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Case Report

Pituitary Stalk Interruption Syndrome: A Case and Literature Review

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ABSTRACT

Background/Objective: Pituitary stalk interruption syndrome (PSIS) is a rare congenital disorder that is characterized by a triad including a thin or interrupted pituitary stalk, absent or ectopic posterior lobe, and agenesis or dysgenesis of anterior lobe.
PSIS is typically diagnosed in childhood. The objective of this report is to describe a patient with PSIS whose diagnosis was missed until adulthood.
Case Report: A 42-year-old-female presented for evaluation of premature menopause, weight loss, and occasional dizziness. On examination she had short stature and absent secondary sexual features. Laboratory tests were consistent with hypopituitarism with follicle stimulating hormone 0.5 mIU/mL (16.7-113); luteinizing hormone 1.2 mIU/mL (10.8-58.6); prolactin 10.4 ng/mL (2.7-19.6); estradiol 20 pg/mL; cortisol 2 mcg/dL (6.7-22.6); adrenocorticotropic hormone 18 pg/mL (6-50); thyroid stimulating hormone 10.33 uIU/mL (0.28-3.8); free T4 0.41 ng/dL (0.58-1.64); insulin like growth factor-1 −3.7 SD (17 ng/mL) (52-328); and adrenocorticotropic hormone stimulation confirmed secondary adrenal insufficiency. The magnetic resonance imaging of the brain revealed an ectopic posterior pituitary with a partially empty sella, absence of the pituitary stalk, and a small anterior pituitary. The patient was initiated on replacement hormones with improvement in her symptoms.
Discussion: PSIS is a rare condition with uncertain pathogenesis and variable presentation requiring a high index of suspicion and presenting with multiple anterior pituitary hormone deficiencies. Diagnosis is confirmed by a dedicated pituitary magnetic resonance imaging, and treatment is tailored to the hormonal deficiency detected.
Conclusion: This case highlights the importance of early diagnosis of PSIS, which presents with multiple anterior pituitary hormonal deficiencies, but diagnosis can remain elusive unless dedicated brain imaging is performed.

Introduction

Pituitary stalk interruption syndrome (PSIS) is a rare congenital disorder of the pituitary gland with distinctive imaging features, such as an interrupted or thin pituitary stalk, absent or ectopic posterior lobe, and agenesis or dysgenesis of the anterior lobe. The pathogenesis and the clinical presentation of PSIS is highly variable, but the diagnosis is commonly made in childhood. We want to bring to light a case of PSIS that was diagnosed at a much older age than previously reported.

Case Report

We present a 42-year-old female, from Dominican Republic who was initially referred to the endocrinology clinic for evaluation of premature menopause. She reported minimal breast growth and recalled only 1 menstrual period at the age of 17 years and had never been pregnant. She had lost about 20 pounds and reported spontaneous, occasional dizziness. She denied previous hospitalizations or a similar history in her family with normal pubertal development in her fraternal twin sister.

Abbreviations: MRI, magnetic resonance imaging; PSIS, pituitary stalk interruption syndrome; TSH, thyroid stimulating hormone.

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On examination she had short stature with a height of 4'11" and weighed 87 lb. She reported her family being taller than her, but actual heights were not available. Her blood pressure was 97/63, with a heart rate of 71/min. Her thyroid was 25 g. She had no axillary or pubic hair. Breast development was Tanner stage II without galactorrhea.

Laboratory results were consistent with panhypopituitarism as noted in the Table 1 and Table 2, respectively.

Bone density showed osteoporosis. L1-L4: Z-Score −3.0, BMD 0.5 g/cm^2; right femoral neck Z-score −1.9, BMD 0.7 g/cm^2.Bone age study revealed adult with closure of all epiphyzes.

The magnetic resonance imaging (MRI) of the brain revealed an ectopic posterior pituitary with a partially empty sella, absence of the pituitary stalk, and small anterior pituitary (Fig. 1 and 2).

Patient was diagnosed with sporadic PSIS with panhypopituitarism and initiated on a physiologic dose of hydrocortisone followed by levothyroxine and birth control pills containing estradiol and progesterone. She has not completed genetic testing or been compliant with her medications, but she has gained weight, her dizziness is resolved and is having regular periods.

