 which is responsible for homologous recombination of the active gene and pseudogene (Timms et al. 1995). IDS gene encodes the synthesis of 550-amino acid protein. The IDS alterations include large gene deletions, rearrangements, and small gene alterations (Froissart et al. 1993). According to the Human Genome Mutation Database (www.hgmdtrial.biobase-international.org), to date, more than 500 distinct mutations of the IDS gene have been identified, most of them point mutations (52%) or small deletions (17%).

Two types of disease have been described: the severe form with progressive neurologic alteration and the mild

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form without or with minimal neurological dysfunction. This classification is challenged by more and more experts, because the severity of cardiac, respiratory, skeletal, and visceral damage and the term of attenuated form of disease are accepted (Wraith et al. 2008; Scarpa et al. 2011).

The patients with Hunter syndrome present wide allelic and phenotypic heterogeneity (Flomen et al. 1992). The genotype–phenotype correlation is present only in large deletions or large rearrangements of the active gene and pseudogene, which lead to inactive enzyme synthesis (zero enzyme activity), with severe forms of disease (Bunge et al. 1992). The genotype–phenotype correlation is not valid in small, point mutations and missense, nonsense mutations, which, in most cases, are “private” mutations. There are cases where the same mutation induces different clinical forms of severity. The relationship between IDS activity and clinical phenotypes was noted.

The clinical characteristics of MPS II are macrocephaly, coarse facial features, hepatosplenomegaly, hernia, stiff joints, respiratory infections, recurrent otitis, deafness, cardiac valve disease, and neurologic impairment, in two-thirds of cases (Beck 2011; Giugliani et al. 2014). The onset of the disease is at age of 12–18 months (severe form) and at age of 2–4 years (attenuated form) (Wraith et al. 2008).

Because there are no studies on MPS II patients in Romania, the objective of this study is to present the clinical and genetic characteristics of Romanian patients with Hunter syndrome and the genotype–phenotype correlation.

Subjects and Methods

Fifteen patients with MPS type II, from unrelated families, aged 3.16–31.25 years, were enrolled. All these patients were specifically diagnosed (enzyme and molecular determination), and they represent all Romanian patients diagnosed with this disease. The study protocol was approved by the hospital ethics committee, and written, informed consent was obtained from participants or their guardians prior to the enrollment in the study. Clinical assessment of the patients included standard auxological assessment, according to www.who.int/childgrowth/standards (using Seca Vogel and Halke Hamburg 702 device), bone radiographs, goniometry, neurological and psychological evaluation, otorhinolaryngology examination with audiogram, ophthalmological examination, cardiology evaluation (ECG, Doppler echocardiography), and spirometry. Hepatic and splenic volumes were determined by ultrasonography (Patlas et al. 2002), and the cutoff values accepted were 2.5% of the body weight for the liver and 0.2% of the body weight for the spleen (Weinreb et al. 2002). The values obtained at ultrasonography were expressed as multiple of normal value. Iduronate-2-sulfa-

tase activity was determined by variable methods which were available at different times, plasmatic activity, or dried blood spot by fluorometry, based on the fluorometric determination of methylumbelliferone (Centogene Laboratory Rostock, Germany). All genetic procedures were done in accordance with the ethical standards on human experimentation, of the hospital committee and with the Helsinki Declaration of 1975, as revised in 2000. The written, informed consent was obtained from participants or their guardians prior to the genetic analysis. The molecular analysis was realized at Centogene Laboratory Rostock. IDS gene was analyzed by PCR and sequencing of both DNA strands of the entire coding region and the highly conserved exon–intron slice junctions. The reference sequence of the IDS gene is NM_000202.5/NM_006123.4.

Novel, unreported mutations were analyzed by Alamut 2.2 software and Polyphen-2, SIFT, Mutation Taster, and Align-GVGD in order to reproduce the effect of each mutation on enzyme activity.

Results

Clinical characterization of the patients is presented in Table 1. The height of the patients was variable, depending on the age (between +3.4 and −4.66 SD): the mean height was 1.8 ± 1.06 SD in the group of patients under 5 years, -2 ± 2.12 SD in the group of 5–10 years, and -3.71 ± 0.25 SD in the group >10 years.

All the patients presented coarse facial features, osteoarthropathy, stiff joints, umbilical hernia, and hepatosplenomegaly (mean hepatic volume was $1.7 \pm 0.79 \times$ normal volume; mean spleen volume was $4 \pm 1.45 \times$ normal volume).

Cardiac involvement consisted in variable grades of left ventricular hypertrophy (73.33% of patients) and valve involvement. All the patients presented mitral valve thickening with different grades of regurgitation, depending of the age at diagnosis. Eight patients (53%) presented aortic regurgitation. Hearing loss was present in 11 patients (73%). Neurological and psychological assessment revealed four patients (26.66%) with normal intellectual development and 11 patients with a variable neuro-intellectual impairment, from mild retardation to dementia.

