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CASE REPORT

# Clinical analysis of 10 cases of pituitary stalk interruption syndrome and literature review

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## Abstract

**OBJECTIVE:** To analyze the clinical characteristics and MRI imaging of the patients with pituitary stalk interruption syndrome (PSIS) in the First Affiliated Hospital of Anhui Medical University in the past four years, and to achieve better comprehension of this disease.
**METHODS:** Ten patients with PSIS (9 males, 1 female) in our hospital were retrospectively analyzed, regarding clinical manifestation, laboratory data and MRI imaging.
**RESULTS:** The clinical features of 10 cases of PSIS were as follows: growth retardation, 55% of patients with hypogonadism, 45% of patients with short stature; the dystocia rate at birth is as high as 90%, of which 61% are breech presentation and 27% are foot presentation; 10 patients with PSIS, the height was between 135 cm and 180 cm, the weight was between 31 kg and 93 kg, the lower part was larger than the upper part, and the finger distance was smaller than the height; bone age is behind 3~7 years old; normal intelligence; 10 patients have clinical manifestations of hypopituitary hypofunction; no manifestations of diabetes insipidus; MRI imaging of pituitary showed that the pituitary stalks were not shown, atrophy or aplasia of anterior pituitary, posterior pituitary ectopic.
**CONCLUSION:** The incidence of PSIS is low, and the etiology and pathogenesis are unknown. Appropriate hormonal replacement therapy is the only effective way but the timing of treatment is very important. Therefore, clinical doctors should strengthen the awareness of the disease, and master the clinical characteristics of the disease to grasp the timing of treatment.

## INTRODUCTION

Pituitary stalk interruption syndrome (PSIS) is a rare disease, whose clinical symptom is various lacking degrees of the anterior pituitary hormone secretion. On MRI, it has been characterized by absent/slender pituitary stalk, posterior pituitary ectopic and anterior pituitary dysplasia (Xu *et al.* 2019). Because few related studies have been undertaken in China, we summarize and analyze the data (clinical manifestations, medical essay results, medical image tests) from 10 patients with PSIS in the First Affiliated Hospital of Anhui Medical University (AMU). Meanwhile, literature about PSIS has been reviewed, compared with our data to get more understanding of the disease.

## MATERIAL AND METHODS

*General Material*

All 10 patients were tested by both the MRI and the anterior pituitary evaluation. The ratio of male to female in 10 cases is 9:1. Although there is only one teenager among the 10 cases, the average age is so young (21.4 years) that the main problems are growth retardation and puberty delay. Additionally, none of them was born from intermarriage. One patient was prematurely delivered while others were term birth. Moreover, 8 patients were dystocia due to the breech presentation while there is no detailed information about the other 2 cases (Table 1). All of them have normal chromosomes corresponds to their genders. Both chronic diseases and chromosomal abnormalities have not been found.

*Method*

Endocrine function evaluation: GH secretion function: insulin hypoglycemia stimulation test (Regular insulin is set as 0.1 U/Kg. Fasting intravenous injection of 2ml diluted saline. Test the blood sugar and GH at 15 minutes, 30 minutes, 60 minutes and 90 minutes before and after the injection. The hypoglycemia is recognized when blood sugar is lower than 2.8 mmol/L or decreases to 50%). At the same time, we undertook the tests for insulin growth factor-1 (IGF-1). When GH reaches the peak (5 ng/ml) or IGF-1 decline, the patient is diagnosed as the growth hormone deficiency (GHD). Axis function of pituitary-adrenal: measure the blood cortisol and adrenocorticotropic hormone (ACTH) at 0:00 am, 8:00 am and 4:00 pm. (3) Axis function of pituitary-thyroid: measure the thyroid-stimulating hormone (TSH), free thyroxine (FT4), free triiodothyronine (FT3). The hypothyroidism is found when FT4 is lower than 7.9 pmol/L (Koulouri *et al.* 2011).

Hormone determination: Electrochemiluminescence is applied to measure GH, IGF-1 and ACTH cortisol with kits provided by the Roche Group. Additionally, we employed the same approach to quantify the thyroid hormone.

