Isolated Growth Hormone Deficiency (IGHD) Associated with 7q11.23 Duplication Syndrome - a Case Report

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Background: Congenital pituitary hormone deficiency is etiologically heterogeneous and occurs in 1:4000 live births (1). Of those, isolated growth hormone deficiency (IGHD) is the most common, followed by combined pituitary hormone deficiency with or without extrapituitary anomalies (2, 3).

Case report: boy, presented at age of 8.7 years with short stature (SDS_h -3.46) (fig. 1 and 2) . No available perinatal data. At examination: mild mental retardation, developmental delay, mutism, loss of hearing, cleft palate, partial IGHD (peak GH 4.1 mU/L) (tabl. 1), 4-years delayed BA, cryptorchidism, refractive anomalies – high degree of hypermetropia and astigmatism, congenital cataracta. Anterior pituitary hypoplasia (MRI) (fig. 3). Institution of rhGH, initially with 0.05 U/kg/24h s.c. No additional pituitary hormone deficits could be established during follow up; spontaneous and fast progressing puberty was evident (tabl. 2).

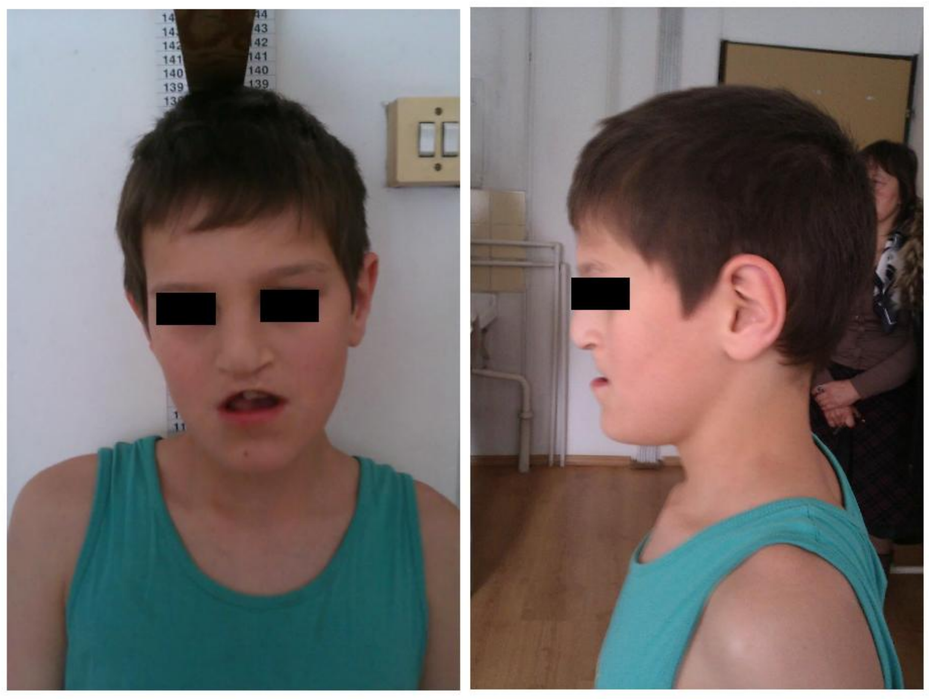


Fig. 1. Picture of the patient at 13.48 years.