The clinical onset was at 1.73 ± 0.84 years; the unspecific diagnosis was established at the age of 4.36 ± 2.6 years, and specific diagnosis was established at 5.14 ± 3.2 years. We described an important gap (3.4 ± 2.36 years) between the clinical onset and specific diagnosis in this group (the limits: 0.9 and 10.1 years).

Enzyme replacement therapy was started at the age of 7.45 ± 5.28 years (limits: 2.1–20.25 years). Iduronate-2-

Table 1 Clinical characteristics of MPS II patients

Nr.	Onset	Age			Specific diagnosis	Starting therapy	Current	SDS for height	Hemia	Liver volume (×N)	Spleenic volume (×N)	Valvulopathy				Osteoarthropathy	Hypoaecusia	Neurological involvement
		Unspecific diagnosis	Specific diagnosis									MI	MS	AI	AS			
H1	1	5	11.83	20.25	31.25	−4.66	+	1.26	1.88	++	+	+	+	+	+	+	+	−
H2	3	5.75	6	12.5	15.91	−3.7	+	1.2	5	+	+	+	+	+	+	+	+	−
H3	2	5.83	6.9	11.25	14.58	−3.1	+	1.45	3.8	++	+	+	+	+	+	+	+	−
H4	1.5	3	3.5	10.16	13.41	−2.8	+	1.23	5.38	+	+	++	+	+	+	+	+	+++
H5	1.5	11.5	11.6	12	12.16	−4.30	+	5.45	7.27	++	+	++	+	+	+	+	+	+++
H6	2	3.5	4.16	8	11.25	−3.5	+	1.2	4	++	+	++	+	+	+	+	+	+++
H7	4	6	6.8	7.8	8.33	−2	+	1.58	3.25	+	+	++	+	+	+	+	+	−
H8	2	6.83	6.9	—	7.33	−2.22	+	1.26	1.3	++	+	++	+	+	+	+	+	++
H9	1	2	2.25	3.25	6.66	+1	+	1.33	3.61	++	+	+	+	+	+	+	+	++
H10	1.5	3.9	4	4.1	5.25	+1.4	+	1.6	3.5	+	+	+	+	+	+	+	+	++
H11	2	2.9	3	3.25	5.08	−0.1	+	1.75	3.55	++	+	+	+	+	+	+	+	++
H12	1	2.5	2.6	3.25	4.91	+3.4	+	2.37	4	++	+	+	+	+	+	+	+	++
H13	1.5	3.75	3.9	4.25	3.75	+2.2	+	1.24	5.1	++	+	+	+	+	+	+	+	+
H14	1	1.5	1.9	2.1	3.66	+1.2	+	4.21	4.86	++	+	+	+	+	+	+	+	+
H15	1	1.5	1.8	2.16	3.16	+2.5	+	1.4	3.5	+	+	+	+	+	+	+	+	++

H Hunter patient, SDS standard deviation score, N normal, MI mitral valve stenosis, MS mitral valve insufficiency, AI aortic valve insufficiency, AS aortic valve stenosis

Table 2 Iduronat sulfate–sulfatase activity

Patient range	Enzyme activity	Normal range	Unit of measure	Sample type
H1	0.0	300–800	mMol/l/4 h*	Plasma
H2	4.5	300–800	mMol/l/4 h*	Plasma
H3	17.452	300–800	mMol/l/4 h*	Plasma
H4	1.5759	300–800	mMol/l/4 h*	Plasma
H5	<0.8	≥5.6	μmol/l/h	DBS
H6	3.409	300–800	mMol/l/4 h ^a	Plasma
H7	3.6	300–800	nM/4h/ml	DBS
H8	0	≥5.6	μmol/l/h	DBS
H9	1	>4	μmol/l/h	Plasma
H10	<0.8	≥5.6	μmol/l/h	DBS
H11	<0.8	≥5.6	μmol/l/h	DBS
H12	1.2	>2	μmol/l/h	DBS
H13	<0.8	≥5.6	μmol/l/h	DBS
H14	1.1	>4	μmol/l/h	DBS
H15	0	0.02–0.25	μmol/spot ^a / 21 h	DBS

H Hunter patient, DBS dried blood spot, * none

sulfatase activity was markedly reduced in all patients (Table 2).

Molecular analysis (Table 3) revealed major genetic defects in two cases (13%) and minor genetic defects, such as deletions and point mutations (nonsense, missense mutations), in 13 patients (87%).

The major genetic defects consisted in deletion of the segment exon/intron 3–7 in one patient and complete deletion of the exon 8 in another case. Both mutations correlated with a severe course of disease.

