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Two Cases of Late Diagnosis Pituitary Stalk Interruption Syndrome and Literature Review

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Background: Pituitary stalk interruption syndrome (PSIS) is a rare congenital condition that includes the triad of a thin pituitary stalk, an ectopic posterior pituitary gland, and an absent or hypoplastic anterior pituitary gland and is usually diagnosed in infancy. This report presents two cases of late diagnosis of PSIS and a literature review of the relevant cases. The objective is to update data on such an uncommon syndrome to avoid the consequences of pituitary dysfunction including short stature, impaired cognitive function, negative impact on bone health, adrenal crises and delayed puberty.

Case Report: In this paper, we report on two cases of late diagnosis of PSIS with a history of growth hormone deficiency. The first case is a 21-year-old female presenting with generalized fatigability, dizziness and delayed puberty, while the second case is a 19-year-old female presenting with secondary amenorrhea. The hormonal profile of the first patient revealed panhypopituitarism; the second case had growth hormone deficiency subsequently had secondary hypogonadism with intact thyroid and adrenal functions. The diagnosis of PSIS was confirmed by magnetic resonance imaging (MRI), and both cases were treated with hormone supplements. Progress was also tracked through planned follow-up sessions. To the best of our knowledge, this is the first case series of such late diagnosis PSIS from Saudi Arabia.

Conclusion: The key message of this paper is that rare etiologies such as PSIS should be kept in mind, especially for young patients presenting with clinical evidence of pituitary hormonal deficiencies, and MRI should be considered to confirm diagnosis. The early diagnosis, hormonal replacement, and long-term follow-up are crucial to reducing negative impacts of pituitary hormonal deficiencies.

Keywords: pituitary stalk interruption syndrome, PSIS, growth hormone deficiency, combined pituitary hormone deficiency

Background

Pituitary stalk interruption syndrome (PSIS) is a congenital pituitary defect that was first described by Fujisawa et al in 1987.[1,2] The estimated incidence is 0.5 cases per 100,000 births, with male predominance.[1] However, the actual prevalence might be underestimated, and many cases are still underdiagnosed due to gaps in the knowledge of this condition.[3] Diagnosis is radiological and based on pituitary magnetic resonance imaging (MRI), with the triad of a thin or interrupted pituitary stalk, an absent or ectopic posterior lobe, and a hypoplastic or aplastic anterior lobe.[4] PSIS patients usually present with a spectrum of symptoms secondary to anterior pituitary hormonal deficiency, mainly short stature and the absence of secondary sexual characteristics.[5] According to an observational study, the frequency of anterior pituitary hormone deficiencies was found to be as follows: growth hormone 100%, gonadotropin 86.5%, corticotropin 75.3%, and thyrotropin 79.8%.[5] Various hypotheses have been proposed to explain PSIS; however, the exact etiology remains unclear.[1,4] Early diagnosis and life-long hormonal replacement are crucial points in reducing morbidity and improving outcomes.[4] This report presents two cases of late diagnosis of PSIS. The first case is a 21-year-old woman with panhypopituitarism, and the second case is of a 19-year-old woman with secondary amenorrhea, low levels of growth hormone and gonadotropin, and preserved thyroid and adrenal function. Additionally, we performed a comprehensive review of the relevant literature.

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Case Reports

Case 1

A 21-year-old female presented to the outpatient clinic with a request for a medical report to be submitted to social services for financial support.

She was born to non-consanguineous parents, full term through normal spontaneous vaginal delivery in a cephalic position with a birth weight of 1.9 kg. The postnatal period was significant because of a history of hypoglycemia, necessitating a hospital stay of 5 days. There was no history of perinatal asphyxia, jaundice, or head trauma. She had normal milestone development and performed well in school.

By the age of 7 years, she was noticed to be short and was taken by her parents to the pediatric service. She was diagnosed with growth hormone deficiency based on bone age and a dynamic stimulation test (no accessible report about bone age, IGF-1 or the result of dynamic stimulation test at this age as done in another hospital). She received growth hormone (GH) therapy until the age of 16 years. At the same age of 16 years, she was complaining of generalized fatigability, dizziness, and attacks of hypoglycemia. She was evaluated at a local hospital, admitted, and diagnosed with hypoadrenalism. A pituitary MRI was performed, and it was reported to the family as being abnormal, but no report is available to us. She was discharged with hydrocortisone tablets, which she chose to discontinue after a few months. During the same hospital admission, she was referred to a gynecologist because of primary amenorrhea and offered hormone replacement therapy, which she declined, and she had no further medical follow-up.

