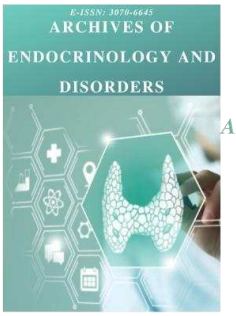

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Case Report

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The Long Diagnostic Gap: Pituitary Stalk Interruption Syndrome Diagnosed in Adulthood with Panhypopituitarism

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Abstract

Background: Pituitary Stalk Interruption Syndrome is rare congenital anomaly characterised by ectopic posterior pituitary, absent or thin pituitary stalk, hypoplastic anterior pituitary on Magnetic Resonance Imaging (MRI). It typically presents in childhood with growth failure or pubertal delay.

Case Presentation: Adult presentations are uncommon and often leads to delayed diagnosis. We report 30-year-old male who exhibited delayed development of secondary sexual characters. Clinical examination revealed underdeveloped secondary sexual characteristics, including absent axillary and pubic hair, small testicular volume 3 ml bilaterally and SPL of 4 cm. Anthropometry showed an arm span of 170 cm with a eunochoid body proportion (upper segment: lower segment ratio of 0.5) and delayed bone age corresponding to approximately 13 years.

Biochemical evaluation demonstrated multiple anterior pituitary hormone deficiencies, including low serum testosterone with inappropriately low gonadotropins (FSH, LH), low insulin-like growth factor 1 and markedly reduced morning cortisol levels (0.64ug/dl), suggestive of secondary adrenal insufficiency. Thyroid function tests were suggestive of central hypothyroidism. Cytogenetic test revealed a normal male karyotype (46XY).

MRI of the hypothalamo- pituitary region showed findings consistent with Pituitary Stalk Interruption Syndrome (PSIS).

Conclusion: PSIS, though congenital, may remain clinically silent for decades before manifesting as overt panhypopituitarism. This case emphasizes that delayed puberty and unexplained multi-axis hormonal deficiency in adults should prompt evaluation for underlying structural hypothalamo-pituitary abnormalities.

Keywords: Pituitary Stalk Interruption Syndrome; Hypogonadotropic Hypogonadism; Panhypopituitarism; Delayed Puberty; Adult Presentation; Magnetic Resonance Imaging (MRI)

Introduction

PSIS is rare developmental disorder characterised through triad consisting of hypoplastic or absent anterior pituitary, displacement or absence of posterior pituitary gland and thin or interrupted pituitary stalk. The occurrence of pituitary stalk interruption syndrome is rare, affecting roughly 0.5 per 1,00,000 live births [1]. PSIS is thought to arise either from mutations in genes critical for pituitary development (namely PROP1, LHX3, HESX1, PROKR2 or GPR161) or as a consequence of perinatal

hypoxic injury [2-4]. Deficiencies of anterior pituitary hormones are common, while posterior pituitary function is typically preserved. Anterior pituitary hormone deficiencies, namely growth hormone (100%), gonadotropins (86.5%), thyrotropin (79.8%), corticotropin (75.3%) are common in individuals with PSIS. Clinically, these deficiencies manifest as hypoglycemia, central hypothyroidism, cryptorchidism, micropenis, delayed puberty and small stature [2].

Late presentation of Pituitary Stalk Interruption Syndrome (PSIS) at 30 years of age is rare but documented, with mechanisms including partial hormonal sufficiency, compensatory endocrine adaptations and delayed recognition of subtle symptoms contributing to survival into adulthood before diagnosis. Management at this stage requires tailored hormone replacement and careful monitoring of metabolic and reproductive health.

This case report highlights the causes resulting in the late presentation of PSIS and details the management of patient diagnosed at the age of 30.

Case Report

A 30 year old male attended the Endocrinology outpatient clinic with complaints of absent secondary sexual development and progressive bilateral breast enlargement over the preceding six months. On examination, the patient exhibited normal adult height of 168 cm and weight of 66 kgs but lacked axillary and pubic hair. Testicular volume was approximately 3 ml bilaterally and the stretched penile length measured 4 cm. Bilateral gynecomastia was evident.

