Australian Paediatric Surveillance Unit

STUDY INFORMATION SHEET

Septo-optic dysplasia

COMMENCED
APRIL 2023

BACKGROUND

Septo-optic dysplasia (SOD) is defined by the presence of two or more of: optic nerve hypoplasia, hypopituitarism and midline defects (agenesis of the corpus callosum or septum pellucidum) forming a clinical triad. SOD is a rare condition with incidence estimates between 1 in 9,000 to 1 in 40,000, but a major cause of hypopituitarism. [1,2] Preliminary data from the Perth Children's Hospital Endocrinology database suggests an incidence of 1 in 15,000-17,500 live births since 2006. The association between hypopituitarism and optic nerve hypoplasia relates to the embryological origin of the optic chiasm being immediately anterior to the infundibular tissue, thus an insult at this location can interrupt both pathways. A highly variable phenotype is seen even within families, and there is no known common mechanism for its aetiology. [3] Although several genetic causes have been identified, these make up less than 10% of cases of SOD. [4] SOD is commonly seen in young, primiparous mothers, (median age of 21 compared to 29 and 71% primiparous compared 43% in the general population in a study from the United Kingdom), [5] and while antenatal exposure to alcohol and drug use have been suggested, there is a lack of evidence to support causality. [6]

More than half (55-80%) of cases have pituitary hormone deficiency, with growth hormone and TSH deficiency being the most common deficiencies, followed by ACTH, with diabetes insipidus/gonadotroph failure in less than 30% of hormone deficient cases. Approximately half of these hormone deficiencies are detected in the first 2 years of life and can present with severe neonatal hypoglycaemia and cardiovascular instability, with the remainder of cases presenting across childhood to adolescence. [7-10] Children with SOD typically have some degree of visual impairment, while epilepsy and behavioural issues can be seen in approximately a quarter of patients, and cognitive impairment in 42.5%. [7] SOD has the potential for considerable burden of disease, as children undergo regular blood tests, medical assessments, and are prescribed multiple medications including nightly growth hormone injections for most patients. Currently, there is limited data on burden of disease to inform interventions to ensure patients health and wellbeing.

The origin of pituitary dysfunction in SOD is likely to be heterogeneous given the complex temporal expression of genes during development of the hypothalamus and pituitary. Understanding the molecular pathophysiology better with appropriate targeted genetic evaluation of patients may allow a more physiological approach to management of pituitary hormone deficiency. Factors suggesting a hypothalamic basis of disease include the presence of hyperprolactinaemia, relative sparing of the pituitary gonadal axis and high rates of obesity. [8-10]

The overall aim of this study is to understand the full spectrum of the condition, both the prevalence and the burden of disease, in order to develop optimal evidence based clinical care models in the future. This project will investigate the incidence, aetiology, risk factors, pathophysiology and disease burden associated with SOD.

The intent of this work is to establish a nation-wide estimate of patient characteristics through collaboration with Endocrine and Ophthalmology units at other tertiary paediatric endocrine sites and the APSU. Other members of the study team have previously established a similar research network for Prader-Willi Syndrome. [13,14].

STUDY OBJECTIVES

1. To determine the current incidence of septo-optic dysplasia and the associated risk factors in the Australian paediatric population.
2. To determine the rates of hypopituitarism, obesity and neurodevelopmental comorbidities of septo-optic dysplasia in the Australian paediatric population.
3. To determine the burden of disease associated with septo-optic dysplasia in the Australian paediatric population.

CASE DEFINITION

Please report any new diagnosis in children and adolescents aged 0-18 years with:

Two or more of:	optic nerve hypoplasia/aplasia **OR** hypopituitarism **OR** septum pellucidum/corpus callosum anomalies

HORMONE DEFICIENCY DEFINITIONS

Growth hormone deficiency:

- Any child on growth hormone where the indication is for biochemical growth hormone deficiency according to PBS criteria (not short stature and slow growth criteria). [15]

Central hypothyroidism:

- Any child on thyroxine, where the T4 was below the lower limit of normal with a low or normal TSH. If additional deficiencies are known, the diagnosis may still be made if the TSH is less than 12mU/L at commencement. [16]

Prolactin:

- Prolactin deficiency: any child with prolactin level below the lower limit of normal on 2 consecutive occasions.
- Prolactin excess: any child with prolactin level above the upper limit of normal on 2 consecutive occasions.

Central adrenal insufficiency:

- Any child on steroid replacement therapy, that was commenced for low cortisol (should be confirmed with inadequate response to short synacthen test). [16]

Hypogonadotrophic hypogonadism:

- Any child requiring ongoing testosterone or oestrogen supplementation during adolescence as a result of LH and FSH levels below the lower limit of normal, or an inadequate response to GnRH stimulation test. [16]

Central diabetes insipidus:

- Children treated with desmopressin or hydrochlorothiazide where the indication is for diabetes insipidus.
    - Exclude patients treated with desmopressin for nocturnal enuresis.
    - Exclude patients treated with hydrochlorothiazide for diuretic effect.

INVESTIGATOR CONTACT DETAILS

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