European Journal of Human Genetics (2010) 18, 393–397

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PRACTICAL GENETICS

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Septo-optic dysplasia

This review summarises the key clinical features of septo-optic dysplasia (SOD), the significant inroads that progress in genetics has made into our understanding of the aetiology of the condition over the last decade, and the pitfalls and challenges that we face in the management of these phenotypically variable patients.

In brief

- Incidence 1 in 10 000 live births.[1]
- Associated with younger maternal age.[2]
- Phenotypically variable disorder.
- Early forebrain developmental abnormality.
- Diagnosed on a clinical basis, with ongoing debate as to the exact diagnostic criteria.
- SOD can be caused by mutations in *HESX1* and *SOX2*.[3–6]
- A genetic diagnosis can currently be made in $<1\%$ of the patients.[7,8]
- Associated features include developmental delay, seizures, visual impairment, sleep disturbance, precocious puberty, obesity, anosmia, sensorineural hearing loss and cardiac anomalies.

INTRODUCTION

The diagnosis of septo-optic dysplasia (SOD) is a clinical one and can be made when two or more features of the classical triad of (i) optic nerve hypoplasia, (ii) pituitary hormone abnormalities and (iii) midline brain defects, including agenesis of the septum pellucidum and/or corpus callosum, are present.[9] It is a rare congenital anomaly, equally prevalent in males and females, and more common in infants born to younger mothers, with a reported incidence of 1 in 10 000 live births.[1,10]

CLINICAL OVERVIEW

Septo-optic dysplasia, previously termed de Morsier syndrome, was first described by Reeves in 1941 as an absence of the septum pellucidum in association with optic nerve abnormalities.[11,12] Subsequently, an association with pituitary dysfunction was described.[13] Classically the diagnosis of SOD can be made clinically when two or more features of the classical triad (see above) are present. Morishima and Aranoff[14] cite that $\sim$30% of SOD cases have complete manifestations, 62% have the complication of hypopituitarism and 60% have an absent septum pellucidum. Isolated features of the triad do not fulfil the diagnostic criteria for SOD, although debate is ongoing as to whether they represent milder cases of the SOD spectrum.[15] The heterogeneous nature of the condition and the variable association with different clinical features led Polizzi *et al*[16] to suggest that SOD should be renamed SOD complex. Debate is ongoing regarding the correct nomenclature, but for the purposes of this review article, we shall use the classical definition of SOD outlined above.[17]

There is a wide variation in the severity of the clinical features found, and in their association with other diagnoses, which follows no clear pattern (Figure 1). The main reported clinical findings are hypopituitarism (62–80%), with growth hormone deficiency being the commonest endocrine abnormality, visual impairment (23% significant visual impairment) and developmental delay (more common in children with bilateral (57%) as opposed to unilateral optic nerve hypoplasia (32%)).[18] Seizures, developmental delay and cerebral palsy are the most frequent neurological associations.[19] Pituitary hormone insufficiencies may evolve over time necessitating life-long medical follow-up.

DIAGNOSTIC APPROACHES

Septo-optic dysplasia can present at birth in association with multiple congenital abnormalities or much later on when growth failure occurs in a child also noted to have visual abnormalities (although not necessarily as may just have growth failure with mild undetected visual abnormalities).[15] The child may present with strabismus, nystagmus, or other visual abnormalities. In the majority of cases, the earlier the diagnosis is made the better the outcome, as untreated hormonal abnormalities place an additional neurodevelopmental burden on a child already compromised by visual impairment, and also place the patient at risk of hypoglycaemia, adrenal crises and consequently death. Clinically the diagnosis should be suspected in newborns with hypoglycaemia, jaundice, a microphallus with or without undescended testes and nystagmus with or without associated midline abnormalities such as cleft palate. In these infants, baseline endocrine tests should be performed as outlined below and an ophthalmology referral made. MRI brain images in conjunction with dynamic studies of pituitary function can then be used to confirm the diagnosis. Hormonal insufficiencies should be treated, and early referral both to a neurodevelopmental team with an interest in visual impairment and to a tertiary centre with expertise in managing these children made. A summary of key points to note while taking the history, undertaking

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European Journal of Human Genetics (2010) **18,** 393–397; doi:10.1038/ejhg.2009.125; published online 22 July 2009

Keywords: optic-nerve hypoplasia; pituitary; septum pellucidum

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Received 16 March 2009; revised 5 June 2009; accepted 5 June 2009; published online 22 July 2009