Laboratory evaluation demonstrated hyperprolactinemia with a serum prolactin level of 35.52 ng/ml. Gonadotropins were suppressed, with FSH at 1.39 mIU/ml and LH <0.01 mIU/ml. ACTH measured 16.8 pg/ml. Growth hormone was undetectable (<0.05 ng/ml) and IGF 1 has been markedly reduced at 25ng/ml. Thyroid profile revealed TSH 2.24μIU/ml, total T4 1.2μg/dl and total T3 0.2 ng/ml, consistent with central hypothyroidism. Serum testosterone was profoundly low (<0.05 ng/ml) and morning cortisol was 0.64 μg/dl, confirming adrenal insufficiency.

The patient's arm span measured 170 cm with a lower segment length of 107 cm. The calculated upper to lower segment ratio was 0.5, consistent with eunuchoid body proportions (Fig. 1). In view of these findings, karyotyping was undertaken considering chromosomal variants such as 47X (ix)(q10)Y cases of 47, XXY with gonadotrope exhaustion secondary to chronic pituitary hyperstimulation from primary testicular failure, Klinefelter's syndrome with possible association with Kallmann's syndrome and mixed germ cell tumors of the pituitary in patients with 47, XXY karyotype. Karyotyping cannot be avoided in hypogonadotropic hypogonadism, as Klinefelter's syndrome may occasionally present with this phenotype.

Bone age assessment revealed a skeletal maturity corresponding to 13 years (Fig. 2), highlighting a marked delay in biological development relative to chronological age.

Sella contrast-enhanced MRI showed an ectopic posterior pituitary bright spot, partially empty sella with a markedly thinned pituitary gland measuring approximately 2 mm in height without pituitary stalk. These results confirmed pituitary stalk interruption syndrome (Fig. 3,4).

Figure 1: Clinical image demonstrating eunochoid body proportions.

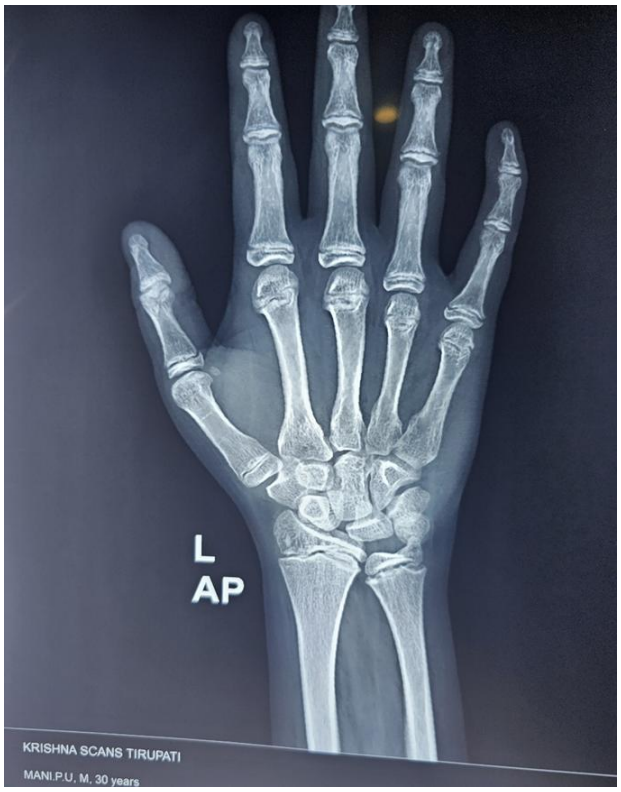

Figure 2: Demonstrates markedly delayed bone age (13 years) in contrast to the chronological age of 30 years.

