Septo-optic dysplasia (SOD) associated with Koolen-de Vries syndrome (KDVS): a case report

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Background: SOD is a rare congenital anomaly, clinically heterogeneous, combining optic nerve and pituitary gland hypoplasia, midline abnormalities of the brain, including absence of the corpus callosum and septum pellucidum. The diagnosis is made when 2 or more features of the classic triad are present. Approximately 30% of patients have complete manifestations, 62% display hypopituitarism, and 60% have an absent septum pellucidum. *HESX1, SOX2, SOX3, FGF8, FGFR1, PROKR1, SHH*, are implicated in the etiology of SOD(2).

Case report: female, presented at 9.8 years with short stature (SDS-2.46) (fig. 2). Born after first uneventful pregnancy, SGA, jaundice, hypotonia, feeding difficulties, and tiredness during neonatal period, mild developmental delay, normal intelligence (IQ=112 by Raven). Facial dysmorphism: high and broad forehead, midline hypoplasia, bulbous nasal tip, pear shaped nose, epicantal folds, wide chin (fig. 1A). Ocular abnormalities: hypoplasia of the macula and optic nerves, nystagmus, strabismus. MRI of the brain: absent septum pellucidum, common ventricular cavity, hydrocephalus, anterior pituitary hypoplasia (fig. 3). Growth hormone deficiency (peak 1.5 mU/l, tabl. 1). Follow up: subsequently developed TSH deficiency. Spontaneous and fast progressing puberty (fig. 1B; tabl. 2).

Fig. 1A. Picture of the patient before rhGH treatment: A – at age of 1; B – age of 3; C- age of 6; D – age of 10

Fig 1B: Pictures of the patient after the rhGH treatment: E – age of 11; F – age of 13; G – age of 15; H – age of 17 years

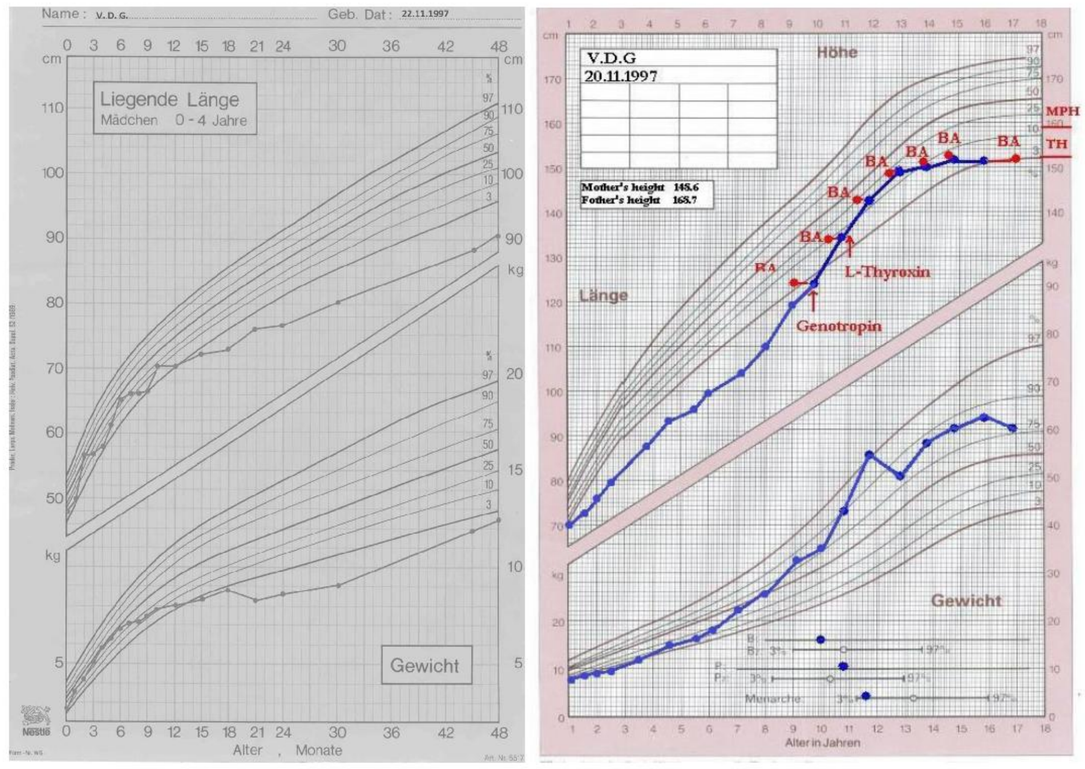

Fig. 2. Growth curve of the patient from 0 to 4 years on the left and from 1 to 18 years on the right

