Clinical Phenotype and Complications, Endocrinopathies and Neuroimaging Findings in a Case Series of SOD

Ioana Maris[1], Caoimhe Howard[1], Conor Bogue[1], Rose Morrisey[1], Louise C Gregory[2], Susan M O'Connell[1], Mehul T Dattani[2], Stephen MP O'Riordan[1]

1. Department of Paediatrics and Child Health, Cork University Hospital, Ireland
2. The Institute of Child Health, University College London, UK

BACKGROUND

- **Septo-optic dysplasia (SOD)** is a highly heterogeneous condition with a variable phenotype, defined as two or more features of the classical triad:
  - i) optic nerve hypoplasia,
  - ii) midline brain defects and
  - iii) pituitary hormone abnormalities.
- Rare congenital anomaly with incidence of 1 in 10,000 live births, equally prevalent in males and females, associated with younger maternal age and primiparity.
- Most instances of SOD are sporadic, a number of familial cases have been described with an increasing number of mutations in developmental transcription factors including *HESX1, SOX2, SOX3* and *OTX2* being implicated in its aetiology.

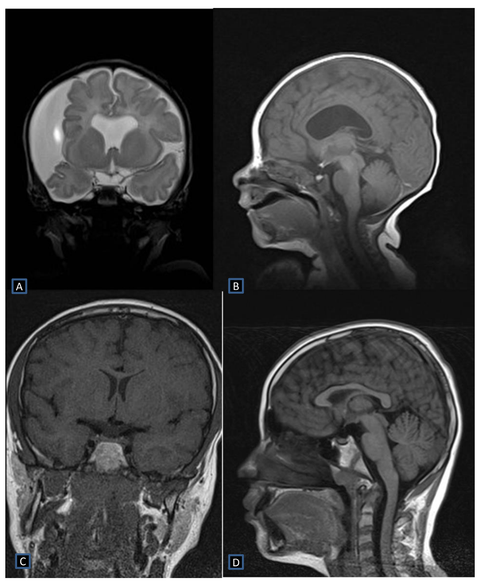


Fig. 1 Typical SOD features on MRI Brain: A - Absent septum pellucidum on coronal T2, B - EPP at superior end of stalk on sagittal T1, C - Tiny optic nerves, D - Thin Infundibulum.

OBJECTIVE

- To describe the clinical spectrum, biochemical and neuroimaging features, as well as to identify possible genotype – phenotype correlations in a series of 8 patients diagnosed with SOD.

PATIENTS AND METHODS

- **Eight (6 male) consecutive patients, diagnosed with SOD in a Regional Paediatric Endocrinology Service**
- **Retrospective review:**
  - Clinical diagnostic features
  - Tests of pituitary function
  - Neuroimaging
  - Ophthalmologic assessment
  - Genetic tests
  - Evolving pituitary hormone insufficiencies and treatment

RESULTS

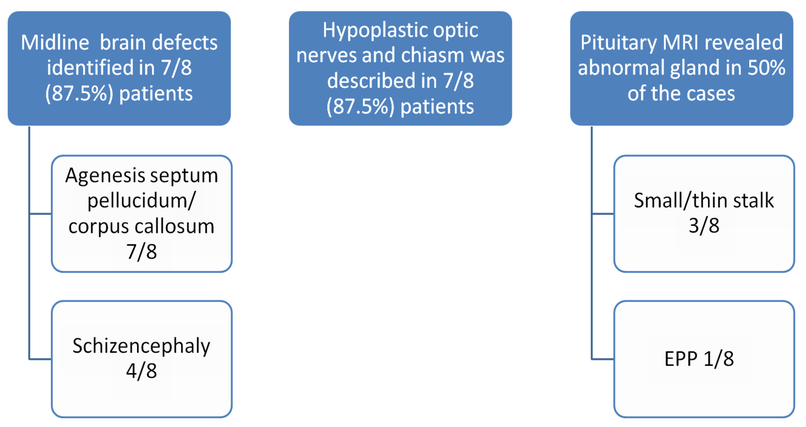
DIAGNOSIS

- 50% of cases had all 3 diagnostic features and 50% 2 out of 3
- Neonatal diagnosis in 5/8 (62.5%) cases
- Maternal age < 25 years in 4/8 (50%) cases
- Primigravida mothers in 6/8 (75%) cases