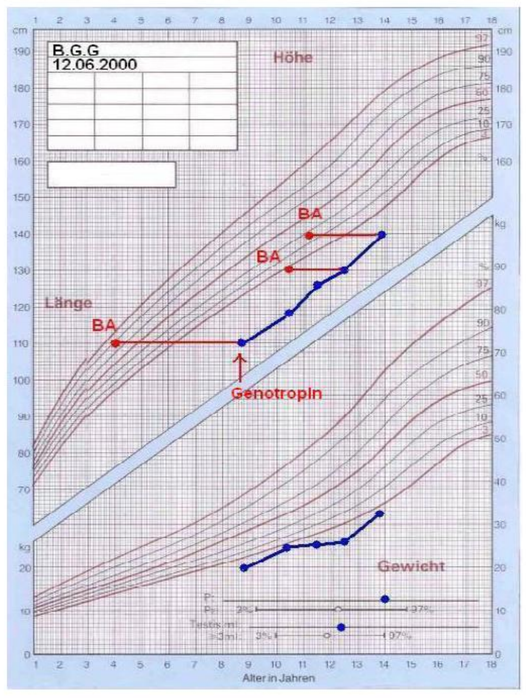


Fig. 2. Growth curve of the patient from 1 to 18 years

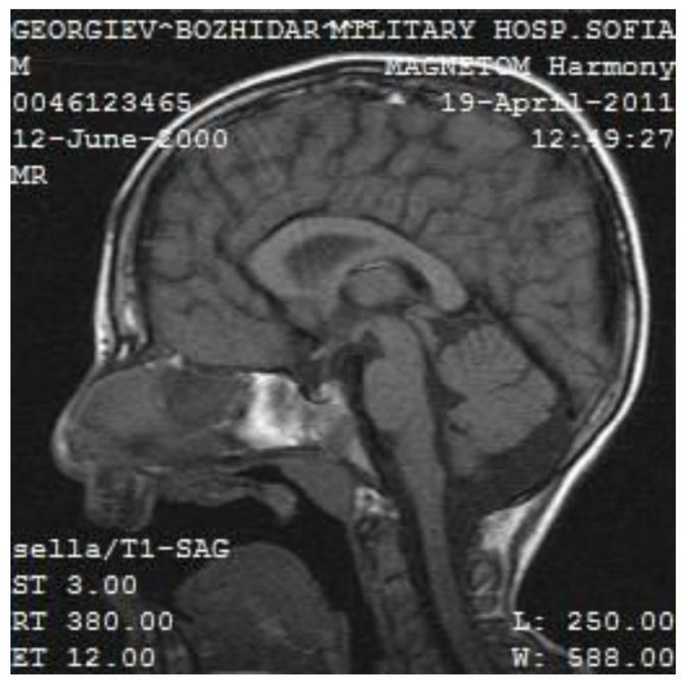


Fig.3. MRI of hypothalomic-pituitary region

Arginin HCL test										Physical exercise		
Minutes	-15	0	15	30	45	60	90	120	150	0	10	20
GH mU/l	3.5	2.1	4.1	3.8	1.5	0.8	0.3	0.3	0.2	0.25	17.0	6.3
BG mmol/l	5.5	4.9	4.7	4.2	4.5	4.5	5.3	5.9	6.0	-	-	-

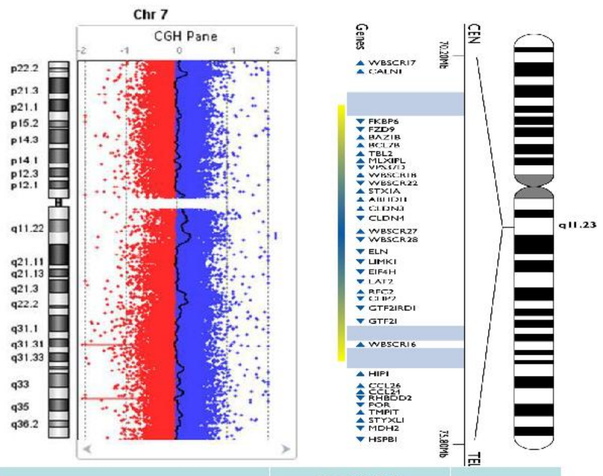
Tabl.1. Stimulation test for GH secretion

Age (decimals)	**8.72**	**10.32**	**11.48**	**12.48**	**13.48**
Height (cm)	110	117.5	124.8	130.4	140
SDS_{Prader}	-3.46	-3.64	-3.07	-2.75	-1.98
Treatment U/24h	0.9	1.8	2.1	2.7	-
IGF-1 ng/ml	114	98	266	288	225
IGFBP3 ng/ml	2537	3083	2973	3773	1020
Growth velocity (cm/year)	-	4.5	6.3	5.6	9.6
Growth velocity (percentiles)	-	10-25th	90-97th	50th	75-90th
Puberty (Tanner)	-	-	-	12y: LT 4ml, RT 3ml; 12.48y: T 6ml, D 18мм	T 10ml P 2-3

Tabl. 2. Treatments follow up for a period of 7 years

Methods: Sequencing analysis of exon 1-4 of HESX1, SOX2 and SOX3. Array comparative genome hybridization was performed.