Highlights

- Pituitary stalk interruption syndrome (PSIS) is rare with a diagnosis based on imaging
- PSIS is associated with variable anterior hormonal deficiencies
- Arginine vasopressin deficiency (AVP) deficiency is rare.
- Most patients are diagnosed in childhood
- Patients diagnosed as adults have absent pubertal development and short stature

Clinical Relevance

Pituitary stalk interruption syndrome is a rare congenital disorder of the pituitary gland characterized by a thin or interrupted pituitary stalk, absent or ectopic posterior lobe, and hypoplastic anterior lobe. It can present as combined anterior pituitary hormone deficiencies at pediatric age, progressing in adulthood to panhypopituitarism. We describe a case of pituitary stalk interruption syndrome that remained undiagnosed until adulthood.

Discussion

PSIS is an extremely rare disorder with an incidence of 0.5/100,00 births with the characteristic imaging features described above. It was first described by Fujisawa et al[1] in 1987 in patients with idiopathic dwarfism.

The pathogenesis of PSIS is linked to several genetic and environmental factors. PSIS has a male predominance and is rarely familial.[2] Several genes such as *PIT 1*, *PROP1*, *HESX1*, *LHX3*/*LHX4*, *PROKR2*, *OTX2*, and *TGIF* in the Wnt, Notch, and Shh signaling pathways related to early hypothalamic-pituitary development, have been associated with PSIS.[3-5] Whole genome sequencing performed on sporadic PSIS patients found various polygenic pathogenic variants in the hedgehog signaling pathway.[6] Breech positioning and perinatal asphyxia are commonly noted in PSIS possibly due to injury to the pituitary stalk.[7] In a study involving PSIS patients, breech delivery had occurred in 88.9% of patients.[8]

PSIS is the most common etiology for multiple pituitary hormonal deficiencies in children but is frequently missed because of a variable presentation.[9] About 15% of PSIS patients with severely affected pituitary development are diagnosed in the neonatal period due of refractory hypoglycemia, jaundice, and in males with micropenis or cryptorchidism. The most common presentation is during childhood with short stature (70%) due to growth hormone deficiency with a 100% prevalence followed by gonadotropins, corticotropin, and thyrotropin deficiency of around 86.52%, 75.28%, and 79.78%, respectively with hyperprolactinemia in 6.9%.[10]

Our patient had evidence of hypopituitarism with low AM cortisol suppressed adrenocorticotropic hormone, confirmed with adrenocorticotropic hormone stimulation testing. In

Table 1
Laboratory Tests

Laboratory test	Value	Normal reference range
Follicle stimulating hormone	0.5 mIU/mL	16.7-113 mIU/mL
Luteinizing hormone	1.2 mIU/mL	10.8-58.6 mIU/mL
Prolactin	10.4 ng/mL	2.7-19.6 ng/mL
Estradiol	20 pg/mL	30-400 pg/mL
Cortisol	2 mcg/dL	6.7-22.6 mcg/dL
Adrenocorticotropic hormone	18 pg/mL	6-50 pg/mL
Thyroid stimulating hormone	10.33 uIU/mL	0.28-3.8 uIU/mL
Insulin like growth factor-1	17 ng/mL (−3.7SD)	52-328 ng/mL
Sodium	137 mmol/L	135-145 mmol/L
Thyroid peroxidase antibody	3 IU/mL	<30 IU/mL
Thyroglobulin antibody	I U/mL	≤3.9

Table 2
ACTH Stimulation Test

Baseline cortisol	1.6 mcg/dL
30 min cortisol	5.5 mcg/dL
60 min cortisol	8.5 mcg/dL

Abbreviation: ACTH = adrenocorticotropic hormone.

