

NEW INSIGHTS INTO SEPTO-OPTIC DYSPLASIA

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Abstract

Septo-Optic Dysplasia (SOD) is a rare disorder with postulated genetic and environmental etiology. Whilst initially considered as a very rare disease (defined as incidence of approx. 1 in 50,000 births) recent data gave a reported incidence of 1 in 10,000, with equal sex distribution. The diagnosis of SOD is predominantly a clinical one, and made with the presence of two or more features of the classic triad: 1) hypopituitarism, 2) optic nerve hypoplasia, and 3) midline brain defects, typically absence or hypoplasia of the septum pellucidum and/or corpus callosum. Hypopituitarism ranges from isolated to multiple hormone deficits, with diabetes insipidus in a minority. The condition is heterogeneous and may also manifest additional brain defects.

Although homozygous mutations in the homeobox gene HESX1 have been identified in SOD, these are uncommon and genetic diagnosis can be made in only < 1% of patients with autosomal recessive inheritance. Autosomal dominant inheritance has also been reported. SOX2, SOX3 and OTX2 mutations have also been identified in some forms of SOD. The aetiology of SOD is uncertain but viral infections, environmental teratogens and vascular or degenerative damage have been postulated to account for its sporadic occurrence. Other factors (endogenous or exogenous) include parental age, parity, smoking, alcohol and substance abuse, antenatal bleeding, and ethnicity. Cocaine abuse during pregnancy, which is a potent vasoconstrictor has recently been identified as a potential external cause. The phenotype of SOD is highly variable; the clinical picture may include visual impairment, short stature, obesity and sleep-wake inversion. Approximately 75–80% of patients exhibit optic nerve hypoplasia, which may be the first presenting feature. Pituitary insufficiency may evolve over time, and children with possible SOD must be kept under careful endocrine follow-up. Untreated hormonal abnormalities will further jeopardize neurodevelopment of children with SOD and could also lead to life-threatening adrenal crises. The attention should be focussed on early diagnosis and treatment and education of paediatricians how to recognize this complex disorder.

Key Words: Septo-optic dysplasia, hypopituitarism, midline brain defects.

Introduction

Septo-Optic Dysplasia (SOD) is a heterogeneous disorder with a variable combination of midline brain defects, eye and pituitary abnormalities. The occurrence may be sporadic or familial. SOD was initially described by Reeves in 1941 as a congenital absence of the septum pellucidum. De Morsier in 1956 further depicted SOD. Abnormal pituitary function was

documented 14 years later. In 1998 mutations in the homeobox genes HESX1/HESX1 in humans and mice were reported [1, 2].

Initially SOD was considered a very rare disease with an incidence of 1 in 50,000 births. Recent reports showed a higher incidence due to a careful search for the disease: 10.9/100 000 [3] and 8.3/100 000 reported by Atapattu et al., 2012, in a regional study in the area of the

West Midlands, UK) (4). Sex distribution is equal. The occurrence may be sporadic or familial.

Genetics of SOD

Whilst homozygous mutations in the homeobox gene HESX1 have been identified in SOD, these are uncommon. The inheritance may be autosomal dominant or recessive. The penetrance may be variable, and the presence of a mutation is not always associated with a phenotype.

Occasionally, one abnormal copy of the gene is carried with no phenotype in the parent but the child is affected. Screening of over 800 patients with SOD and hypopituitarism identified mutations in less than 1% of individuals with HESX1 mutations [2, 5].

A number of other developmental genes, SOX2, SOX3 and OTX2, may also be involved: all extrapolated from animal studies. SOD in humans matches quite well with the animal model of the disease, where gene prioritization based on phenotype is proposed [6].

The human HESX1 gene maps to the short arm of chromosome 3 and consists of 4 exons, spanning 1.7 kilobases [7]. HESX1 is a member of the paired-like class of homeobox genes and is first expressed during embryogenesis, by 9.5 embryonic days, and continues until E13.5 days, which corresponds to 4 to 6 embryonic weeks in humans, when progressive pituitary cell differentiation occurs. Any insult that acts during this critical period of development may result in serious malformations because the embryological origins of the anterior lobe of the pituitary, septum pellucidum, corpus callosum, optic placodes and olfactory placodes are very closely related. Inductor signals are required from the hypothalamus for normal pituitary growth. It appears that the pituitary "talks back" to the hypothalamus, so that connections between them are genetically vital for normal development of both structures [2, 7].

