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HUNTER SYNDROME (MUCCOPOLYSACCHARRIDOSIS TYPE II) IN MACEDONIA AND BULGARIA

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A b s t r a c t: *Background:* Mucopolysaccharidosis II (MPS II) is caused by a deficiency of iduronate-2-sulfatase (IDS; EC 3.1.6.13).

Methods and results: We describe 11 boys from Bulgaria and Macedonia detected in the period from 1998 to 2008. The mean age at diagnosis was 4.77+/-1.29 years. All children were severely retarded: IQ ranged from 34–80, and they all had coarse faces and hepatomegaly. In addition, splenomegaly was found in 81.81% patients, dysostosis in 45.45%, kyphosis in 27.27%, deafness in 18.08%, growth below the third percentile in 45.45%, growth below the parental target height in all patients, stiff joints in 56.56% and hypertrophic myocardiopathy in 18.18% children. Two patients died at the age of 11 and 35 years. Plasma iduronate-2-sulfatase was low in all probands and normal in parents and relatives.

Two new mutations were discovered: p.K236N (c.708G>C) in a child with a moderately severe phenotype, and p.Q80K (c.238C>A) which resulted in a severe phenotype and early death at the age of 11 years. Heterozygote carriers of the pathogenic allele were 29 female relatives. The calculated incidence rate for MPS II in Macedonia (censuses 1994 and 2002, children under 14 years: 483,923 and 426,280) and Bulgaria (censuses 1992 and 2006, children under 14 years: 1 126, 598 and 1,077,020) are 0.36 and 0.46 respectively, while the calculated prevalence rate are 3.6 and 4.6 per 1,000,000 boys (aged 0–14 years). Correlating phenotype and genotype remains a complex endeavour.

Conclusions: We report calculated incidence and prevalence rates in two South Eastern European countries, and 2 novel genetic alterations correlated with their phenotypes.

Key words: Bulgaria, Hunter disease, iduronate-2-sulfatase, Macedonia, mutational analysis.

Introduction

Hunter syndrome (HS; Mucopolysaccharidosis type II) is a rare, X-linked disorder of glycosaminoglycan metabolism. It is caused by a deficiency in the lysosomal enzyme iduronate-2-sulfatase (IDS), and results in the accumulation of glycosaminoglycan in lysosomes of various tissues. Patients may suffer from severe airway obstruction, skeletal deformities, cardiomyopathy. In addition, there may be progressive neurological decline.

Mucopolysaccharidosis type II (MPS II) has frequencies reported between 1 in 34,000 males [1] and 1 in 165,000 male births in Western Australia [2]. So far, respective frequencies in Macedonia and Bulgaria have not been reported.

Various genetic alterations have been reported in MPS II: missense and nonsense mutations, mutations affecting splicing, small insertions and deletions, partial gene deletions, and deletions or rearrangements of the whole IDS gene [3–5, 6–9, 10–12, 13–21].

We report the genetic alterations of MPS II patients in Macedonia and Bulgaria. In addition, we have calculated the incidence and prevalence rates for both countries.

Patients and methods

We describe 11 patients diagnosed in Bulgaria and Macedonia in the period 1998–2008. Clinical data were collected from medical histories of the patients in both countries. When necessary, additional interviews and clinical examinations were performed by their physicians in both countries. Informed consent was obtained from the patients for the study and the publication of figures.

Biochemical diagnosis was performed by assay of IDS in plasma as previously described [22]. Urinary glycosaminoglycans (GAGs) collected from the middle stage of urination of the patients and their parents were tested using the methods of agarose gel electrophoresis and toluidine blue with standard dermatan sulfate (DS), heparan sulfate (HS), keratan sulfate (KS) and chondroitin

sulfate (CS) as positive controls and the urine of healthy individuals as negative controls [23]. Leukocytes β-galactosidase, leukocytes arylsulfatase A, plasma α-iduronidase, and plasma iduronate 2-sulfatase were determined as previously reported [24–27].

Genotyping

The genomic DNA was extracted from patients' blood using the QIAamp Blood Mini Kit (Qiagen GmbH, Hilden, Germany) and subjected to PCR for the amplification of the 9 exons and the flanking regions of the *IDS* gene (Table 1). The PCR was carried out in a total volume of 50 µl containing 200 ng genomic DNA, 1.25 U AmpliTaq Gold Polymerase (Applied Biosystems, Foster City, California), 1.5 mM $MgCl_2$, 10 mM of each of dNTPs, 3% DMSO and 120 nmol of each primer (Table 1). The reactions were performed in an Eppendorf Mastercycler according to the following cycle conditions: 95°C for 10 min, then 35 cycles 95°C 30 s, 60–64°C 30 s and 72°C 30 s and the final incubation of 72°C for 7 min using the specific annealing temperatures for each primer pair according to Table 1. The resulting DNA was sequenced, including approximately 100 bp of the flanking introns. The reference sequence of the cDNA is GenBank NM_000202.2. The identified mutations were confirmed by restriction analysis. 112 control alleles were analysed in the case of novel mutations to exclude a potential polymorphic character.