At the time of the current presentation to the clinic and upon clinical interview, she gave a history of intermittent attacks of generalized fatigability and dizziness but no history of abdominal pain, nausea, vomiting, or changes in bowel habits. She also stated that she continued to be amenorrheic and did not exhibit any signs of secondary sexual characteristics. There was no family history of a similar condition. On recent examination, her vital signs were as follows: a blood pressure of 93/62 mmHg, without a postural drop, and a pulse rate of 69 beats/min. The patient's height was 159 cm, with a weight of 36 kg and a body mass index (BMI) of 14.24. She had breast tanner stage 2 and pubic hair tanner stage 1. There were no features suggestive of Turner's syndrome or other dysmorphic features. Other systemic examinations were unremarkable.

Her hormonal profile showed low serum estradiol, low progesterone, low follicle-stimulating hormone (FSH) and low luteinizing hormone, indicating secondary hypogonadism. It also revealed a low morning cortisol level, inappropriate normal adrenocorticotropic hormone (ACTH) and a peak cortisol level of (110.8 nmol/l) with a high dose 250 mcg ACTH (Cosyntropin) stimulation test (a normal response defined as a cortisol level above 500 nmol during any part of the stimulation test), confirming the existence of secondary adrenal insufficiency. Furthermore, it showed secondary hypothyroidism with inappropriate normal thyroid stimulating hormone and low free thyroxine. As three hormonal axes are impacted, this finding is consistent with the occurrence of panhypopituitarism (Table 1). Chromosomal analysis revealed a 46 XX karyotype. The patient was referred and

Table 1 Laboratory Parameters for Case Number 1 and Case Number 2

Parameter		Result Case 1	Result Case 2	Normal Range
CBC	WBC	7.73×10^9	10.75×10^9	$3–10\times10^9$/l
	HGB	12.5	12.6	11.5–15.5 g/dl
	Platelet count	271×10^9	400×10^9	$150–450\times10^9$/l
RFT	Creatinine	82	53	49–90 umol/l
	Urea	3.6	4.1	3.2–8.2 mmol/l
	Sodium	141	140	136–146 mmol/l
	Potassium	3.8	5	3.5–5.1 mmol/l
	Chloride	108	111	98–107

(*Continued*)

Table 1 (Continued).

Parameter		Result Case 1	Result Case 2	Normal Range
Hormone panel	Cortisol AM	16.87	166	94.9–619.4 nmol/l
	Serum ACTH	2.38	4.80	1.6–14 pmol/l
	Serum estradiol	18.35	66.51	73–551 pmol/l
	Progesterone	0.159	0.00	6–76 nmol/l
	Follicle-stimulating hormone	0.287	2.33	1.4–9.9 IU/l
	Luteinizing hormone	0.100	1.69	1.7–15 IU/l
	Prolactin	207.1	154.3	70–469 mIU/l
	Human growth hormone	0.088	0.127	0–3.6 ug/l
	Thyroid Stimulating Hormone	2.48	5.469	0.3–5.6 mIU/l
	Free thyroxine	8.57 ≫ 8.73	11.12	10.3–23 pmol/l
	Free triiodothyronine	3.26	4.34	3.1–6.8 pmol/l
	Testosterone	0.087	0.151	0–2.6
	DHEAS	0.354	2.85	0.51–11
Glucose	Glucose Fasting	5.8	5.1	4.1–5.9 mmol/l
	Glycosylated HB	5.7	5.9	4–6%
ACTH Stimulation Test	Cortisol 0 min	50.83	–	171–536 nmol/l
	Cortisol 30 min	88.14	–	171–536 nmol/l
	Cortisol 60 min	110.8	–	171–536 nmol/l
Glucagon Stimulation Test	Cortisol 0 min	–	287	171–536 nmol/l
	Cortisol 30 min	–	482.24	171–536 nmol/l
	Cortisol 60 min	–	433.07	171–536 nmol/l
	Cortisol 90 min	–	334.37	171–536 nmol/l
	Cortisol 120 min	–	444.99	171–536 nmol/l
	Cortisol 150 min	–	333.62	171–536 nmol/l
	Cortisol 180 min	–	213.54	171–536 nmol/l
	GH 30 min	–	0.024	0–5 ug/l
	GH 60 min	–	0.017	0–5 ug/l
	GH 90 min	–	0.019	0–5 ug/l
	GH 120 min	–	0.037	0–5 ug/l
	GH 150 min	–	0.031	0–5 ug/l
	GH 180 min	–	0.027	0–5 ug/l