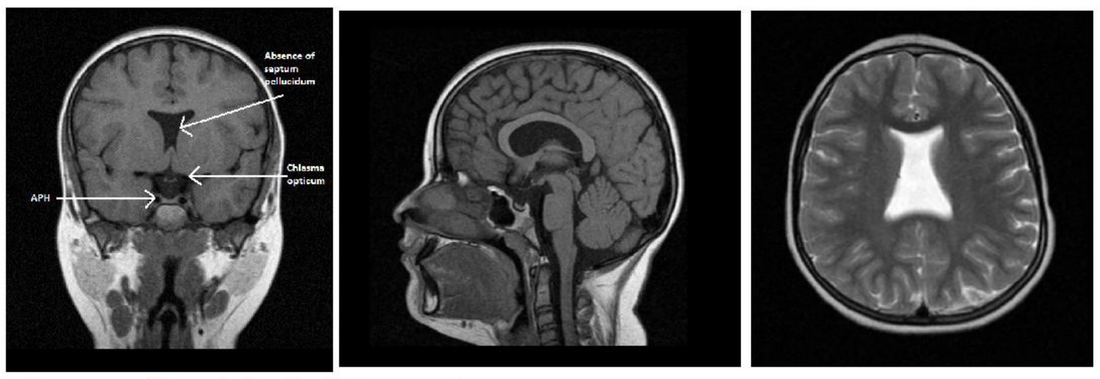

Fig.3. MRI of hypothalamic-pituitary region

	Arginin HCL test										Physical exercise	
minutes	-15	0	15	30	45	60	90	120	150	180	10	20
GH mU/l	0.5	0.4	0.7	0.7	0.6	0.7	0.5	0.5	0.5	1.5	1.7	1.3

Tabl.1. Stimulation test for GH secretion

Age (decimals)	**9.8**	**10.88**	**11.88**	**12.88**	**13.88**	**14.72**	**15.8**	**16.8**
Height (cm)	124.5	135.5	142.4	147.8	148.5	150.1	150.2	150.6
SDS_{Prader}	-2.46			-1.08	-1.10	-1.71		
rhGH (U/24h)	0.9	2.7	4.2	4.8	5.4	4.8	3.6	3.0
IGF-1 ng/ml	-	-	276	472	576,5	685,9	664	250
IGFBP3 ng/ml	-	-	2556	5999	10166	5098	4812	3405
Growth velocity (cm/year)	-	13.1	6.9	6.2	0.7	1,7	0.1	0.4
Growth velocity (percentiles)	-	> 97th	50th	10-25th	< 3th	10-25th	< 3th	< 3th
Puberty (Tanner)	-	P_2 T_{1-2} A_0	P_3, T_3,A_2, menarche 11.48	RM	RM	RM	RM	RM

Tabl. 2. Treatment follow up for a period of 7 years, RM – regular menstruation

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

Results: The patient harbors 599 kb deletion 17(q21.31)(44188501-44787179)x1[hg19], containing a pseudogene LOC644246 and the gene KANSL1, known to cause KDVS (4,5). The estimated prevalence is 1:16000 births(3) and is characterized with mental retardation (MR), facial dysmorphism, hypotonia, developmental delay, SGA, short stature, brain anomalies, refraction anomalies, strabismus, one reported case with PSIS causing hypopituitarism.

A 551 kb duplication X(p11.3p11.3)(45838699-46389900)x3[hg19] was also found, including ZNF673, ZNF674 genes. Duplications/deletions are known to cause MR, retinal dystrophy and short stature, probably because of dose-dependent effect.