Results: . A 3.297 Mb duplication 7(q11.23q11.23)(72366111-75663082)x3[hg19], containing 59 genes and 13 pseudogenes was found by aCGH after the negative screen for *HESX1, SOX2 and SOX3* (fig. 4). There is 87% match with the autosomal dominant 7q11.23 microduplication syndrome (tabl. 4). The estimated prevalence is 1:12000 live births (4). Symptoms include mild facial dysmorphic features, mental retardation, developmental and speech delay, language and hearing difficulties, short stature, cleft palate, cryptorchidism, ocular abnormalities which showed an overlap with our patient's phenotype (tabl. 3) (5). Up to now, none of the 7q11.23 patients are described to have hypopituitarism.



Symptoms	7q11.23 microdeletion syndrome	Patient
Facial dysmorphism	~100%	+
Speech delay	~100%	+
Decreased hearing	25%	+
Mild to moderate mentalretardation	83%	+
Developmental delay	70%	+
Short stature	10-15%	+
Cryptorchidism	25%	+
Cleft plate	11%	+
Muscle hypotonia	70%	-
Behavior abnormalies	~100%	+
Seizures	25%	-
Cardiac anomalities	20%	-
Ocular abnormalities	27%	+
Constipation	75%	-

Tabl. 3. Comparison of the phenotype of the index patient with patients with 7q11.23 microduplication syndrome

	Genesincluded in the 7q23.11 microduplication syndrome		Additional genes included in the patient's duplication	
	Gene		Gene	
7q23.11	HIP1	huntingtin interacting protein 1	GTF2IRD2B,	GTF2I repeat domain containing 2B
	WBSCR16	Williams-Beuren syndrome chromosome region 16	TRIM73	tripartite motif containing 73
	GTF2I	general transcription factor IIi	GATSL2	GATS protein-like 2
	GTF2IRD1	general transcription factor II I repeat domain-containing 1	GATSL1	GATS protein-like 1
	CLIP2	CAP-GLY domain containing linker protein 2	STAG3L2	stromal antigen 3-like 2
	LAT2	linker for activation of T cells family, member 2	NCF1	neutrophil cytosolic factor 1
	EIF4H	eukaryotic translation initiation factor 4H	GTF2IRD2	GTF2I repeat domain containing 2
	WBSCR28	Williams-Beuren syndrome chromosome region 28	MIR590	microRNA 590
	RFC2	eplication factor C (activator 1) 2, 40kDa	WBSCR26	Williams-Beuren syndrome chromosome region 26
	ELN	elastin	MIR4284	microRNA 4284
	LIMK1	LIM-domain containing, protein kinase	TBL2	transducin (beta)-like 2
	WBSCR27	Williams-Beuren syndrome chromosome region 27	BAZ1B	bromodomain adjacent to zinc finger domain, 1B
	CLDN4	claudin 4	FKBP6	FK506 binding protein 6, 36kDa
	ABHD11	abhydrolase domain containing 11	TRIM50	tripartite motif containing 50
	CLDN3	Claudin 3	NSUN5	NOP2/Sun domain family, member 5
	WBSCR22	Williams-Beuren syndrome chromosome region 22	POM121	POM121 transmembrane nucleoporin
	WBSCR18	Williams-Beuren syndrome chromosome region 18	BCL7B	B-cell CLL/lymphoma 7B
	STX1A	syntaxin 1A	TRIM74	tripartite motif containing 74
	VPS37D	vacuolar protein sorting 37 homolog D	POM121C	POM121 transmembrane nucleoporin C
	MLXIPL	MLX interacting protein-like	TMEM120A	transmembrane protein 120A
	POR	P450 (cytochrome) oxidoreductase	SPDYE5	speedy/RINGO cell cycle regulator family member E5
	FZD9	frizzled class receptor 9	SNORA14A	small nucleolar RNA, H/ACA box 14A
	CCL24	chemokine (C-C motif) ligand 24		
	CCL26	chemokine (C-C motif) ligand 26		
	RHBDD2	rhomboid domain containing 2		

Tabl. 4. Genes included in the 7q11.23 microduplication in the index patient.

Conclusion: : Patients with complex hypopituitarism phenotype associated with extrapituitary anomalies should undergo screening of the whole genome. This approach may contribute to new etiological insights of hypopituitarism. The 7q11.23 microduplication syndrome is very rare, up to now there are about 50 patients described worldwide. To our knowledge this is the first patient with IGHD due to pituitary hypoplasia as part of the 7q11.23 microduplication syndrome.

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