The minor genetic defects affected the exons in nine cases and the introns in four cases. In six patients point mutations of the exons 3, 6, 7, and 9 were identified, and two novel mutations were described. Three patients presented mutations of the exon 9.

Exonic Mutations

We found a previously unreported hemizygous variant in *exon 6* (c.823G>T, p.D275Y). It is located at a highly conserved nucleotide and amino acid position, with physiochemical differences between the amino acids aspartate and tyrosine. The second previously unreported hemizygous mutation was in *exon 9* (c.1600A>C, p.N534H). Both mutations indicate an attenuated phenotype.

In three patients microdeletions were identified. In one patient, with attenuated form of disease, a previously unreported hemizygous variant in *exon 1* (c.102_10delAG, p.D5Cfs*11) was described. It creates a shift in the reading frame starting from codon D35. The new reading frame

ends in a stop codon 10 position downstream, which is very likely to result in a truncated protein production.

Two novel microdeletions were identified at *exon 4*: c.448_471del (p.P150_P157del) and c.421delA (p.I141Yfs*72). Both mutations determined a severe course of the disease. We detected two hemizygous mutations in exon 4 of the IDS gene: c.448_471del (p.P150_P157del), which creates the loss of eight residues, which is very likely to result in a shortened protein that may function improperly, and c.421delA (p.I141Yfs*72), which creates a premature stop codon which is very likely to result in a truncated protein or loss of protein production. These mutations were the first time detected in Centogene's internal mutation/variation database (CentoMDTM).

Intronic Mutations

In four patients the mutations were located in the introns, and all mutations were correlated with severe forms of disease with early clinical onset and progressive neurological impairment. *Intron 4* was affected in two patients and *intron 2* and *intron 3* in one patient, respectively. We detected a previously unreported hemizygous mutation in *intron 3* (c.419-1G>C). It is located in a highly conserved region within the acceptor splice site of intron 3. Five patients presented mutation c.438C>T (p.T146T) in intron 4, and one patient presented mutation c.418 + 12T>C in intron 3. These mutations are considered as polymorphisms, without effect on the enzyme activity.

Discussion

This is the first study on the clinical and molecular characterization of the MPS type II Romanian patients. All patients presented coarse facial features, organomegaly, arthropathy, cardiac involvement, and respiratory difficulties, but variable neurological impairment. In the first years of life, the height of most patients with MPS II is normal; subsequently, the growth velocity decreases with age (according Patel et al. 2014).

Eleven patients (73.4%) presented a severe form of disease, which exceeds the rate of approximately two-thirds reported by Martin et al. (2008), Beck (2011), and Giugliani et al. (2014). Two of them presented major genetic defects (deletion of exon/intron 3–7 and deletion of exon 8), and nine patients presented minor genetic defects. The incidence of large deletions (13.3%) in our group is according to results obtained by Goldenfum et al. (1996), Lissens et al. (1997), Vafiadaki et al. (1998), and Froissart et al. (1998), but in contrast to 19–29% reported by Brusius-Facchin et al. (2014), Hartog et al. (1999), and Zhang et al. All the gross deletions caused severe course of disease accordingly with

Table 3 Molecular characteristics of the MPS II patients

Patient range	Location	Nucleotide change	Amino acid change	Reference	Mutation effect	Clinical form
H4	Exon03/exon 7	Deletion encompassing 3 to exon 7		–	Low enzyme activity	Severe
H6	Exon 08	Deletion		Zhang et al. (2011)	Low enzyme activity	Severe
H2	Exon 01	c.102_103delAG>T	p.D35Cfs*11	–	Low enzyme activity	Attenuated
H1	Exon 04	c.438C>T	p.T146T	Rs.1141608	SNP	–
	Exon 03	c.253G>A	p.A85T	Rathmann et al. (1996)	Low enzyme activity	Attenuated
H8	Exon 04	c.448_471del	p.P150_P157del	–	Low enzyme activity	Severe
H13	Exon 04	c.421delA	p.I141Yfs*72	–	Low enzyme activity	Severe
H3	Exon 06	c.823G>T	p.D275Y	–	Low enzyme activity	Attenuated
H11	Exon 07	c.998C>T	p.S333L	Flomen et al. (1992)	Low enzyme activity	Severe
H7	Exon 09	c.1600A>G	p.N534H	–	Low enzyme activity	Attenuated
H14	Exon 04	c.438C>T	p.T146T	Rs.1141608	SNP	–
	Exon 09	c.1294T>C	p.C432R	Lualdi et al. (2006)	Low enzyme activity	Severe
H5	Exon 04	c.438C>T	p.T146T	Rs.1141608	SNP	–
	Exon0 9	c.1402C>T	p.R468W	Crotty et al. (1992)	Low enzyme activity	Severe
H10	Intron 03	c.418+12T>C	–	rs148419392	SNP	–
	Intron 02	c.241-3C>G	–	Gort et al. (1998)	Low enzyme activity	Severe
H9	Intron 03	c.419-1G > C	–	–	Low enzyme activity	Severe
H12	Intron 04	c.419-2A > G	–	Bunge et al. (1993)	Low enzyme activity	Severe
H15	Exon 04	c.438C>T	p.T146T	Rs.1141608	SNP	–
	Intron 04	c.507+1G>A	–	Karsten et al. (1998)	Low enzyme activity	Severe
	Exon 04	c.438C>T	p.T146T	Rs.1141608	SNP	–