**Tab. 1.** Clinical manifestations of 10 patients

| No. | Gender | Age of onset | Age of diagnosis | bone age | Height at diagnosis (cm) | Body mass index (kg/m$^2$) | Testicular volume (ml) | Penis stretch (cm) | Dystocia history | Pituitary height (mm) |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | M | 13 | 23 | 15 | 151.5 | 22.2 | 2.0 | 3.0 | Breech birth | 2.5 |
| 2 | M | 10 | 18 | 13 | 148.5 | 24.5 | 4.5 | 5.0 | Breech birth | 2.0 |
| 3 | F | 8 | 20 | 12 | 137 | 25.0 | | | | 1.4 |
| 4 | M | 16 | 21 | 17 | 176 | 27.4 | 4.0 | 3.5 | Breech birth | 4.0 |
| 5 | M | 13 | 26 | 16 | 161.5 | 26.1 | 1.0 | 2.0 | Breech birth | 2.5 |
| 6 | M | 7 | 15 | 8 | 135 | 17.0 | 1.5 | 3.0 | Breech birth | 1.2 |
| 7 | M | 10 | 26 | 16 | 170 | 27.7 | 2.0 | 5.0 | | 3.5 |
| 8 | M | 12 | 22 | 14 | 151 | 17.3 | 1.0 | 2.0 | Breech birth | 2.7 |
| 9 | M | 8 | 18 | 15 | 161 | 17.4 | 2.5 | 5.0 | Breech birth | 2.5 |
| 10 | M | 10 | 25 | 15 | 165 | 20.1 | 1.5 | 2.5 | Breech birth | 3.0 |

Notes: M: male, F: female.

**Tab. 2.** Laboratory examinations of 10 patients (thyroid function and function of adrenal cortex)

| No. | FT3 (pmol/L) | FT4 (pmol/L) | TSH (μIU/ml) | ACTH 8Am (pg/ml) | ACTH 4Pm (pg/ml) | ACTH 0Am (pg/ml) | COR 8Am (ng/ml) | COR 4Pm (ng/ml) | COR 0Am (ng/ml) | 24 h UFC (nmol/d) |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 5.13 | 10.55 | 3.66 | 27.9 | 16.5 | 18.9 | 456.6 | 185.6 | 39.6 | 123 |
| 2 | 5.73 | 8.36 | 5.41 | 13.6 | 15.6 | 30.1 | 211.3 | 136.3 | 352.1 | - |
| 3 | 4.57 | 7.97 | 7.91 | 16.6 | 17.7 | 21.6 | 131.2 | 136.6 | 178.9 | 67 |
| 4 | 4.63 | 4.41 | 3.5 | 22.2 | 25.1 | 17.6 | 20.1 | 12.6 | 6.9 | 15 |
| 5 | 4.91 | 4.96 | 5.04 | 11.6 | 11.1 | 10.9 | 132.6 | 85.6 | 61.1 | - |
| 6 | 4.18 | 4.97 | 1.86 | 33.5 | 32.9 | 27.6 | 19.4 | 16.9 | 2.1 | - |
| 7 | 4.84 | 5.12 | 4.04 | 19.2 | 15.4 | 13.0 | 19.9 | 11.4 | 6.5 | 25 |
| 8 | 4.66 | 4.1 | 7.98 | 19.8 | 10.1 | 6.9 | 100.2 | 56.3 | 21.9 | 5 |
| 9 | 5.25 | 7.91 | 0.09 | 12.9 | 10.2 | - | 25.6 | 16.9 | - | - |
| 10 | 7.28 | 12.82 | 0.02 | 14.2 | 19.0 | 8.8 | 14.0 | 12.5 | 5.6 | - |

Notes: FT3: free triiodothyronine 3, FT4: free triiodothyronine 4, TSH: thyroid-stimulating hormone, ACTH: adrenocorticotropic hormone, COR: Cortisol, UFC: Urine free cortisol

Imaging exam: We have undertaken the sellar MRI before and after the injection of the gadopentetate dimeglumine. The bone age and conditions of osteophyte closure are recognized by X-ray on the left wrist joint.

## RESULTS

*Laboratory endocrine examination*

Half of the patients have the hypothyroidism (FT4<7.9 pmol/L). 8 cases are diagnosed as the adrenal insufficiency. All the details have been shown in Table 2. Moreover, the results of all 10 patients show the decline of the gonadotropin, estrogen or testosterone (Table 3). Table 3 also indicates the decrease of the basal growth hormone in all the cases. Some of them have much lower levels compared to peers.