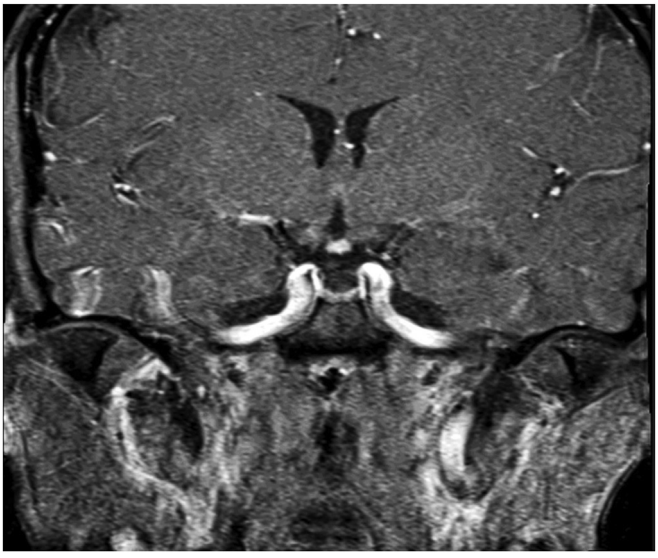

Fig. 1. Sagittal view of the brain MRI shows partially empty sella. The ectopic posterior pituitary is located at the median eminence and the pituitary stalk is not visualized. MRI, magnetic resonance imaging.

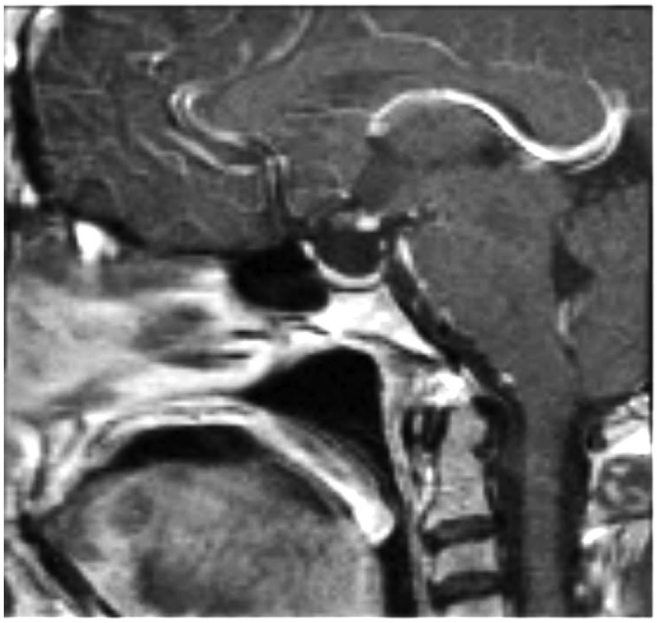

Fig. 2. Coronal view of the brain MRI shows partially empty sella. The pituitary stalk is not visualized. The adenohypophysis appears small. MRI, magnetic resonance imaging.

contrast to central hypothyroidism, where thyroid stimulating hormone (TSH) is expected to be low to normal, our patient's TSH was noted to be elevated. This has been noted in other studies as well due to the secretion of immunoreactive TSH without full biological activity.[10] The associated very low free T4 and negative thyroid antibodies confirmed the diagnosis of secondary hypothyroidism. Prolactin level is expected to be elevated secondary to the stalk defect but in a few cases as our patient prolactin level was noted to be low possibly due to the lack of portal blood supply to the lactotroph cells.[11] Arginine vasopressin deficiency is exceedingly rare. The incidence of panhypopituitarism is significantly higher in patients with invisible pituitary stalks on imaging.

Pituitary hormone deficiencies may appear over time, as some patients are not diagnosed until adulthood.[12] Our patient most likely had progressive development of hormonal deficiencies leading to the diagnosis in adulthood. Extra-pituitary manifestations are common and range from extra-axial polydactyly to midfacial hypoplasia to psychomotor delay. No congenital abnormalities were noted in our patient.

The MRI is the most useful diagnostic modality used for the diagnosis of PSIS. A study by Yang et al[4] looking at MRI finding in PSIS patients revealed the distinctive features of absent pituitary stalk in 98.3%, hypoplastic anterior pituitary in 98.3%, and ectopic posterior pituitary in 91.4% of the patients. The location of the ectopic posterior was commonly observed in the infundibular recess (60.4%), followed by the hypothalamus (18.9%).

Conclusion

Pituitary stalk interruption syndrome is a rare disorder with multifactorial pathogenesis and requires a high index of suspicion for an earlier diagnosis. Early replacement of hormonal deficiencies may help prevent the long-term complications associated with multiple pituitary hormonal deficiencies seen commonly with PSIS.

Disclosure

The authors have no conflicts of interest to disclose.

Acknowledgment

Patient consent was obtained.

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