Etiology of SOD is uncertain

SOD is a story of complex interplay between genes and environment with the influence of endogene factors. Viral infections, environmental teratogens and vascular or degenerative damage have been postulated to account for its sporadic occurrence. Other factors (endogenous

or exogenous) include parental age, parity, smoking, alcohol and substance abuse, antenatal bleeding, and ethnicity. Cocaine abuse during pregnancy, which is a potent vasoconstrictor, has recently been identified as a potential external cause. Young maternal age is a risk factor because of the greater possibility of adverse antenatal exposures and abuse behaviours.

In the study by Attapatu et al. [4] 40% of mothers admitted to smoking during their pregnancy, 21% admitted to drinking alcohol and 4.3% to taking recreational drugs such as cocaine, during pregnancy. Tornquist et al. [8] also demonstrated increased maternal smoking, young maternal age, preterm delivery and first parity as risk factors for optic nerve hypoplasia, whereas other authors identified reduced maternal age, primiparity and increased caesarean section rate. Alcohol consumption is thought to be damaging to the developing brain. Consanguinity and ethnicity are important. South Asian families, less likely to consume alcohol and smoke due to religious reasons and in spite of other risk factors (social deprivation, unemployment, young maternal age), have a lower risk of having a child with SOD [4].

Kelberman and Dattani reported the first HESX1 mutations in SOD in two siblings from a consanguineous family. The mutation identified in the affected siblings resulted in the substitution of a highly conserved arginine at residue 160 (position 53 of the homeodomain) by cysteine (R160C) which leads to a loss of DNA binding of the mutant protein. The parents were heterozygous for the mutation and phenotypically normal, consistent with an autosomal recessive mode of inheritance [1, 2].

SOD phenotype

The phenotype of SOD is highly variable; its clinical picture may include visual impairment, short stature, obesity and sleep-wake inversion. Approximately 75–80% of patients exhibit optic nerve hypoplasia, which may be the first presenting feature. Pituitary insufficiency may evolve over time, and children with possible SOD must be kept under careful endocrine follow-up. Elevated serum PRL and GH deficiency are the most common hormonal abnormalities (73% and 58% respectively), followed by central hypothyroidism (39%) and adrenal insufficiency (31%). Neurological defi-

cit is common, ranging from global retardation to focal deficits such as epilepsy or hemiparesis. Untreated hormonal abnormalities will further jeopardise the neurodevelopment of children with SOD and could also lead to a life-threatening adrenal crisis [2, 4].

Absence of septum pellucidum is present in 75–80% of patients, followed by absence of corpus callosum, cerebellar hypoplasia and chizencephaly. The spectrum of congenital midline defects is large and includes a large array of clinical phenotypes from those incompatible with life to severe palato/facial cleft, the conditions that include various forms of holoprosencephaly, SOD and agenesis of the corpus callosum, with isolated cleft lip or palate and abnormalities in pituitary development.

The consequences of forebrain anomalies are numerous and variable: fits, behavioural difficulties, learning difficulties, developmental delay, hemiplegia, hemiparesis and epilepsy.

The eye is a window to rare diseases and SOD is the leading one. The hypoplastic optic nerve appears small and pale in a child with SOD, on ophthalmologic investigation. Optic nerve hypoplasia (ONH) is the first presenting feature in SOD and represents the major cause of congenital blindness. ONH may be unilateral or bilateral (12% versus 88%), associated with anophthalmia or microphthalmia, variable visual impairment (complete to compensated). In some cases only nystagmus and poor vision are present. The presence of strabismus or nystagmus in a child with multiple congenital abnormalities at birth should alert an ophthalmologist to seek the opinion of an endocrinologist [9, 10].

