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Dr. Sibi KR
Pediatric Endocrinologist, Valluvanad Hospital, Kerala India

Dr. Aleena Joseph
Department of pediatrics
Valluvanad hospital
Kerala India

Corresponding Author:
Dr. Sibi KR
Pediatric Endocrinologist, Valluvanad Hospital, Kerala India

Pituitary stalk interruption syndrome (PSIS) in a Newborn: A rare case report

Dr. Sibi KR and Dr. Aleena Joseph

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Abstract
Pituitary stalk interruption syndrome presents with a combination of a thin or disrupted pituitary stalk, underdeveloped or absent anterior pituitary, and a missing or ectopic posterior pituitary (EPP) as observed on magnetic resonance imaging (MRI). This condition, a congenital pituitary anomaly, lacks a precise prevalence estimate. In certain instances, the anomaly manifests solely as EPP or pituitary stalk interruption. Common indicators include tertiary hypothyroidism characterized by reduced thyroid stimulating hormone levels, hyperprolactinemia, and deficiencies in other pituitary hormones.

Case presentation: A 5-day-old newborn was admitted due to poor feeding, lethargy, and hypoglycemic seizure. Upon examination, he was found to have undescended testes on one side with a micropenis (SPL 0.8cm). Laboratory investigations revealed low cortisol levels at 0.49ug/dl (normal range: 4-20ug/dl) alongside decreased growth hormone levels (0.94ng/ml) during hypoglycemia. Additionally, on day 10 of life, serum LH was 0.100 mIU/ml (normal range: 0.3-4.9mU/ml), testosterone was 0.025ng/dl (normal range: 75-400ng/dl), Free T4 was 0.64ng/dl (normal range: 0.93-1.7ng/dl), TSH was 5.24uUI/mL (normal range: 0.58-5.57uUI/mL), and Prolactin was significantly elevated at 201.8ng/ml (normal range: 10-20 ng/mL). Given the markedly high prolactin levels, the possibility of Pituitary stalk interruption syndrome was considered, which was subsequently confirmed by MRI imaging. Whole exome sequencing was done which revealed PROP 1 gene mutation. Treatment commenced with hydrocortisone replacement initially, followed by thyroid and testosterone replacement.

Conclusion: Given the relatively rare occurrence of pituitary stalk interruption syndrome, it is advisable to include magnetic resonance imaging (MRI) of the pituitary when evaluating a patient with suspected pituitary deficiency to ensure timely diagnosis and treatment. Hormone replacement therapy serves as the cornerstone of treatment for pituitary stalk interruption syndrome and should be initiated promptly. The correlation between neuroimaging findings and endocrine data is crucial for enhancing our comprehension of the condition and establishing a foundation for molecular diagnosis, genetic counselling, and improved patient management.

Keywords: Pituitary stalk interruption syndrome (PSIS), ectopic posterior pituitary (EPP), magnetic resonance imaging (MRI), Hypopituitarism, PROP 1 gene, hypothyroidism, neonatal hypoglycemia

Introduction
Pituitary stalk interruption syndrome (PSIS), alternatively known as pituitary stalk transection syndrome, is an uncommon condition occurring with an estimated incidence rate of 0.5 per 1,000,000 births, showing a male predominance. It is characterized by the absence or underdevelopment of the anterior pituitary gland, a thin or absent infundibulum/pituitary stalk, and ectopic posterior pituitary. This syndrome can manifest with midline defects and various deficiencies in pituitary endocrine function, ranging from isolated growth hormone deficiency (IGHD) to combined pituitary hormone deficiency (CPHD). The co-occurrence of hyperprolactinemia and hypothyroidism is termed Pickardt syndrome.

The endocrine outcome seems to be a progressive onset of hormone deficiencies leading to panhypopituitarism, but posterior pituitary function is usually maintained, occasionally it may be disturbed depending on the position of the posterior pituitary. PSIS is also associated with higher than normal frequency of breech presentation, difficult delivery, or the consequence of adverse perinatal factors such as birth trauma, prolonged labor, or forceps delivery is unclear. Later in childhood, children may present with short stature, decreased growth rate, seizures, hypotension, intellectual delay and delayed puberty.

During the neonatal period and infancy, the signs and symptoms of PSIS often remain unnoticed, leading to delayed diagnosis. Early detection of hormone deficiencies and prompt treatment initiation can significantly impact both the quality of life and the prevention of reproductive health issues in individuals with PSIS.

