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, FGFR3, FGFR1, PAX6, SHH, are implicated in the etiology of SOD2,3.

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, epicanthal 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 μIU/ml, tabl. 1). Follow up: subsequently developed TSH deficiency. Spontaneous and fast progressing puberty (fig. 1B; tabl. 2).

Results: The patient harbors 599 kb deletion 17q21.31[44188501-44787191]cg[h919], containing a pseudogene LOC644246 and the gene KANSL1, known to cause KDVS (4,5). The estimated prevalence is 1:16000 births(6) 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 Xp11.3p11.3[46838699-46838990]cg[h19] was also found, including 2NFE673, ZNF674 genes. Duplications/deletions are known to cause MR, retinal dystrophy and short stature, probably because of dose-dependent effect.

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.

Table 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.

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