Notes: Case 1: ACTH stimulation test with peak cortisol of 110.8 nmol/L (a normal response defined as a cortisol level above 500 nmol during any part of the stimulation test) which confirms the presence of secondary adrenal insufficiency. Case 2: Glucagon stimulation showed an inappropriate peak of growth hormone level 0.037 μg/L at 120 min (Normal peak of GH above or equal 7 Ug/L during any part of stimulation test) and a peak cortisol level of 482.24 mmol/L, indicating growth hormone deficiency with an intact adrenal axis.
Abbreviations: CBC, complete blood count; WBC, White blood cell count; RFT, Renal Function Test; ACTH, Adrenocorticotropic hormone; DHEAS, dehydroepiandrosterone sulfate.

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encouraged to do the molecular genetic test at another hospital as it was unavailable at ours, but she declined. A pituitary MRI revealed agenesis of the pituitary stalk associated with a high oval-shaped T1 signal on the sagittal image in the posterior aspect of the pituitary fossa, a finding that is in keeping with posterior ectopic pituitary. In addition, the clivus showed a superior soft tissue band in contact with the sphenoid sinus, with minimal peripheral enhancement (possibly non-fused sphenoid-occipital synchondrosis). Normal homogenous brain parenchyma, normal brain structures, a normal ventricular system, and no mass effect or midline shift were observed (Figure 1). Pelvic ultrasound (US) showed a small uterus and both ovaries were not visualized. A pelvic MRI was done for better characterization which showed small ovaries on both sides of the pelvis, the right one measuring 14×9.2 x 25 mm and the left one measuring 7.8×19.8 x 21 mm; the uterus was not visualized at the expected location, and free trace fluid was seen. The dual-energy X-ray absorption (DEXA) scan revealed a left hip Z-score of −3.6 and a lumbar spine Z-score of −5.2, indicating a low bone mass for the patient's age.

She was treated with hydrocortisone (15 mg in the morning and 5 mg in the afternoon), levothyroxine (50 mcg once daily), estradiol therapy, calcium carbonate and vitamin D supplements, and her symptoms improved significantly. She gained about 4 kg over six months without any episodes of dizziness or hypoglycemia. She also began to develop secondary sexual features.