Patient history and clinical findings: We report a 5 day old male baby, referred to our NICU on day 5 of life with poor feeding and symptomatic hypoglycaemia (poor activity and neonatal seizures). He was delivered to a 27 year old primi mother of non-consanguinous marriage, with no significant antenatal history with a birth weight of 2.600 kg. No history of documented immediate postnatal complications was there. Physical examination showed unilateral (right) undescended testes with micropenis (SPL -0.8 cm) (Fig 1).

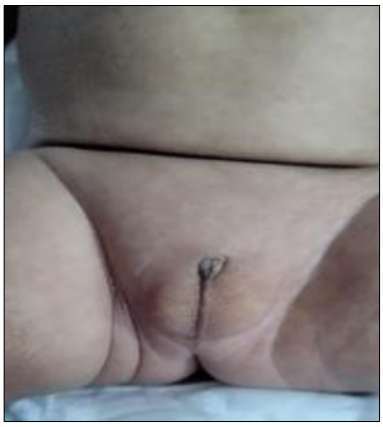

Fig 1: Physical examination showed unilateral (right) undescended testes with micropenis (SPL -0.8 cm)

Endocrine Evalution

Critical sample evaluation during hypoglycaemia showed low cortisol response: 0.49mcg/dL (Normal-5-25mcg/dL), low levels of growth hormone: 0.94ng/ml. Further evaluation on day 10 showed low s.LH:0.100 (Normal:1.1-7mIU/mL) and testosterone:0.025ng/ml (Normal-3-10 ng/mL).Also thyroid profile was suggestive of central hypoparathyroidism (FT4-0.64 and TSH-5.24) and prolactin levels were very high (201.8ng/mL; normal- 10-20ng/ml)

Table 1: Table of clinical laboratory values showing "Test" performed, Normal range and Lab Value with units provided.

Cortisol	5-25 mcg/dL	0.49 mcg/dL
Growth hormone	>3ng/dl	0.94 ng/dL
LH	1.1 – 7.0 mIU/mL	0.100mIU/mL
Testosterone	3 – 10ng/mL	0.025ng/ml
Ft4	0.93 – 1.7 ng/dL	0.64ng/dl
TSH	0.58-5.57 uUI/mL	5.24uUI/ml
Prolactin	10 – 20 ng/mL	201.8ng/ml

Pituitary MRI

Relatively small sized anterior pituitary gland with ectopic posterior pituitary and hypoplastic aberrant pituitary stalk. (Fig 2 and Fig 3)

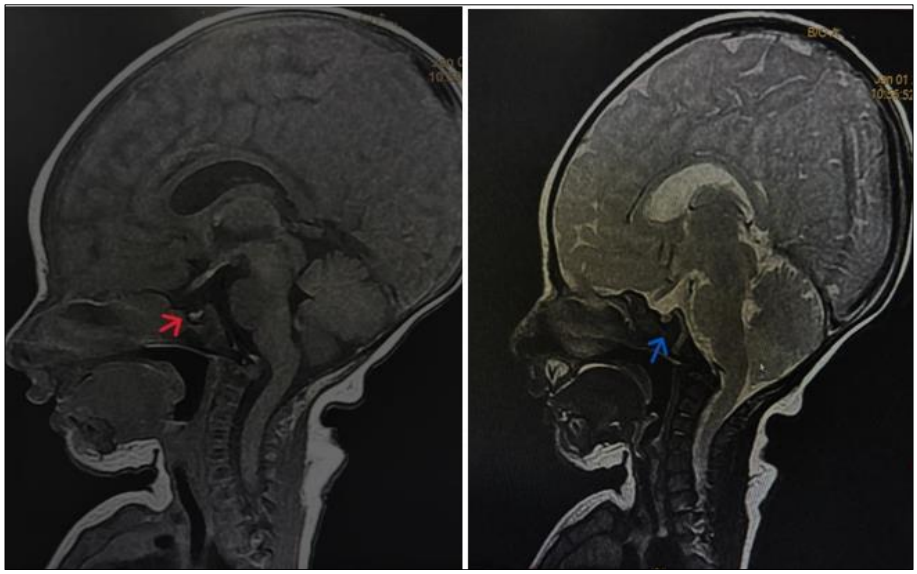

Fig 2 and Fig 3: Relatively small sized anterior pituitary gland with ectopic posterior pituitary and hypoplastic aberrant pituitary stalk

Genetic Evaluation

Whole exome sequencing was done, which showed PROP 1 gene mutation

Gene# (Transcript)	Location	Variant	Disease (OMIM)	Inheritance
PROP1 (-) (ENST00000308304.2)	Exon 2	c.135G>C (p.Arg45Ser)	Pituitary hormone deficiency-2 (OMIM#262600)	Autosomal recessive**

**This is an autosomal recessive disorder caused by bi-allelic (homozygous or compound heterozygous) pathogenic variants in the PROP1 gene. No other clinically relevant variant is detected in the coding region and exon intron boundaries of these genes.