The classic triad of structural hypothalamic and pituitary abnormalities visible on magnetic resonance imaging (MRI) investigation involves the hypoplastic anterior pituitary, pituitary stalk hypoplasia/agenesia and ectopic posterior pituitary. Fig 1 represents a sagittal and coronal MRI scan of our patient diagnosed as SOD, with ONH, pituitary and stalk hypoplasia. Growth hormone deficiency (GHD), isolated or combined, was the most frequent hormonal disturbance present in 40.9% in the largest cohort of 88 SOD patients [4]. GHD combined with TSH, ACTH and antidiuretic hormone deficiency is also possible. Delayed or early puberty can be explained on the basis of LH and FSH

deficiency or hypothalamic involvement. The possibility of adrenal insufficiency development in child with diagnosis of SOD deserves special clinical attention. Five deaths in a large cohort of 88 SOD patients were registered, 3 from adrenal crisis, 2 from additional neurological problems [4].

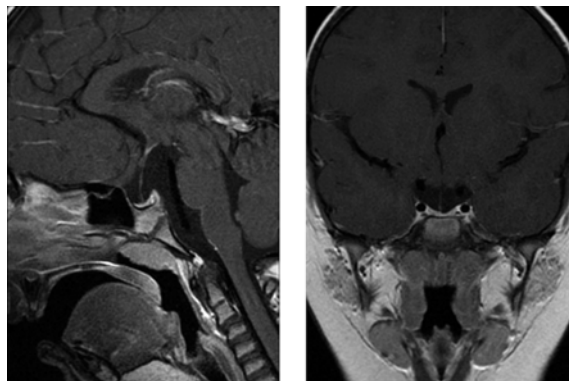


Fig. 1 – Sagittal and coronal MR scan of our patient showing pituitary, stalk and optic nerve hypoplasia

With the courtesy of dr Ivana Markovic

Other clinical features are possible, but not specific, such as conjugated jaundice, hypoglycaemia, and variable visual loss, impaired sense of smell and behavioral disturbances, e.g. autism and sleep disturbance (sleep-wake inversion).

Many children with SOD become obese because of pituitary and hypothalamic dysfunction. We recommended investigation of PRL levels in short and obese children and we found that hyperprolactinaemia and obesity are common in children with microprolactinomas [11]. It is generally accepted that hyperprolactinaemia is a marker of interrupted signalling between the hypothalamus and pituitary. Vedin et al. demonstrated that elevated initial serum prolactin levels may be a potential marker for hypopituitarism in children with ONH [12].

Diagnosis of SOD

The diagnosis of SOD is predominantly a clinical one, based on the presence of two or more features of the classic triad: a) midline brain defects, typically absence or hypoplasia of the septum pellucidum and/or corpus callosum, b) optic nerve hypoplasia, and c) hypopituitarism, ranging from isolated to multiple hormone deficits, with diabetes insipidus in a minority.

Prenatal diagnosis may be genetic in familial occurrence and on the basis of foetal brain neuroimaging in familial and sporadic cases. MRI tells more about pituitary stalk interruption and absence of septum pellucidum than ultrasound [13, 14].

Management of SOD

Treatment of SOD is complex and multidisciplinary; based on cooperation of at least 3 specialists (neurologist, ophthalmologist and endocrinologist). The mainstay of the treatment

is endocrine replacement therapy. Despite general success this has many intrinsic hidden imperfections. SOD needs lifelong monitoring. Growth hormone treatment is rewarding; KIGS data on long-term effects of GH substitution in 395 subjects with SOD showed excellent results [15]. Our experience is also favourable. Fig 2 shows growth normalization during GH treatment in a girl with SOD and combined deficiency of GH, TSH and ACTH. However, the prognosis in SOD patients remains dubious.