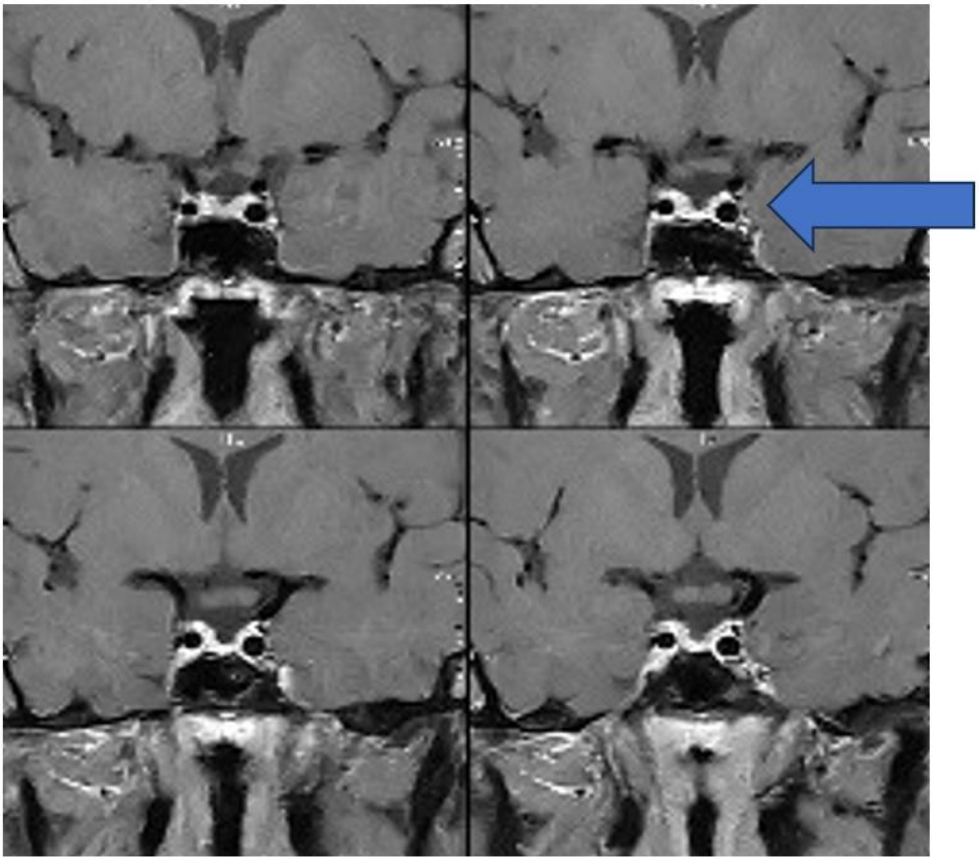

Figure 3: Contrast enhanced MRI of the sella demonstrating a partially empty sella with a markedly thinned pituitary gland measuring approximately 2 mm in height along with absent pituitary stalk.

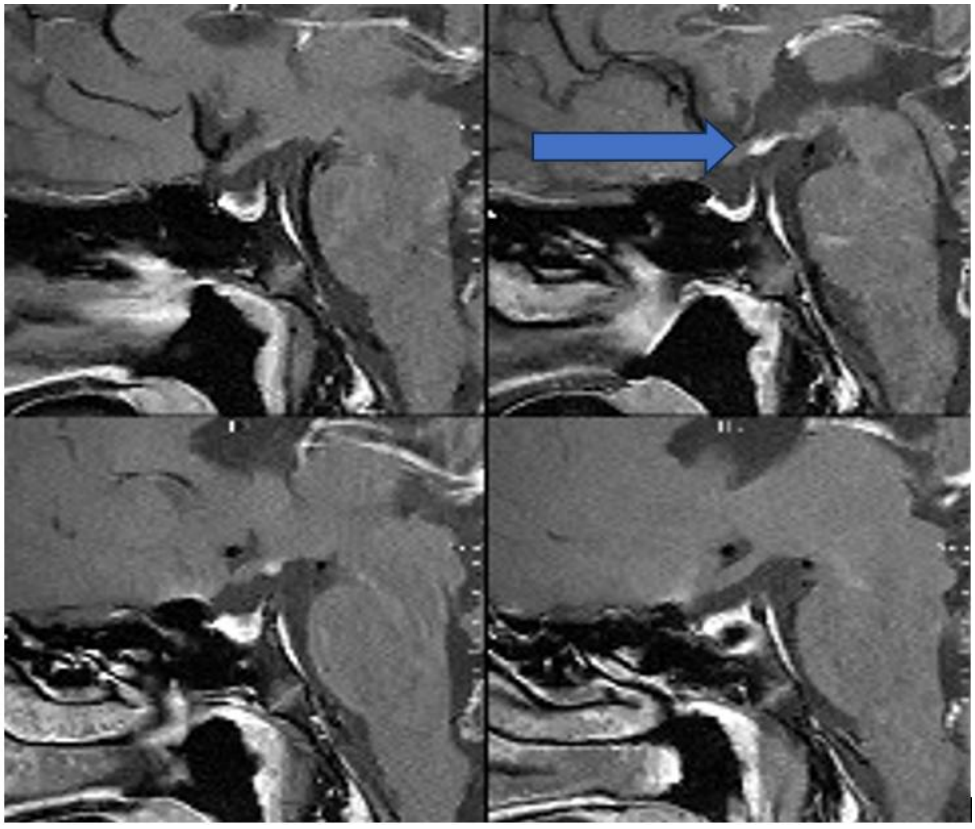

Figure 4: Contrast enhanced MRI demonstrating an ectopic posterior pituitary bright spot.