Diagnosis

1. Pituitary stalk interruption syndrome
2. Neonatal Hypoglycemia
3. Hypogonadotropic Hypogonadism
4. Secondary Adrenal Insufficiency
5. Growth Hormone Deficiency
6. Central Hypothyroidism
7. Hyperprolactinemia

Treatment

1. Cortisone acetate 1.5mg BD (10mg/m2/day)
2. Levothyroxine 25mcg/day
3. Testosterone 25mg IM monthly

Discussion

Pituitary Stalk Interruption Syndrome (PSIS), also referred to as pituitary stalk transection syndrome, is a rare form of congenital hypopituitarism characterized by various clinical features falling within the spectrum of the holoprosencephaly phenotype [10]. The incidence stands at 0.5 per 100,000 live births, with a slight male predominance It is characterized by the triad of thin or interrupted pituitary stalk, absent or ectopic posterior lobe, and hypoplastic or aplastic anterior lobe [1]. It can be linked with midline defects and a range of pituitary endocrine deficiencies, spanning from isolated growth hormone deficiency (IGHD) to combined pituitary hormone deficiency (CPHD). When hyperprolactinemia and hypothyroidism co-occur, it is termed Pickardt syndrome. The progression of PSIS often leads to a gradual onset of hormone deficiencies culminating in panhypopituitarism, although posterior pituitary function typically remains intact, though occasionally may be compromised depending on its positioning.

During the neonatal period and infancy, the signs and symptoms of PSIS often remain unnoticed, leading to delayed diagnosis. Early detection of hormone deficiencies and prompt treatment initiation can significantly impact both the quality of life and the prevention of reproductive health issues in individuals with PSIS. The exact cause of PSIS remains largely unknown or only partially confirmed in many cases.

The development of the pituitary gland relies on the coordinated action of signal molecules and transcription factors, which interact synergistically or in opposition, creating gradients and orchestrating cell responsiveness in a spatially and temporally coordinated manner. Transcription factors including Ptx1 and 2, Lhx3 and 4, Isl1, Otx1, 2, Hesx1, Six1, 3, 4, and 6 play crucial roles in cell proliferation, survival, and differentiation. Specific genes such as Pitx1 activate POMC, while Pitx1 and 2 activate genes responsible for TSH, gonadotropins, GH, and prolactin production. Notably, the Wnt signaling pathway influences the expression of Bmp and Fgf, while Sox2 and 3 activate Shh but are counteracted by Tbx2 and 3. The Notch signaling pathway is also vital for anterior pituitary cell specification.

Proposed mechanisms of PSIS include mutations in genes involved in anterior pituitary development such as PIT1, PROP1, LHX3/LHX4, PROKR2, OTX2, TGIF, HESX1, ROBO1, and GPR161. Additionally, genetic mutations in HESX1, LHX4, and SOX3 genes may be associated with undescended testes and micropenis. Perinatal events like breech presentation and perinatal asphyxia could also damage the pituitary stalk [3]. In our case genetic evaluation showed PROP1 gene mutation.

The disorder exhibits intrafamilial and interindividual variability, with incomplete or variable penetrance. PSIS presents with a heterogeneous clinical, biological, and radiological profile, reflecting the complex interplay of genetic and environmental factors in its pathogenesis. Affected individuals may present with hypoglycaemia during the neonatal period (those diagnosed in the neonatal period appear to be affected by a particularly severe form of the disorder). Short stature and delayed puberty are present in most cases and may be combined with extra pituitary malformations. Later in childhood, children may present with short stature, decreased growth rate, seizures, hypotension, intellectual delay and delayed puberty

Our case is interesting and unique because the patient presented on early neonatal period and we hope early detection of hormone deficiencies and prompt treatment initiation can significantly impact both the quality of life and the prevention of reproductive health issues in this child.

Conflict of Interest

Not available

Financial Support

Not available

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