Table 1

Oligonucleotide primers for IDS amplification (5'→3')

Exon	Forward	Reverse	PCR product [bp]
1	CTGTGTTGCGCAGTCTTCAT	GAAAAATGGAGGGAGGGAAC	388
2	AGGACTCAGGCTTCCTCCTC	TAACAAGATGTCCCGCACAA	429
3	TGGTTTGAGCTCTGCATGAC	GCACTGACTAGCGAGGGACT	440
4	GGCTTAGGGACCAGGAAGTC	AATGAAGCCACTGCTCCTGT	482
5	TGCCTGGAAAACAAGAAACA	ATGTAGCCACCTTCCCTGTG	468
6	ACGTGGGGAATGCTAGTGAG	CCCAGCACTTTGCCTGATAA	451
7	GCTGTGACTCTGTGGGTGAA	GCAAAGCATGTTTCACAGGA	383
8	GCAGCATTCAGTTGAAATAACC	CAGGGGCCATACTTGTCAAT	579
9	CATATGGAGCCCAGACAGGT	GGAAGGGAGCACATCACATT	610

Results

Eleven boys, diagnosed between 1998 and 2008 year, had a mean age at diagnosis of 4.77+/-1.29 years (Table 2). Severe mental retardation was found in all 11 children: the IQ ranged between 34->80. the classical coarse face was present in all boys (Fig. 1), as well as various degrees of liver enlargement. Other findings included: splenomegaly in 81.81% patients, dysostosis in 4.45%, kyphosis in 27.27%, deafness in 18.18%, growth below the third percentile in 45.45%, growth below the parental target height in all patients. Muscle tone was low in 27.27% of the children, while one boy was hypertonic (9.09%). Skin lesions were present in 18.18%, inguinal hernia was found in 18.18% children, hypertrichosis in one boy (9.09%) and recurrent infections (especially middle ear) in 36.36% children. Stiff joints (flection contractures) were observed in 63.63% (Fig. 2), hypertrophic myocardiopathy in 18.18% and osteoporosis in one boy (9.09%). X-ray studies in most of the patients showed platyspondily with ovoid vertebrae, a bulging sternum and flaring of the rib cage. The long bones were short, with irregular trabeculation. Metaphyses were widened, the femoral head was flattened. The metacarpals had conical bases. MRI of the brain revealed ventriculomegaly, periventricular leukomalation and widened subarachno-idal space. Two patients died at ages 11 and 35 years.

Table 2

Clinical characteristics of Hunter syndrome in Macedonian and Bulgarian patients

Patient	1	2	3	4	5	6	7	8	9	10	11
Age at diagnosis	4 y	6 y	4–5 y	2–3 y	2–3 y	6 y	3 y	3–4y	5	5	6
Mental retardation (IQ)	34	50	49	50	30	80	49	35	49	80	49–35
Coarse facies	+	+	+	+	+	+	+	+	+	+	+
Hepatomegaly	+	+	+	+	+	+	+	+	+	+	+
Splenomegaly	+	+	+	+	+	+	+	+	+	+	+
Dysostosis	+	+	+	+	+	+	+	+	+	+	+
Corneal opacity						+			-	-	-
Spine kyphosis									-	-	-
Deafness						+			-	-	-
Short Stature	+	+	+	+	+		+	+	-	-	+
Muscle Hipotony									-	-	+
Hernia inguinal	+	+	+	+	+	+	+	+	-	-	-
Skin lesions			+	+			+		-	-	-
Hypertrichosis	+	+	+	+	+	+	+	+			
Re\urrent infections	+	+	+	+	+	+	+	+			
Flection contractures	+	+	+	+	+	+	+	+			
Heart	+	+	+	+	+	+	+	+			
Osteoposis				+							

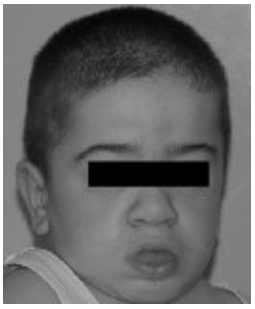

Figure 1 – Coarse facial appearance in boy with MPS II (MS, AK, DP)

Figure 2 – Flection contractures of the joints (AK)

The activity of β̃-galactosidase (nmol MU/h/mg protein), arylsulfatase A (nmol pNC/17h/mg protein) in isolated leukocytes as well as of α-iduronidase (nmol MU/4h/ml) in plasma were within the normal age and sex range in both the parents and the index case. Plasma iduronate 2-sulfatase was low in all patients,but normal in parents.