H Hunter patient, *SNP* single nucleotide polymorphism

Zhang, but contrary to Bonuccelli et al. (1998) who found an association with an intermediate form of the disease.

Minor genetic defects (9/11 patients with neurological involvement, 81.81%) consisted in point mutations and small deletions in six and three patients, respectively. The intronic splice mutations in the present study (26%) are more frequent than those reported by Bertoli et al. (10.9%), but less frequent than those reported by Alvares (36%).

The missense mutation S333L (c.998C>T), described by Flomen et al. (1992) in a Korean patient with severe form of disease, was also present in our study and has induced a similar evolution.

Mutation c.1402C>T (R468W) located on exon 9 was described for the first time by Crotty in 1992 in a patient with attenuated form of disease (IQ = 115). This mutation

was associated in our study with a severe form of disease in a boy who has lost his cognitive acquisitions at the age of 12 years. Zhang et al. (2011) also reported the absence of genotype–phenotype correlation of this mutation in three patients. These data suggests that there could be other mechanisms involved in the clinical course of this disease.

Mutation c.419-1G>C, located on intron 3, reported for the first time in this study, was present in a patient with severe form of disease.

Missense mutation c.1294T>C (C423R), located on exon 9, described for the first time in an Italian patient with “intermediate” form of disease who died at the age of 23 years, was identified in our study in a 21-month-old patient who presented mild neuro-intellectual retardation.

Another patient with mild neurological impairment presented mutation c.241-3C (deletion of 44bp) which was reported by Gort in 1998 in a Spanish patient with intermediate form of disease.

Mutation c.507+1G>A located on intron 4 was correlated with a severe phenotype, as Karsten described in 1998.

Four patients presented an attenuated form of disease. In three cases, new “private” mutations were identified. These novel mutations were located in exons 1, 6, and 9, respectively. In one patient with attenuated form of disease, the point mutation c.253G>A, P.A85T (described by Rathmann in 1996) was identified, located on exon 3.

Conclusions

This is the first study on the clinical and molecular characterization of the MPS II Romanian patients. Fifteen different mutations of which seven novel unreported mutations were identified. The results of this study support the evidence of the mutational heterogeneity of the IDS gene as well as the difficulty to correlate genotype and phenotype in the patients with MPS II.

Contributions of Individual Authors

Camelia Alkhzouz: study design, acquisition, analysis and interpretation of data, writing, and literature search

Cecilia Lazea: cardiac assessment of the patients and writing

Simona Bucerzan: acquisition, analysis, and interpretation of data

Ioana Nascu: acquisition, analysis, and interpretation of data

Eva Kiss: acquisition, analysis, and interpretation of data

Carmencita Lucia Denes: ultrasound assessment of the patients

Paula Grigorescu-Sido: study design; acquisition, analysis, and interpretation of data; and writing

Name of One Author Who Serves as Guarantor

Camelia Alkhzouz

The Conflict of Interest Statements

1. *Camelia Alkhzouz* declares she has received speaker honorarium and travel and accommodation funding from Shire and Genzyme companies in the past 5 years.

2. *Cecilia Lazea* declares she has received travel and accommodation funding from Shire and Genzyme companies in the past 5 years.
3. *Simona Bucerzan* declares she has received travel and accommodation funding from Shire and Genzyme companies in the past 5 years.
4. *Ioana Nascu* declares she has received speaker honorarium and travel and accommodation funding from Shire and Genzyme companies in the past 5 years.
5. *Eva Kiss* has nothing to declare in the past 5 years.
6. *Carmencita Lucia Denes*.
7. *Paula Grigorescu-Sido* has nothing to declare in the past 5 years.

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All the authors confirm independence from the sponsors; the content of the article has not been influenced by the sponsors.

Details of Ethics Approval

The research study was approved by the hospital’s ethics committee.

Patient Consent Statement

The written, informed consent was obtained from participants or their guardians prior to the genetic analysis. All genetic procedures were done in accordance with the ethical standards on human experimentation, of the hospital committee, and with the Helsinki Declaration of 1975, as revised in 2000.

Approval from the Institutional Committee for Care and Use of Laboratory Animals

This article does not contain any studies with animal subjects performed by any of the authors.

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