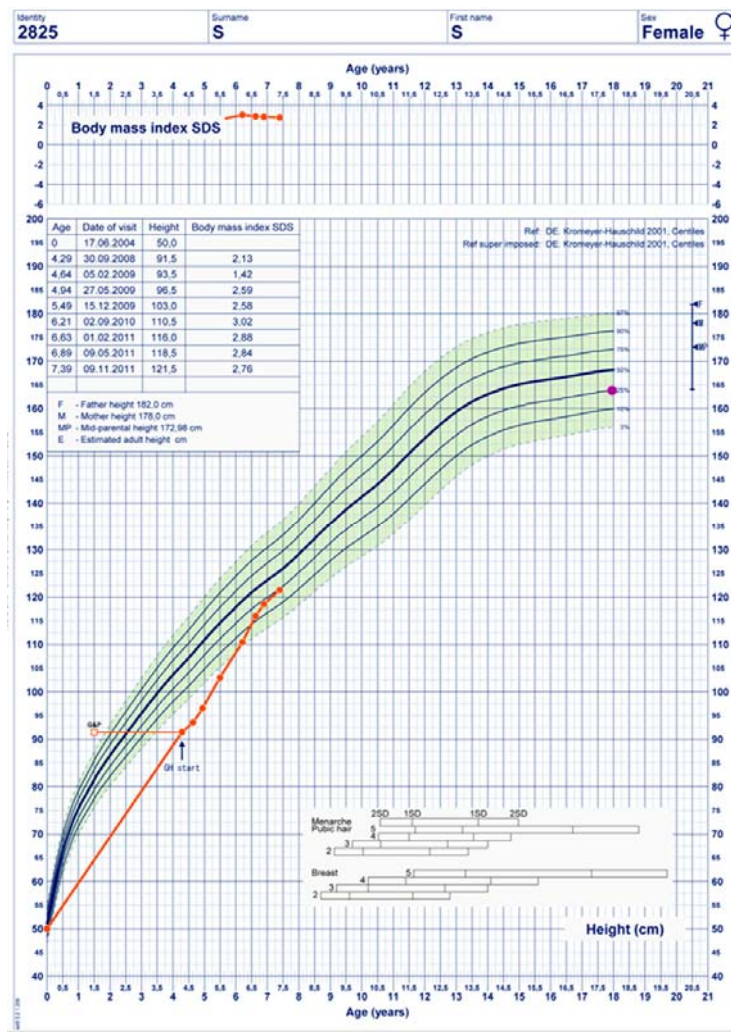


Fig. 2 – Growth curve of our patient with SOD during GH treatment

Conclusion

SOD is the result of a complex interaction between genetics and environment. The understanding of this is still incomplete. Further study of critical factors may shed light on the aetiology of SOD. Some children experi-

ence a whole spectrum of SOD, from blurred vision and short stature to life-threatening adrenal crisis. The attention should be focussed on early diagnosis and treatment and education of paediatricians in how to recognize this complex disorder.

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Резиме

НОВИ СФАКАЊА ЗА СЕПТО-ОПТИЧКАТА ДИСПЛАЗИЈАЛилјана Шаранац¹, Зоран Гучев²¹ Педијатриска клиника, Медицински факултет, Ниш, Универзитетски клинички центар, Ниш, Србија² Медицински факултет, Скопје, Р. Македонија

Септо-оптичката дисплазија е ретко нарушување со претпоставена генетска и етиологија на фактори на околината. Процената за нејзината зачестеност се менува нагоре: од 1 во 50.000 раѓања на 1/10.000 раѓања, со еднаква полова дистрибуција. СОД дијагностата е клиничка врз основа на два од вкупно три дела на класичната тријада: 1) хипопитуитаризам; 2) хипоплазија на оптичкиот нерв; и 3) дефекти на средната линија на мозокот, обично отсуство или хипоплазија на *septum pellucidum* и/или *corpus callosum*. Хипопитуитаризмот може да е изолиран или мултиплен, со инсипиден дијабетес кај помал број случаи.

Хомозиготни мутации на хомеобоксниот ген HESX1 се опишани кај пациенти со СОД, тие се ретки и се опишани > 1% од пациентите. Опишани се автозомно доминантно и автозомно рецесивно наследување. SOX2, SOX3 и OTX2, исто така, се опишани. Покрај генетските, во етиологијата на СОД се имплицирани и вирусим тератогени, како и васкуларно и дегенеративно оштетување. Исто така, свој удел имаат возраста на родителите, пушење, алкохол, дроги, антенатално крвање и етничка присутност. Фенотипот е варијабилен: нарушување на видот, низок раст, дебелина, инверзија на сон-будност. 75–80% од пациентите имаат хипоплазија на оптичкиот нерв, а питуитарната инсуфициенција може да се појави подоцна, што е факт кој бара следење на овие пациенти. Адреналната криза може да е животна загрозувачка. Потребно е да се инсистира на рана дијагноза, лекување, следење на болеста, како и едукација на лекарите за рано откривање на болеста.

Клучни зборови: септо-оптичка дисплазија, хипопитуитаризам, мозочни аномалии.