Among the Macedonian patients DNA genotyping revealed the presence of a known mutation, c.998C>T (p.S333L) in two patients (9.19%), and a novel mutation, p.K236N (c.708G>C), in a third one (Table 3). The X-recessive inheritance pattern was confirmed with positive carrier status in 29 female relatives (mothers, aunts, sisters). An example of a family pedigree is given in Fig. 3. It is of note that the novel mutation in the Macedonian patient resulted in a moderate clinical phenotype.

Table 3

Genotypes of Macedonian and Bulgarian MPS II Patients. Summary of Rare Mutations

Protein	Phenotype	Genotype		Exon	Reference
		Coding effect	Nucleotide change		
1		p.K227M	c.680C>T	5	Isogai, 1998
2		p.S333L	c.998C>T	7	Flomen, 1992
3		p.R468W	c.1402C>T	9	Crotty, 1992
4		*	*		female relatives carry p.D334G
5		p.D334G	c.1001A>G	7	Li, 1996
6		No genetic	lesion detected*	–	–
7		p.Q80K	c.238C>A	2	novel
8		inversion			Bunge, 1998
9		p. S333L	c.998C>T	7	Flomen, 1992
10		p.K236N	c.708G>C	5	novel
11		p.R468W	c.1402C>T	9	Crotty, 1992

***** Clinical and biochemical diagnosis.

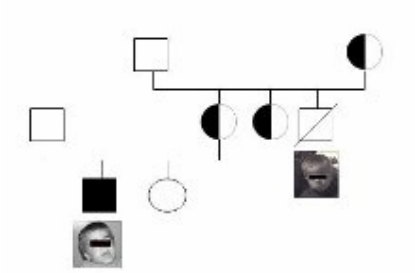

Figure 3 – MPS II pedigree in two patients with three generations of female carriers

Six Bulgarian patients carried previously described mutations: p.R468W (c.1402C>T), p.K227M (c.680C>T), and p.D334G (c.1001A>G). In addition, a previously described inversion (Bunge *et al*. 1998) was also detected (Table 3). It is of note that the novel p.Q80K (c.238C>A), found in a Bulgarian boy, resulted in a severe phenotype and death at the age of 11 years.

The public census data from Macedonia and Bulgaria were used to calculate data on disease frequency. The calculated incidence rate for MPS II in Macedonia (censuses 1994 and 2002, children under 14 years: 483,923 and 426,280) and Bulgaria (censuses 1992 and 2006, children under 14 years: 1 126,598 and 1,077,020) are 0.36 and 0.46 respectively, while the calculated prevalence rate are 3.6 and 4.6 per 1,000,000 boys (aged 0–14 years).

Discussion

MPS II affects multiple organs and physiological systems and has a variable age of onset and variable rate of progression. The phenotype can be severe with facial coarseness, short stature, hepatosplenomegaly, bone abnormalities, heart valve disease, mental retardation and death in the second decade [28]. At the other end of the phenotype spectrum the mild forms have no brain involvement and are compatible with prolonged survival [29–31].

About 347 different mutations underlying MPS II have been identified so far in different ethnic groups and populations [15, 16, 32–38]. Mutations tended to be more frequent in exons III, VIII, and IX, in the so-called hot-spots [30]. Only two of our patients had mutations located in exon IX, a further three were located in exon VII, two in exon VII and one in exon II.

In fact, the results published so far show pronounced mutational and deletional heterogeneity of the IDS [32, 39]. This renders genotype-phenotype correlations difficult [40], if not impossible [31, 41, 42]. Nevertheless, large de-

letions, or complete deletion of the IDS gene [9, 33, 40] result in a more severe form of Hunter syndrome. Beck and colleagues reported a complete lack of the IDS coding sequences and the simultaneous deletion of both DXS466 and DXS304 [IDS, DEL], an alteration resulting in severe mental retardation and no bladder and bowel control.