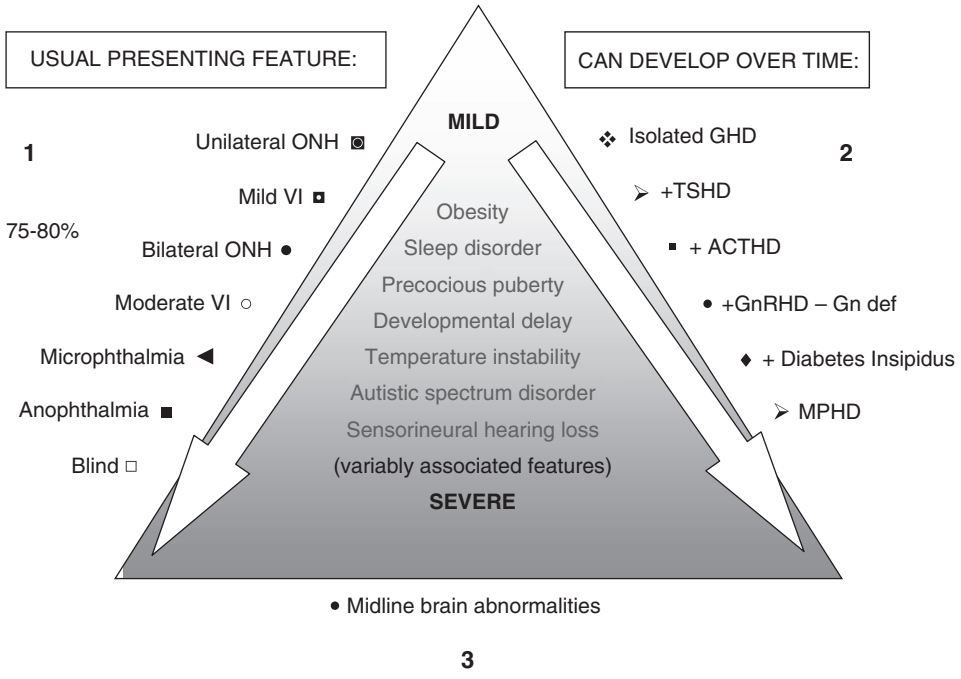

Figure 1 Spectrum of severity of the triad of abnormalities found in septo-optic dysplasia and the variably associated clinical features.

ophthalmology assessment, interpreting MRI brain images and investigating pituitary function are outlined below.

Associated features to ask about when taking history

1. Consanguinity.
2. Hearing abnormality – sensorineural.
3. Developmental delay.
4. Anosmia.
5. Other congenital anomalies such as cardiac, oesophageal atresia and micropenis.
6. Seizures – commonly related to underlying abnormality of the brain anatomy, important to rule out hypoglycaemia as a cause.
7. Stereotypical behaviours – for example, mannerisms suggestive of a diagnosis of autistic spectrum disorder.
8. Sleep disorder – arrhythmicity.[20]
9. Excessive appetite.
10. Temperature instability.
11. Symptoms suggestive of hormonal deficiencies such as fatigue, polyuria and polydipsia, constipation, dry skin, hair loss and sweating.

Ophthalmology

1. Is there strabismus or nystagmus, and if so is it unilateral or bilateral?
2. Perform ophthalmological examination to identify clinical signs of ONH, which include a double-ring sign, pale and/or small optic discs/neuroretinal rim area.
3. Are optic nerve hypoplasia or dysplasia, microphthalmia, coloboma and/or other ophthalmological signs present?
4. Assess degree of visual impairment.

MRI of the brain

1. Are hypothalamo-pituitary axis appearances normal, checking specifically for:
   (a) Anterior pituitary size.
   (b) Presence and location of posterior pituitary.
   (c) Presence and thickness of infundibulum.
2. Is the septum pellucidum present?
3. Are the optic nerves and chiasm normal?
4. Is the appearance of the corpus callosum normal?
5. Are there any other associated brain abnormalities such as schizencephaly, cavum septum pellucidum, cerebellar hypoplasia and aplasia of the fornix.