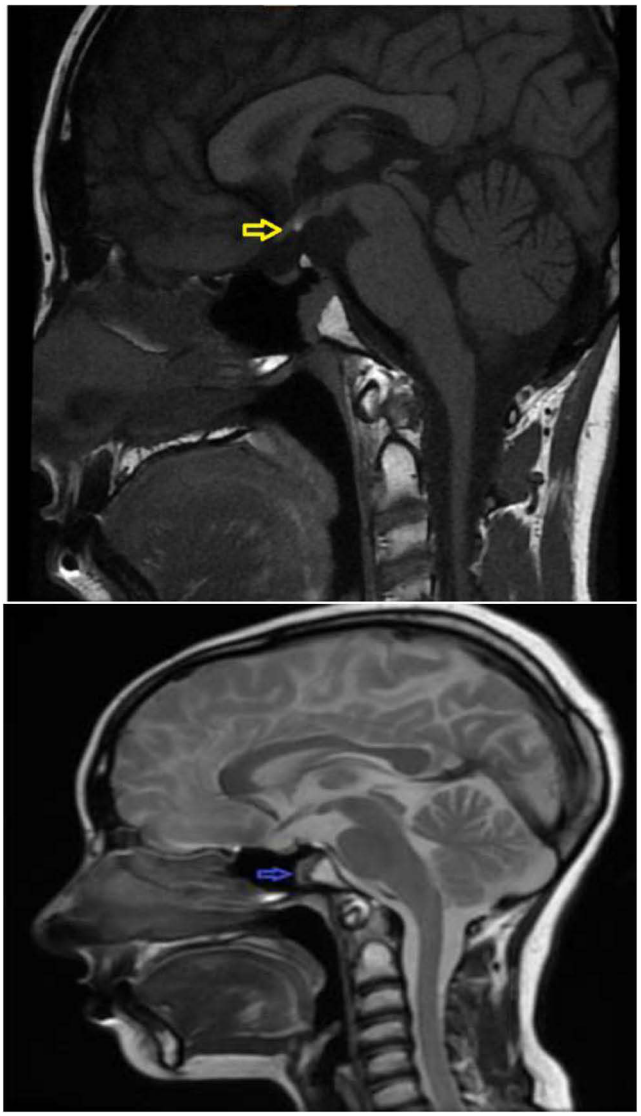

Figure 1 Pituitary MRI Image for Case number 1 revealed agenesis of the pituitary stalk associated with a high oval-shaped T1 signal on the sagittal image in the posterior aspect of the pituitary fossa, a finding that is in keeping with posterior ectopic pituitary (Yellow arrow). In addition, the clivus showed a superior soft tissue band in contact with the sphenoid sinus, with minimal peripheral enhancement (possibly non-fused sphenoid-occipital synchondrosis) (Blue arrow). Normal homogenous brain parenchyma, normal brain structures, a normal ventricular system, and no mass effect or midline shift were observed.

Six months later, she started to have intermittent brownish vaginal discharge. Repeated pelvic US nine months after starting estradiol therapy revealed that the uterus was anteverted, with maximal anteroposterior and transverse dimensions of 5.59×1.97 cm, respectively. The left ovary was 1.64 mL in size and showed normal echogenicity; the right ovary was not seen. Eighteen months later, pelvic US revealed that the uterus is anteverted and measuring 5.56×2.31 cm in maximum length x anteroposterior dimensions, respectively. The endometrial thickness was 10 mm, without obvious sonographic evidence of focal lesions. The right ovary was approximately 1.29 mL in size and showed normal echogenicity. The left ovary was approximately 2.29 mL in size and had normal echogenicity, indicating an increase in size when compared to prior pelvic US.

Case 2

A 19-year-old female presented to the outpatient clinic with secondary amenorrhea for the past 2 to 3 years.

She was born full-term to non-consanguineous parents through a cesarean section with a birth weight of about 3 kg. There were no significant pregnancy or post-partum complications, no history of head injury or trauma, and no family history of a similar condition.

At the age of eight, her parents took her to the pediatric clinic because she was noticeably shorter than her siblings and other schoolchildren. She was diagnosed with GH deficiency based on bone age and a dynamic stimulation test (no accessible report about bone age, IGF-1 or the result of dynamic stimulation test at this age as done in another hospital). She received GH therapy until the age of 16 years with a good response.

Secondary sexual characteristics appeared between 13 and 14 years of age. Her first cycle started at the age of 14 years; she had two periods 6 months apart. Then, she was amenorrheic for 1 year. Because of this, she sought medical advice from a gynecologist and was treated with hormonal replacement therapy for a few months. On physical examination, her vital signs were as follows: a blood pressure of 131/74 mmHg, without a postural drop, a pulse rate of 90 beats/min, a height of 150 cm, a weight of 99 kg, and a BMI of 44. She had breast tanner stage 5 and pubic hair tanner stage 4. There were no dysmorphic features or features suggestive of Turner's syndrome. Other systemic examinations were unremarkable.

A complete blood count was carried out, showing hemoglobin level of 12.6. The lipid profile revealed low-density lipoprotein (LDL) of 3.38 mmol/L, high-density lipoprotein (HDL) of 1.92 mmol/L, and a normal triglyceride level. The 25 OH vitamin D level was 26 nmol/L. The hormonal profile showed low serum estradiol, low progesterone, inappropriate normal FSH, low luteinizing hormone, normal thyroid stimulating hormone, and normal free thyroxine, indicating hypogonadotropic hypogonadism with an intact thyroid axis. Moreover, the Glucagon stimulation test revealed an inappropriate peak of GH 0.037 µg/L at 120 min (normal peak of GH above or equal 7 Ug/L during any part of stimulation test) and the appropriate peak of cortisol about 482.24 nmol/L, indicating GH deficiency with an intact adrenal axis (Table 1).

The pituitary MRI revealed a triad of hypoplastic anterior pituitary, ectopic posterior pituitary with an absent pituitary stalk, and characteristics of pituitary stalk interruption syndrome (Figure 2). Pelvic US showed a uterus of normal size and echogenicity, which is compatible as she had secondary amenorrhea. Both ovaries were normal in size and echogenicity. The DEXA scan revealed a left hip Z-score of −0.8 and a lumbar spine Z-score of −1.7. The patient was referred and encouraged to do the molecular genetic test at another hospital as it was unavailable at ours, but she declined.

