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Beyond Idiopathic Short Stature: Pituitary Stalk Interruption Syndrome Associated with Congenital Heart Disease and Small for Gestational Age

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Abstract: **Case Report**

***Background*:** Pituitary Stalk Interruption Syndrome (PSIS) is a rare congenital anomaly of the hypothalamic-pituitary axis characterized by the triad of an absent or thin pituitary stalk, an ectopic neurohypophysis, and anterior pituitary hypoplasia. It frequently presents with growth hormone deficiency (GHD) and severe short stature. Congenital heart defects (CHDs) are rarely reported in association with PSIS. ***Case Presentation*:** We report the case of an 8-year-and-11-month-old girl referred for evaluation of severe growth failure (height: 121 cm, -2.2 SDS; weight: 20 kg, 3rd percentile). Her medical history was notable for being born small for gestational age (SGA, birth weight 2,200 g at term) and a known ostium secundum atrial septal defect (ASD) without pulmonary arterial hypertension. Growth deceleration began around 1 year of age. Hormonal evaluation revealed intact baseline thyroid and adrenal axes, but an IGF-1 level at the lower limit of normal (165 ng/mL). An insulin tolerance test (ITT) demonstrated a partial GH response (peak GH: 13.95 mIU/L, equivalent to 4.65 ng/mL). Hypothalamic pituitary Brain magnetic resonance imaging (MRI) confirmed PSIS. Recombinant human growth hormone (rhGH) replacement therapy was initiated at 0.025 mg/kg/day under close cardiological surveillance. ***Conclusion*:** Growth failure in children with congenital heart disease should not be systematically attributed solely to cardiac hemodynamics. The co-occurrence of PSIS, ASD, and SGA points toward a potential early neuro-embryological developmental defect or an underlying pleiotropic genetic mutation.

Keywords: Pituitary Stalk Interruption Syndrome, Growth Hormone Deficiency, Congenital Heart Disease, Small for Gestational Age.

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1. INTRODUCTION

Pituitary Stalk Interruption Syndrome (PSIS) is a congenital anomaly characterized by a classic radiological triad: a thin or absent pituitary stalk, an ectopic posterior pituitary gland, and hypoplasia or aplasia of the anterior pituitary gland [1].

Although PSIS is classically considered an isolated midline defect, extra-pituitary malformations (particularly craniofacial, ocular, and central nervous system anomalies) have been reported in up to 20–30% of cases [2]. However, associated congenital heart defects (CHDs) remain exceedingly rare. Here, we present the case of an 8-year-old girl with severe growth failure caused by PSIS, associated with a congenital ostium secundum atrial septal defect (ASD) and a history of being born small for gestational age (SGA).

2. Case Presentation

An 8-year-and-11-month-old girl was referred to the Endocrinology Department for investigation of severe growth failure. She was born via scheduled cesarean section following a term pregnancy (described as post-term, although this was not formally documented), with a birth weight of 2,200 g (<10th percentile, classified as small for gestational age (SGA)). There was no history of perinatal asphyxia, neonatal hypoglycemia, or prolonged jaundice.

Her past medical history was notable for an isolated ostium secundum atrial septal defect (ASD) without pulmonary arterial hypertension (PAH) or left ventricular dysfunction, managed conservatively. Family history was negative for short stature (paternal height: 180 cm; maternal height: 172 cm; mid-parental target height: 169.5 cm) or endocrine disorders. However, family history was positive for premature sudden cardiac events (three paternal uncles deceased from cardiac conditions). Growth deceleration was first noted by the family at 1 year of age.

On physical examination, the following findings were noted:

- Height: 121 cm (-2.2 SDS below target height)
- Weight: 20 kg (3rd percentile)
- BMI: 13.6 kg/m²
- Pubertal status: Tanner stage B1P1
- Dysmorphic features: Absent (no midline facial defects, normal hairline and neck)
- Cardiovascular: Normal S1/S2, soft systolic ejection murmur at the left upper sternal border; blood pressure 100/70 mmHg; heart rate 85 bpm.

Laboratory investigations excluded several systemic, non-endocrine causes of growth failure: anti-tissue transglutaminase IgA antibodies were negative, renal and liver function tests were normal (serum creatinine: 4.8 mg/L), and hemoglobin was normal (13.5 g/dL). Karyotype analysis was 46,XX, excluding Turner syndrome. Bone age was delayed at 7.0 years compared with a chronological age of 8 years and 11 months (a delay of approximately 23 months).