Classically MRI brain images show hypoplasia of the optic nerves (unilateral or bilateral) and optic chiasm, agenesis of the septum pellucidum, abnormalities of the corpus callosum and hypothalamo-pituitary axis (Figure 2). However, MRI findings vary considerably between patients.[21]

Tests of pituitary function

1. Thyroid function (low TSH of secondary hypothyroidism may be missed by neonatal screening).
2. Cortisol
   (a) Random cortisol sufficient in neonate, 8 am cortisol appropriate in individuals aged >1 year.
   (b) If abnormal cortisol, proceed to synacthen test or 24-h cortisol and glucose profile.
3. Growth hormone
   (a) Ask for symptoms of hypoglycaemia and measure glucose profile on adequate hydrocortisone replacement. If hypoglycaemia detected measure IGF-1 and IGFBP-3, and consider GH replacement.
   (b) Monitor growth and if poor growth velocity measure GH response to provocation testing in patients over the age of one year.
4. Monitor pubertal status – SOD can be associated with precocious puberty secondary to hypothalamic dysfunction, or hypogonadotrophic hypogonadism secondary to LH and FSH deficiency.

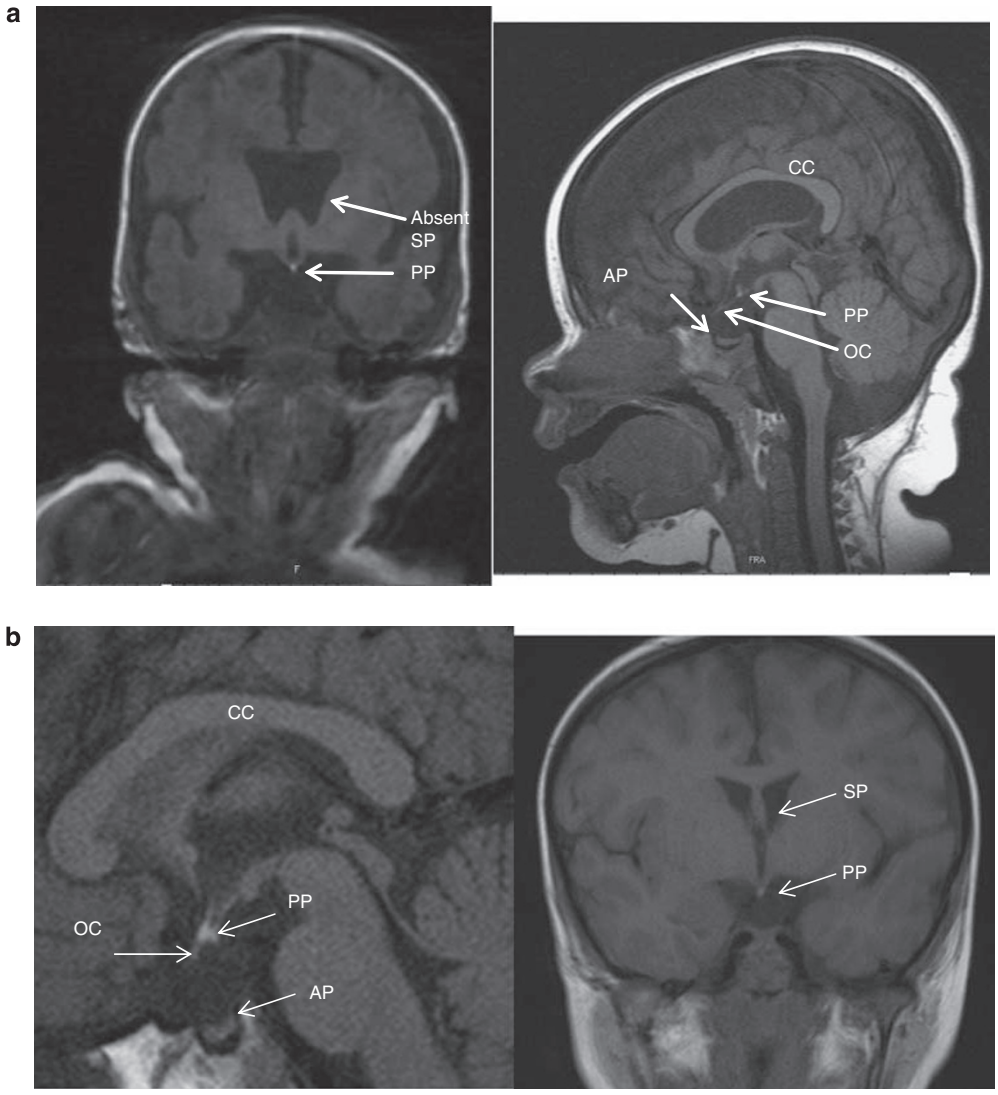

Figure 2 MRI appearances of septo-optic dysplasia. (**a**) Anterior pituitary hypoplasia and absent infundibulum associated with bilateral optic nerve hypoplasia. The posterior pituitary is ectopic. There is an absence of the septum pellucidum. (**b**) Ectopic posterior pituitary, anterior pituitary hypoplasia, absence of the infundibulum and partial absence of the septum pellucidum associated with optic nerve hypoplasia. CC, corpus callosum; AP, anterior pituitary; PP, posterior pituitary; SP, septum pellucidum; OC, optic chiasm.