In total, we found four known mutations in six patients: p.S333L (c.998C>T), p.R468W (c.1402C>T), p.K227M (c.680C>T), and p.D334G (c.1001A>G). p.S333L has been described as severe resulting in low residual enzyme activity. This was confirmed in two Macedonian patients bearing this mutation. They both have a severe phenotype: at the age of 5 and 13 years they do not speak, do not control their sphincters and have a profound mental retardation (IQ 49–35). The younger one is hyperactive, the older has contractures of all joints.

Others described additional "severe" mutations: p.P86L, p.S349I, p.R468Q [42], p.R468L. ARG468GLN was found in a severe phenotype with death at an age of 23 months [43].

Other mutations (p.R48P, p.A85T, p.W337R, 78-BP INS [30] were found to be attenu-ated, resulting in more enzyme residual activity and in a milder clinical phenotype. p.R468W was described as mutation leading to a mild phenotype (ARG468TRP). Patients with this mutati-on in our series were also mildly affected. The same p.R468W mutation was examined by Crotty and colleagues by an *in vitro* mutagenesis experiment showing that the defective enzyme activity resulted precisely from this mutation. In addition, p.R468W showed a normal precursor with little or reduced mature forms, indicating incorrect targeting of the mutant enzyme [41].

The two novel mutations found in our patients resulted in a different severity of phenotype: p.K236N (c.708G>C) was found in a child with a moderate phenotype, while p.Q80K (c.238C>A) resulted in a severe phenotype and early death at the age of 11 years.

The frequency of the Hunter syndrome is approximately 1 in 34,000 males born in Israel between 1967 and 1975, 1 in 132,000 male births in the United Kingdom [44]. In UK the severe form was 3.38 times more frequent than the mild form. In British Columbia the estimated frequ-ency was of 1 in 110,950 live male births [45]. Nelson and colleagues (2003) estimated the incidence rate for Hunter syndrome in Western Australia of approximately 1 in 320,000 live birt-hs (1 in 165,000 male live births). The calculated prevalence rate for MPS II in Macedonia and Bulgaria are 0.72 and 0.92 respectively, while the calculated prevalence rates are 7.2 and 9.2 per 1,000,000 children (aged 0–14 years).

We here described 11 Macedonian and Bulgarian patients, their genetic alterations, inclu-ding two novel genetic alterations. In addition, we have analysed the phenotype-genotype correlation confirming previous observations and

characterizing the novel mutations. The Macedonian and Bulgarian incidence and prevalence rates have also been calculated.

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Резиме

HUNTER СИНДРОМ (МУКОПОЛИСАХАРИДОЗАТА ТИП II) ВО МАКЕДОНИЈА И БУГАРИЈА

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Вовед: Мукополисахаридозата тип II (МПС II) е резултат на дефицит на идуронат-2-сулфатаза (IDS; EC 3.1.6.13).

Методи и резултати: Опишуваме 11 момчиња од Бугарија и Македонија детектирани во периодот од 1998 до 2008 година. Средната возраст во моментот на дијагностицирање е 4,77+/-1,29 години. Сите деца беа со тешка ретардација: ИК меѓу 34–80 и сите имаат груби лицеви црти и хепатомегалија. Дополнително, кај 81,81% од пациентите е најдено спленомегалија, дизостоза кај 45,45%, кифоза кај 27,27%, глувост кај 18,08%, раст околу третиот перцентил кај 45,45%, раст под родителската целна висина кај сите пациенти, вкочанети зглобови кај 56,56% и хипертрофична миокардиопатија кај 18,18% од децата. Двајца пациенти на возраст од 11 и 35 години починаа. Плазматските концентрации на идуронат-2-сулфатазата беа ниски кај сите испитаници, а нормални кај нивните родители и роднини.

Беа откриени 2 нови мутации p.K236N (c.708G>C) – кај дете со умерено тежок фенотип и p.Q80K (c.238C>A) – релутирала со тежок фенотип и рана смрт на возраст од 11 години. Хетерозиготни носители на патогените алели беа 29 роднини од женски пол. Определените рати на инциденца за МПС II во Македонија (според пописите од 1994 и 2002, деца под 14 години: 483,923 и 426,280) и Бугарија (според пописите од 1992 и 2006, деца по: 1 126, 598 и 1,077,020) се 0,36 и 0,46, додека определените рати за преваленца се 3,6 и 4,6 на 1,000,000 момчиња (на возраст од 0–14 години). Корелирачкиот фенотип и генотип остануваат комлексен потфат.

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Заклучоци: Опишуваме определени рати на инциденца и преваленца во земји од Југоисточна Европа и 2 нови генетски алтерации кои корелираат со нивните фенотипови.

Клучни зборови: Бугарија, Хантерова болест, идуронат-2-сулфатаза, Македонија, мутациона анализа.

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