She began combined hormonal replacement therapy (Estradiol valerate and Norethisterone 12-14 days per month) with calcium and vitamin D supplements. Also, she was advised to reduce her weight through lifestyle modification. During follow-up, she lost about 5 kg, and Hba1c dropped from 5.7% to 5%. Moreover, she had regular withdrawal bleeding with the hormonal replacement therapy.

Review of the Literature

A literature review was carried out utilizing MEDLINE (PubMed) for similar case reports published between January 2014 and January 2024. The search terms were "pituitary stalk interruption syndrome", "PSIS", and "ectopic posterior pituitary". Furthermore, the reference lists were manually checked to ensure the inclusion of all relevant papers, which revealed 68 cases (Figure 3). Relevant data were extracted from the entire text (Supplementary Table 1).

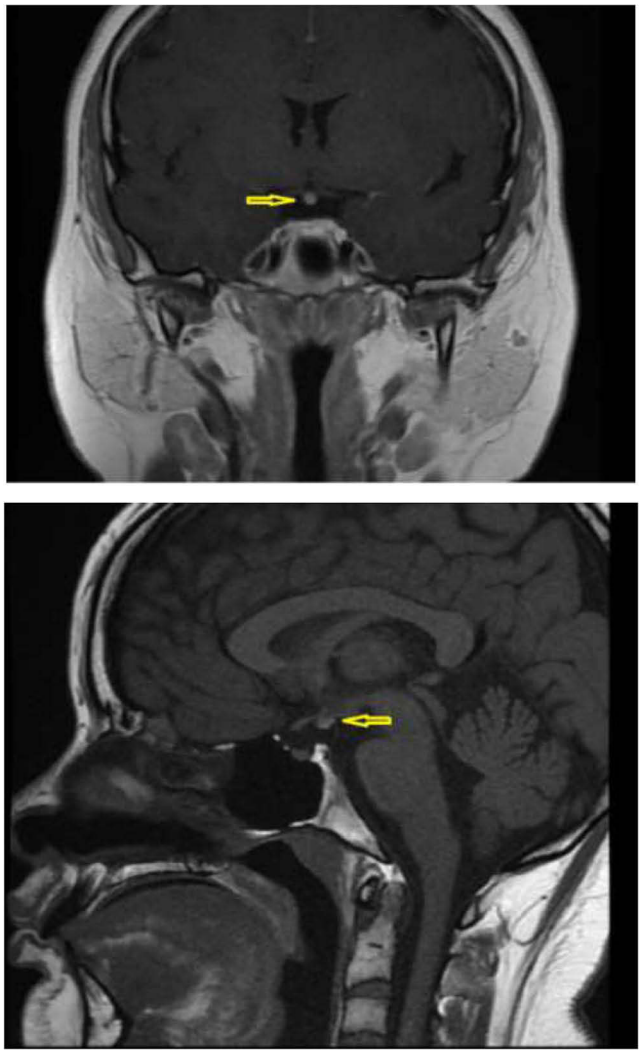

Figure 2 Pituitary MRI Image for Case number 2 revealed a triad of hypoplastic anterior pituitary, ectopic posterior pituitary (Yellow arrow) with an absent pituitary stalk, and characteristics of pituitary stalk interruption syndrome.

Discussion

This report emphasizes the necessity of a hormonal profile in early detection, as well as the MRI to confirm the diagnosis of PSIS. Also, it verifies the previous literature and highlights the need to monitor patients' progress through follow-up sessions to guarantee the best possible outcome.

PSIS is a rare congenital defect of the pituitary gland that is characterized by the triad of a thin or interrupted pituitary stalk, an absent or ectopic posterior lobe, and a hypoplastic or aplastic anterior lobe.[1,2] This characterization has also been broadened to include patients with an absent or thin pituitary stalk with either a nonvisible or hypoplastic anterior pituitary lobe or a nonvisible or ectopic posterior pituitary lobe.[2]