Discussion

This case highlights the unusual presentation of PSIS in 30 year old male. Despite normal adult height and weight, the patient exhibited absent secondary sexual characteristics, gynecomastia and eunuchoid body proportions. Hormonal evaluation confirmed panhypopituitarism with hypogonadotropic hypogonadism, explaining the lack of pubertal development.

Our patient maintained linear growth despite deficiencies in several hormones, including growth hormone, thyroid hormones and gonadal steroids. This might have been by compensatory variables such as hyperinsulinemia, hyperprolactinemia, high leptin levels and GH Variants [5].

The bone age assessment revealed skeletal maturity corresponding to 13 years, underscoring the profound delay in biological development relative to chronological age. This discrepancy reflects the absence of sex steroid exposure, which normally drives epiphyseal closure and skeletal maturation during adolescence. The persistence of open growth plates accounts for the patient's eunuchoid proportions, with increased arm span relative to height.

Our case also underscores the importance of performing karyotyping in patients with hypogonadotropic hypogonadism presenting in adulthood to exclude chromosomal abnormalities such as 47X (ix)(q10)Y, 47, XXY variants with gonadotrope exhaustion and Klinefelter's syndrome with possible association to Kallmann's syndrome.

MRI findings of a partially empty sella, thinned pituitary gland, bright spot, ectopic posterior pituitary absent stalk have been consistent with PSIS [1,2]. While majority cases are diagnosed in childhood or adolescence because of growth failure and delayed puberty, this case illustrates the rare scenario of late presentation in adulthood.

Hyperprolactinemia in this patient could be attributed to the lack of dopaminergic inhibition secondary to pituitary stalk interruption, a mechanism well recognized in such cases [1]. Interestingly, despite long standing central hypothyroidism and secondary adrenal insufficiency, the patient did not develop endocrine emergencies such as myxedema coma or adrenal crisis. Several mechanisms may explain this [6,7]:

- Partial residual function: Even minimal secretion of cortisol and thyroid hormones may have provided sufficient baseline activity to prevent acute decompensation
- Gradual adaptation: The slow onset of hormone deficiency allowed physiological systems to adapt over time, reducing the likelihood of sudden collapse
- Compensatory mechanisms: Peripheral sensitivity to low hormone levels, altered metabolic set points and reduced stress exposure may have mitigated the risk of crisis
- Absence of mineralocorticoid deficiency
- Lifestyle and environment: Absence of major stressors such as severe infections, trauma or surgery likely prevented precipitation of acute endocrine emergencies.

Management consisted of comprehensive hormone replacement therapy for documented deficiencies of gonadal steroids, cortisol, thyroxine or growth hormone. As per standard endocrine treatment, glucocorticoid replacement was started first, followed by levothyroxine and then androgen therapy. The patient's height was 168 cm, with a bone age corresponding to 13 years. However, in view of socioeconomic constraints, Growth hormone replacement was declined.

This case emphasizes the importance of comprehensive endocrine, anthropometric and radiological assessment in adults presenting with delayed puberty and hypogonadism. To prevent long-term complications, enhance metabolic health and handle mental health problems, early recognition and timely hormone replacement are essential.

Conclusion

This case illustrates the rare late presentation of pituitary stalk interruption syndrome in adulthood. Despite profound hormonal deficiencies and markedly delayed skeletal maturation, the patient remained clinically stable without developing endocrine emergencies such as myxedema coma or adrenal crisis, likely due to gradual adaptation, partial residual hormonal activity and absence of major stressors. The coexistence of normal adult height with eunuchoid proportions, delayed bone age and

panhypopituitarism underscores the importance of thorough endocrine, anthropometric and radiological evaluation in adults presenting with hypogonadism and absent pubertal development. Early diagnosis and hormone replacement are crucial to prevent long term metabolic, skeletal and psychosocial complications. Delayed puberty and unexplained multi-axis hormonal deficiency in adults should prompt evaluation for underlying structural hypothalamo-pituitary abnormalities.

Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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Data Availability Statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Ethical Statement

The project did not meet the definition of human subject research under the purview of the IRB according to federal regulations and therefore was exempt.

Informed Consent Statement

Informed consent was obtained from all participants included in the study.

Authors' Contributions

All authors contributed equally to this paper.

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