Endocrine evaluation revealed the following:

- Normal TSH (3.47 µIU/mL) and free T4 (16.03 pmol/L)
- Normal 8 AM serum cortisol (154 µg/L)
- Baseline IGF-1 of 165 ng/mL (normal range: 50–410 ng/mL, but below the age-matched median).

An insulin tolerance test (ITT) was performed to assess GH reserve: The peak GH concentration was 13.95 mIU/L (approximately 4.65 ng/mL, using the conversion factor). This result may be consistent with partial growth hormone deficiency (peak < 5 ng/mL during adequate hypoglycemia) (Table 1).

Table 1: Insulin tolerance test showing a partial growth hormone deficiency

Time Point	Glycemia (g/L)	Serum GH (mIU/L)
T -15 min	0.74	9.60
T 0 min	0.74	11.40
T 15 min	0.74	13.44
T 30 min	0.43 (Hypoglycemia achieved)	10.59
T 45 min	0.32 (Hypoglycemia achieved)	**13.95 (Peak)**
T 60 min	0.77	12.78
T 90 min	2.09	3.48

Hypothalamic-pituitary MRI confirmed Pituitary Stalk Interruption Syndrome (PSIS), demonstrating an absent or severely hypoplastic pituitary stalk, an ectopic posterior pituitary lobe at the infundibular recess, and anterior pituitary hypoplasia (Figure 1).



Figure 1: Hypothalamic-pituitary MRI confirming Pituitary Stalk Interruption Syndrome

Recombinant human growth hormone (rhGH; Omnitrope) replacement therapy was initiated at a dose of 0.025 mg/kg/day (0.5 mg/day). Given the atrial septal defect, treatment was initiated in close coordination with pediatric cardiology. Follow-up every 3–6 months was planned to monitor growth velocity, IGF-1 levels, cardiac hemodynamics, and the possible emergence of additional anterior pituitary hormone deficiencies.

3. DISCUSSION

Pituitary Stalk Interruption Syndrome (PSIS) can mimic constitutional growth delay or non-endocrine causes of growth failure. This case highlights several diagnostic and pathophysiological considerations:

First, growth failure in children with congenital heart disease (CHD) is often attributed to hemodynamic instability, increased metabolic demand, or chronic tissue hypoxia. However, marked short stature (height below -2.0 SDS) in a hemodynamically stable child with an isolated defect, such as an ostium secundum ASD, should prompt an endocrine evaluation. In this case, growth deceleration began at 1 year of age, but the investigation was not undertaken until the age of 8 years.

Second, from an embryological perspective, the co-occurrence of PSIS, CHD, and SGA raises the possibility of an early developmental disturbance affecting multiple organ systems during gastrulation and organogenesis (weeks 3–6 of gestation). Lee *et al*., (2024) reported that, among children with congenital combined pituitary hormone deficiency, 16.3% were born SGA and 14% had associated CHDs, suggesting that extra-pituitary malformations and impaired fetal growth may form part of the broader phenotypic spectrum of congenital hypopituitarism [8]. At the molecular level, shared developmental pathways may contribute to this phenotype: transcription factors such as PROKR2, HESX1, LHX3/4, TGIF, and GLI2 have been implicated in PSIS and midline structural defects [4, 5], while the Sonic Hedgehog (SHH) pathway plays important roles in forebrain and pituitary morphogenesis and cardiac septation [6].

Finally, because PSIS can be progressive, long-term surveillance of all pituitary axes is essential, as thyroid, adrenal, or gonadotropic deficiencies may emerge later in childhood or during puberty. Although rhGH replacement therapy is a cornerstone of management [7], dose titration and regular clinical and cardiological follow-up are important in a child with an uncorrected ASD. The need for echocardiographic monitoring should be determined in collaboration with the treating cardiologist.

4. CONCLUSION

This case emphasizes that growth failure in children with congenital heart defects should not automatically be attributed to cardiac pathology alone. Endocrine evaluation and pituitary MRI should be considered when growth failure is disproportionate to the cardiac condition, particularly in hemodynamically stable children. Early diagnosis of PSIS allows timely consideration of rhGH replacement and long-term surveillance for evolving pituitary hormone deficiencies.

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