Although the etiology and pathogenesis of PSIS are not yet fully understood, two theories have emerged: perinatal injuries and genetic mutations involved in pituitary development, such as mutations in *HESX1, OTX2, LHX4, SOX3, ROBO1, GPR161*, and *PROKR2*, which have been reported in less than 5% of cases, probably indicating that some genes are still unknown.[2,49,50] In the current literature review, less than one-fifth (14.71%) of all cases were confirmed to have a genetic mutation. However, genetic testing was not conducted for our cases since it was unavailable at our center. In addition, PSIS cases have an increased incidence of perinatal complications, such as a breech presentation, dystocia, a cesarean section, and a low Apgar score.[1,2] Regarding our cases, the first case was born through normal vaginal delivery but with a low birth weight of 1.9 kg, while the second case was born through a cesarean section. Of the 68 cases that were identified in our review, 18 cases (26.47%) were

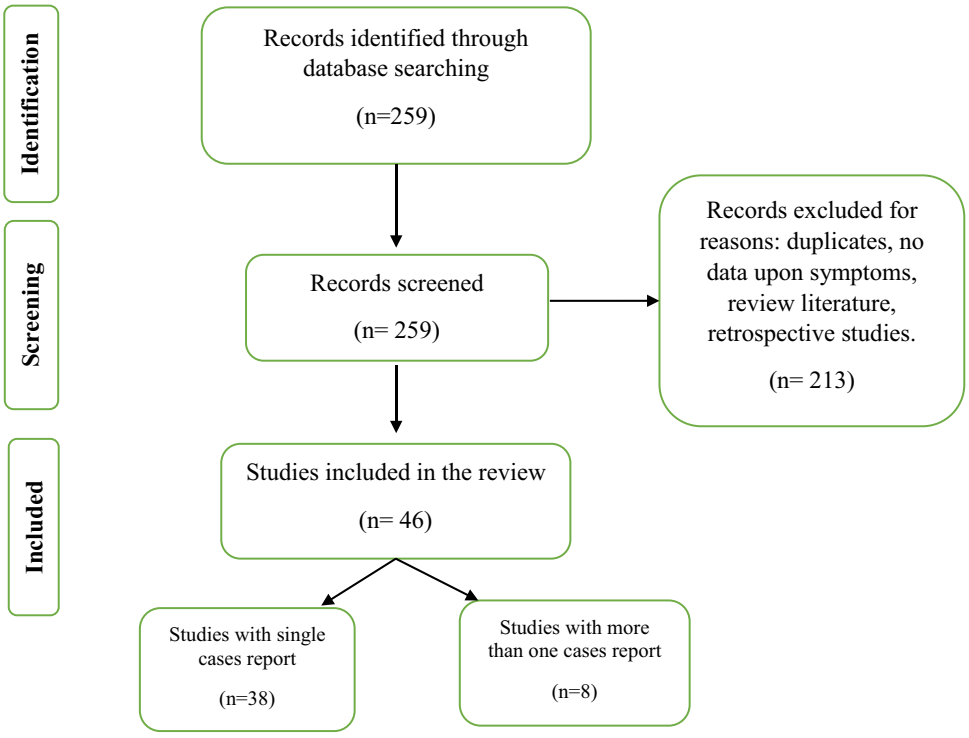

Figure 3 Flowchart studies included in the review.

born through a cesarean section, 12 cases (17.65%) showed a breech presentation, and 11 cases (16.18%) experienced neonatal hypoxia. The hypothalamic pituitary adrenal axis plays a vital role for the fetal lung maturity and initiation of labor (glucocorticoid impact on pulmonary surfactant). The placenta and fetal hypothalamus produce the corticotropic releasing hormone (CRH), which stimulates ACTH release from the pituitary. CRH serves as a vasodilator of fetoplacental circulation and enhances the effects of prostaglandins and oxytocin, which promote myocardial contractility during labor.[51] Therefore, these birth conditions are probably a direct or indirect consequence of hypothalamic-pituitary-adrenal axis dysregulation rather than the cause of PSIS.