CLINICAL FEATURES

moderate/severe visual impairment (62.5%)
developmental delay (62.5%)
endocrine disorders (62.5%)
seizures (62.5%)
3 cases (37.5%) developed hydrocephalus, with acute onset in 2/3, requiring urgent VP shunt insertion and resulting in a fatal outcome in one child
dysmorphic features and associated anatomical abnormalities (62.5%) - cardiac anomalies (1/7), bilateral hip dislocation (1/7), microcephaly (2/7), cryptorchidism (1/7)

NEUROIMAGING



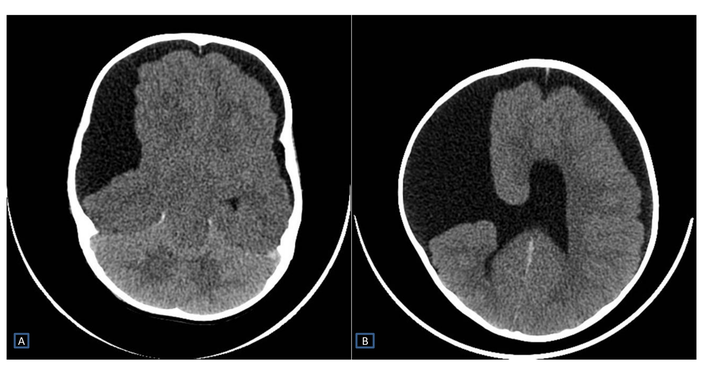


Fig. 2 CT Brain Acute Hydrocephalus: A - Obliteration of cisterns surrounding the midbrain, resulting into raised intracranial pressure; B - Right schizencephaly with chronic encysted wide extra axial fluid and remodelling of overlying skull, new bilateral extra axial fluid.

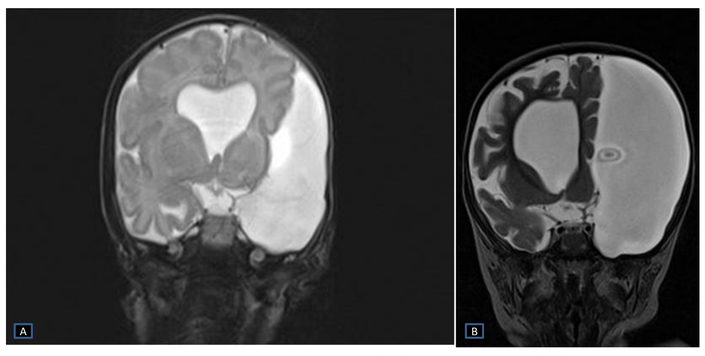


Fig. 3 MRI Brain coronal T2 pre (A)- and post (B) acute hydrocephalus

RESULTS

Case	Genetics	Endocrine deficiencies	Neuroradiology
1	Negative	GH, TSH, ACTH, DI	ASP/CC, SE, PH, ONH
2	Negative	GH	ASP/CC, SE, EPP, ONH
3	pending	GH,TSH	ASP/CC, PH, ONH
4	pending	GH	ASP/CC, SE, NP,ONH
5	Negative	-	ASP/CC, PH
6	Negative	GH,ACTH	NP, ONH
7	Negative	-	ASP/CC, NP
8	pending	-	ASP/CC, SE, ONH, NP

Fig. 2 Genotype – Phenotype correlations
ASP/CC agenesis septum pellucidum/corpus callosum, SE schizencephaly, PH pituitary hypoplasia, EPP ectopic posterior pituitary, NP normal pituitary, ONH optic nerve hypoplasia

ENDOCRINOPATHIES

Growth
5 patients were Growth Hormone deficient (1 panhypopytuitarism).

GH therapy - 2/5 patients experienced normal height velocity (-0.97 – 1.14 SDS) and normal BMI.

Growth was normal in the absence of endocrine dysfunction.

Puberty
Only 2 of these children (boys) were at age of normal puberty. Both had normal onset and normal LHRH testing despite GH and ACTH deficiency in one and no endocrinopathy in second boy.

GENETICS

Karyotype was normal in all cases.

Screening for *HESX1, PROKR2, FGFR1, FGF8, LHX4, SOX2* mutations was negative in 5/8 cases (3/8 pending).

CONCLUSIONS

- This case series confirms that the phenotypic heterogeneity in SOD is high.
- Genetic screening was negative, in keeping with previous series.
- The acute complication of sudden onset hydrocephalus is novel and has not been described to date.
- These complex patients with a life threatening condition require careful clinical management.

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- The authors have no disclosures