5. Ask about fluid intake: if excessive, measure paired fasting plasma and urine osmolalities; may need to perform water deprivation test to confirm diagnosis of diabetes insipidus.

MOLECULAR AND GENETIC BASIS OF THE DISEASE

The association of abnormalities of the forebrain found in SOD is likely to reflect an early forebrain developmental abnormality, occurring at 4–6 weeks of gestation, a critical period of morphogenesis for the anterior neural plate. Improved understanding of the development of the pituitary gland and forebrain, and the identification of transcription factors important in this process has led to the discovery of genes (so far only two), which when mutated cause SOD. *HESX1*, a paired-like homeobox gene, which acts as a transcriptional repressor, is one of the earliest markers of murine pituitary development. The study of *Hesx1* null mice identified it as a possible candidate gene for SOD, and subsequent investigation of the human homologue *HESX1* (OMIM 601802) has led to the identification of five homozygous (autosomal recessive inheritance) and eight heterozygous (autosomal dominant inheritance) pathogenic mutations[3,4] (Table 1). The homozygous mutations are fully penetrant, whereas heterozygous mutations are variably penetrant and usually associated with a milder phenotype.[22,23] Mutations have also been identified in *SOX2* in association with severe bilateral eye abnormalities (anophthalmia, microphthalmia) and defects of the corpus callosum with anterior pituitary hypoplasia.[24] Additional features described in association with *SOX2* mutations include developmental delay, short stature, oesophageal atresia, male genital tract abnormalities and sensorineural hearing loss.[25]

Establishing the genotype not only furthers our understanding of the aetiology of SOD but also aids patient management, enabling accurate genetic counseling and early diagnosis.

Currently genetic abnormalities are identified in $<1\%$ of the patients, with the aetiology of SOD remaining unclear in the majority of patients. This has led to debate as to other factors, which may also have a role in the pathogenesis of SOD. Many studies have reported an

Table 1 Reported mutations in *HESX1* and *SOX2* in association with pituitary phenotypes

HESX1 mutation	*Inheritance*	*Endocrine phenotype*	*Neuroradiological findings*	*Reference*
Q6H	Dominant	GH, TSH, LH, FSH deficiency	AP hypoplasia, ON hypoplasia	Thomas *et al*[22]
I26T	Recessive	GH, LH, FSH deficiency; evolving ACTH, TSH deficiency	AP hypoplasia, ectopic PP	Carvalho *et al*[29]
c.306_307insAG	Dominant	GH, LH, FSH deficiency; hypothyroidism	AP aplasia, normal PP, normal ON	Tajima *et al*[30]
Q117P	Dominant	GH, TSH, ACTH, LH, FSH deficiency	AP aplasia, hypoplastic sella, normal PP and infundibulum	Coya *et al*[31]
c.357+ 2T>C	Recessive	GH, TSH, ACTH, PRL deficiency	AP hypoplasia, ectopic PP, infundibular hypoplasia	Sobrier *et al*[32]
Alu insertion (exon 3)	Recessive	Panhypopituitarism	AP aplasia, normal PP, normal ON, thin CC, hydrocephalus	Sobrier *et al*[33]
E149K	Dominant	GH deficiency	AP hypoplasia, ectopic PP, infundibular hypoplasia	McNay *et al*[8]
c.449_450delCA	Recessive	GH, TSH, ACTH deficiency	AP aplasia, normal PP, normal ON, thin CC, hydrocephalus	Sobrier *et al*[32]
R160C	Recessive	GH, TSH, ACTH, LH, FSH deficiency	AP hypoplasia, ectopic PP, ON hypoplasia, ACC	Dattani *et al*[3]
S170L	Dominant	GH deficiency	Normal AP, ON hypoplasia, ectopic PP, partial ACC	Thomas *et al*[22]
K176T	Dominant	GH deficiency, evolving ACTH, TSH deficiency	Ectopic PP	Coya *et al*[31]
g.1684delG	Dominant	GH deficiency	AP hypoplasia, ON hypoplasia, ACC, absent PP bright spot	Cohen *et al*[23]
T181A	Dominant	GH deficiency	AP hypoplasia, normal ON, absent PP bright spot	Thomas *et al*[22]
SOX2		*Eye phenotype*	*Pituitary phenotype*	
c.70del20		Left anophthalmia, right microphthalmia	HH, APH, Hippocampal abnormalities	Zenteno *et al*[34]
c.70del29		Bilateral anophthalmia	HH	
c.60_61insG		Bilateral anophthalmia	HH, APH, hypothalamic hamartoma	Williamson *et al*[35]
p.Q61X		Bilateral anophthalmia	HH	Kelberman *et al*[5]
p.L75Q		Right anophthalmia	HH	Sato *et al*[6]
c.387delC		Left microphthalmia, right coloboma	HH, APH, hypothalamic hamartoma, cryptorchidism, micropenis	Williamson *et al*[35]
c.479delA		Bilateral anophthalmia	HH, APH, micropenis	Williamson *et al*[35]
p.Y160X		Bilateral anophthalmia	HH, APH, cryptorchidism, micropenis	Williamson *et al*[35]
p.Q177X		Bilateral anophthalmia	HH, cryptorchidism, micropenis	Kelberman *et al*[4]
SOX2 deletion		Right anophthalmia, left microphthalmia	APH, thin corpus callosum	Bakrania *et al*[36]