The age of diagnosis varies greatly throughout the literature and depends on the degree of hormone insufficiency.[52,53] PSIS is suspected based on clinical findings, and MRI is the key technique for reaching a definite diagnosis.[2,49] During the neonatal period, PSIS patients may exhibit hypoglycemia, prolonged jaundice, and a microphallus and/or cryptorchidism related to hypothalamic-pituitary hormonal deficiency.[42] Later in childhood, growth retardation and short stature are typically observed and delayed puberty is common in adolescence and early adulthood.[42,53] Our first case had an attack of neonatal hypoglycemia that required ICU admission for a few days; later in childhood, she developed short stature; and finally, at the age of 16, she developed symptoms of secondary adrenal insufficiency, including fatigue, dizziness, and hypoglycemia attacks, as well as secondary hypogonadism. The second case presented with short stature in childhood and later developed secondary amenorrhea in adolescence. In our literature review, we found that around half of the total cases had a history of neonatal hypoglycemia (44.12%) and that less than one-fifth experienced neonatal jaundice (14.7%). Additionally, we found that around two-thirds of the cases had short stature (69.12%). Meanwhile, only around one-fifth (23.53%) of the patients were diagnosed during the neonatal period. Based on the literature review PSIS diagnosis is typically challenging and delayed since it is an uncommon condition with a variety of clinical symptoms, signs of PSIS might be overlooked throughout the neonatal period, and clinicians are unfamiliar with the syndrome.

Moreover, PSIS can be associated with extra-pituitary malformations, such as a Chiari I malformation, optic nerve and chiasm hypoplasia, agenesis of the corpus callosum, septo-optic dysplasia, atrial septal defects, and Ventricular septal defects.[54] Some studies found extra-pituitary malformations associated with multiple pituitary hormonal deficiency, while other studies, such as Bar et al,[55] found no association between malformations and hormonal disturbance. In our review, we found that more than one-quarter (29.4%) of the cases had an extra-pituitary malformation and two-thirds (75%) of all

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cases had multiple pituitary hormone deficiency, which emphasized the importance of screening for these malformations. Regarding our case reports, the first case had non-fused sphenoid-occipital synchondrosis on pituitary MRI scans.

PSIS diagnosis reveals a chronic GH deficit.[2,8] In addition, it is essential to determine if it is an isolated GH deficiency or multiple pituitary hormone deficiency. Our first case showed pan-hypopituitarism, while the second case had GH deficiency and, after puberty, developed secondary hypogonadism with an intact thyroid and adrenal axis. This is consistent with what has been documented about PSIS, namely that it shows a progressive worsening of pituitary hormone abnormality, indicating the need for periodic long-term follow-up.[55] Furthermore, before diagnosing PSIS, it is necessary to consider other disorders causing pan-hypopituitarism, such as Sheehan syndrome, where hemorrhagic shock during pregnancy is a key point in diagnosing a female with Sheehan syndrome.[56]

Early diagnosis and initiation of hormonal replacement are crucial for preventing adverse outcomes and improving patients' quality of life.[4] Intellectual delay from thyroid deficit, seizures from hypoglycemia, hypotension from cortisol shortage, short stature, and infertility can all be caused by delayed diagnosis and treatment. As a consequence of all of these risks, PSIS patients have greater rates of death and morbidity than the general population.[52,53] Based on the current review, 80.88% of the patients started with hormone replacement, and 30.1% of these treated cases showed improvement. Therefore, we recommend early diagnosis and long-term follow-up for PSIS patients to assess the whole pituitary axis as PSIS has a progressive course. The frequency of follow-up is determined by the hypothalamic-pituitary axis involved and is typically based on the Endocrine Society recommendations for hypopituitarism therapy.[57] Moreover, we recommend doing early follow-up during dose modification more frequently then once a year following a stable replacement regimen.

It should be noted that our case reports had some limitations such as genetic abnormality could not be ruled out as molecular genetic tests were not done. Also during the literature review, we encountered various limitations, particularly regarding the availability of data. Some of the reviewed studies lacked descriptions of the symptoms, neonatal history, genetic testing, treatment plans, and/or prognosis. As a result, reporting according to the CARE guidelines is critical. Despite these limitations, this paper provided a detailed description of the patient's imaging and clinical features, which could be beneficial in raising awareness and facilitating early PSIS identification.

Conclusion

The key message of this report is that rare etiologies such as PSIS should be kept in mind, especially for young patients presenting with clinical evidence of pituitary hormonal deficiencies, and that pituitary MRI should be considered. To enhance the clinical outcomes of these patients, the early replacement of the deficient hormones and long-term follow-up is required as it is progressive in nature. Moreover, this paper proposed that future studies should focus more on genetic tests to better understand the pathophysiology of this rare syndrome, as well as the urgent need to raise awareness about PSIS among physicians to avoid delays in diagnosis.

Consent for Publication

Patients gave written informed consent for the publication of these cases and images in this journal. Institutional approval from the Dammam Medical Complex research department was obtained for the publication of both cases' details.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no other conflicts of interest in this work.

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