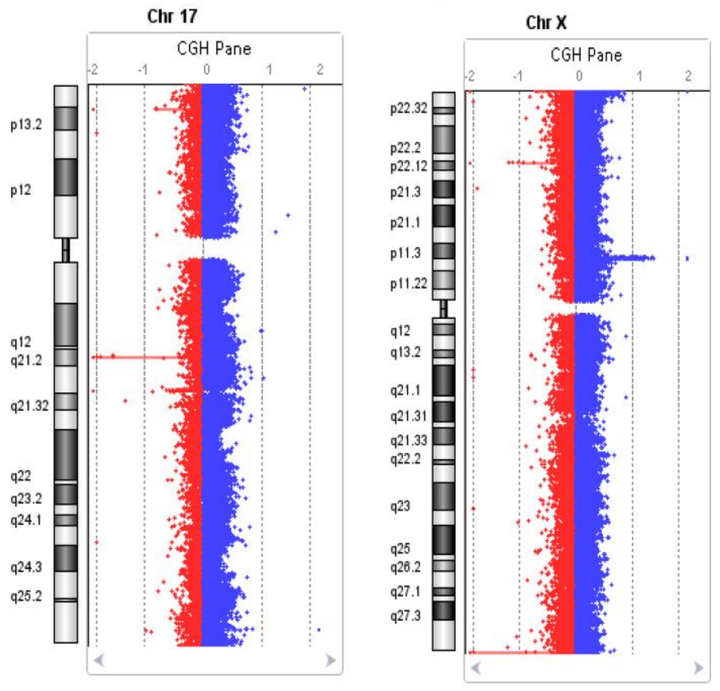

Fig. 2. Chromosome aberrations: microdeletion 17q21.31 on the left; microduplication Xp11.3 on the right.

Symptoms	17q21.31 microdeletion syndrome	Index patient
Facial dysmorphism	~100%	+
Neonatal muscle hypotonia	~100%	+
Neonatal feeding difficulties	~100%	+
Speech delay	~100%	+/-
Mild to severe mental retardation	~100%	-
Developmental delay	~100%	+
Short stature	20%	+
Cryptorchidism	70%	-
Brain anomalies	20-30%	+
Luxation of the hip	20%	-
Kidney and urologic anomalies	30%	-
Epilepsy	20%	-
Congenital heart defects	50%	-
Ocular abnormalities	30%	+

Tabl. 3. Comparison of the phenotypic manifestation of the index patient with previously described patients with 17q21.31 microdeletion syndrome

Conclusion: This is the first case of Koolen-de Vries syndrome without MR and only the second case with hypopituitarism as a part of SOD. Analogous to the X-linked SOX3, duplication/deletions in ZNF673 and ZNF674 could result in short stature without MR and may be implicated in the etiology of hypopituitarism. The patient's phenotype is probably a result of combination between the two aberrations.

Sponsored by Medical University Sofia, "Mlad Izsledovatel 40-D"

Ani Aroyo and Iva Stoeva contributed equally to this work and should be considered as joint first author.

References:

1. Dattani M., J. Martinez-Barbera, P. Thomas et al. Mutations in the homeobox gene HESX1/Hesx1 associated with septo-optic dysplasia in human and mouse. Nat Genet. 1998, 2:125-133. 2. Kelberman D., M. Dattani. Septo-optic dysplasia: novel insights into the aetiology. Horm Res. 2008, 5:257-265. 3. Koolen D., L. Vissers, R. Pfundt,N. de Leeuw et al. A new chromosome 17q21.31 microdeletion syndrome associated with a common inversion polymorphism. Nat Genet. 2006, 38:999-1001. 4. Koolen D, J. Kramer, K. Neveling et al. Mutation in the chromatin modifier gene KANSL1 cause the 17q21.31 microdeletion syndrome. Nat Genet. 2012, 44: 639-641. 5. Zollino M, D. Orteschi, M. Murdolo, S. Lattante et al. Mutations in KANSL1 cause the 17q21.31 microdeletion syndrome phenotype. Nat Genet. 2012, 44: 636-638.

ESPE 2015 160--P1

Pituitary

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DOI: 10.3252/pso.eu.54espe.2015

Poster presented at: 54th Annual Meeting 1-3 October ESPE 2015 BARCELONA European Society for Paediatric Endocrinology

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