ACC, agenesis of the corpus callosum; AP, anterior pituitary; APH, anterior pituitary hypoplasia; HH, hypogonadotrophic hypogonadism; ON, optic nerve; PP, posterior pituitary.

increased prevalence of antenatal drug and alcohol abuse and younger maternal age in SOD cohorts.[2,26] This in combination with the pattern of neurological abnormalities found in individuals with SOD led Lubinsky[27] to suggest that septo-optic dysplaisa occurs secondary to a vascular disruption sequence.[28] It is likely that although other genetic abnormalities are likely to be identified in the future, environmental factors such as drugs, alcohol and anterior cerebral artery supply during the neonatal period may also play a significant role in the aetiology of SOD.

MANAGEMENT

Patients with SOD need regular (at least six-monthly) ongoing follow-up by a multi-disciplinary team. Management centres on identifying evolving hormonal insufficiencies and optimising hormonal replacement, ensuring appropriate ophthalmological follow-up, instigating neurodevelopmental support early on in life from a team with experience in looking after children with visual impairment, and monitoring closely for the development of other associated features such as autism and obesity.

Genetic counseling

The majority of cases of SOD are sporadic, and therefore, in the absence of any family history of the disorder, the recurrence risk is <1%. In consanguineous families, the likelihood of recessive inheritance is significantly higher, and parents should be counseled that even if there is no identifiable genetic mutation, the likely recurrence risk is one in four. *SOX2* mutations are *de novo* with a very low risk of recurrence. The variable penetrance and phenotypes associated with dominant *HESX1* mutations make genetic counseling difficult, as it would be impossible to predict whether the mutations would be associated with a distinct phenotype.

CONCLUSION

Septo-optic dysplasia remains a rare, heterogeneous and phenotypically variable disorder, which can pose significant diagnostic challenges; namely, the delay in diagnosis, the later development of hormonal deficiencies and the presence of other phenotypic features such as obesity and autism. Challenges such as this highlight the need for the careful longitudinal follow-up of large patient cohorts, to enable the development of more accurate diagnostic criteria and ongoing management plans.

Research is ongoing into the genetic aetiology of SOD. To date, the overall frequency of pathological genetic mutations identified in the SOD population is low, with no mutations identified in many familial cases, suggesting that mutations in other known or unknown genes may have a role in this complex disorder. Our knowledge and understanding of the transcriptional factors involved in the development of the forebrain remains rudimentary and future work identifying these may uncover other molecular causes for SOD. The multi-faceted interaction between these transcription factors and the

environment is also likely to play a role in the significant variability in phenotype and penetrance associated with SOD.[1,31] Further investigation of these intricate relationships may help us to better understand the aetiology of this complex disorder, possibly enabling us in the future to develop an improved diagnostic algorithm and to predict which children are likely to go on to develop hormonal abnormalities, developmental problems, and so on.

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Further reading
The last four references (37–40) are for further references.