*Endocrine function examination*

GnRH stimulation tests have been performed for all patients to evaluate the reserved function of pituitary secreting gonadotropin cells by measuring the LH. Except for Case 1 and 2, the base value of LH is lower than 0.1 mlU/ml. The curve of LH is flat without any obvious peaks. The maximum LH is just 0.29 mlU/ml, denoting those bad reserved functions (Table 4). Results of growth hormone (GH) shows similar behaviours, obtained by the insulin hypoglycemia stimulation tests (base value is 0.1 u/kg). Curves of GH is flat with a maximum lower than 1.4 ng/ml (except Case 8). All the results are shown in Table 5.

*Imaging examination*

MRI shows that the dysplasia of anterior pituitary with absence or slenderness of pituitary stems and ectopic

**Tab. 3.** Laboratory examinations of 10 patients (gonadal function and growth hormone)

| No. | FSH (mIU/ml) | LH (mIU/ml) | Estradiol (pg/ml) | Progesterone (ng/ml) | Testosterone (ng/ml) | Prolactin (ng/ml) | Growth hormone (ng/ml) | IGF-1 (ng/ml) |
|---|---|---|---|---|---|---|---|---|
| 1 | 2.97 | 1.24 | 36.0 | 0.26 | 0.13 | 5.5 | 0.3 | - |
| 2 | 2.51 | 1.66 | <10.0 | 0.12 | 0.28 | 20.3 | 0.2 | 5.64 |
| 3 | 0.47 | 0.1 | <10.0 | 0.18 | <0.1 | 16.47 | <0.05 | 1.39 |
| 4 | 0.1 | 0.01 | <10.0 | <0.1 | <0.1 | 12.32 | <0.05 | 21.01 |
| 5 | 0.32 | 0.02 | <10.0 | <0.1 | <0.1 | 21.85 | <0.05 | - |
| 6 | 0.27 | 0.04 | <10.0 | <0.1 | <0.1 | 17.28 | <0.05 | 49.6 |
| 7 | 0.52 | 0 | 20.0 | 0.15 | 0.09 | 16.22 | <0.05 | 0.78 |
| 8 | 0.33 | 0.02 | 15.0 | 0.16 | 0.18 | 15.43 | 0.3 | - |
| 9 | 0.99 | 0.05 | <10.0 | <0.1 | 0.17 | 41.15 | 0.3 | - |
| 10 | 0.24 | 0.04 | <10.0 | 0.27 | <0.1 | 6.08 | <0.05 | - |

Notes: FSH: follicle stimulating hormone, LH: luteinizing hormone, IGF: insulin growth factor-1

**Tab. 4.** GnRH stimulation test of 10 patients

| No. | -15′ FSH (mIU/ml) | -15′LH (mIU/ml) | 0′ FSH (mIU/ml) | 0′LH (mIU/ml) | 30′ FSH (mIU/ml) | 30′LH (mIU/ml) | 60′FSH (mIU/ml) | 60′LH (mIU/ml) | 120′FSH (mIU/ml) | 120′LH (mIU/ml) |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 3.53 | 1.22 | 3.84 | 1.08 | 5.05 | 3.74 | 5.94 | 4.71 | 7.05 | 4.55 |
| 2 | 1.73 | 1.17 | 1.75 | 1.18 | 2.34 | 4.18 | 2.61 | 5.06 | 3.00 | 5.92 |
| 3 | 0.44 | 0.03 | 0.46 | 0.07 | 0.93 | 0.17 | 1.09 | 0.22 | 1.48 | 0.28 |
| 4 | 0.14 | 0.01 | 0.12 | 0.02 | 0.17 | 0.02 | 0.22 | 0.01 | 0.24 | 0.01 |
| 5 | 0.3 | 0.01 | 0.31 | 0.01 | 0.92 | 0.1 | 1.12 | 0.1 | 1.68 | 0.11 |
| 6 | 0.24 | 0.05 | 0.27 | 0.04 | 0.46 | 0.07 | 0.57 | 0.11 | 0.38 | 0.11 |
| 7 | 0.44 | 0 | 0.45 | 0 | 0.72 | 0 | 0.94 | 1.14 | 1.04 | 0 |
| 8 | 0.43 | 0.02 | 0.34 | 0.01 | 0.89 | 0.08 | 0.99 | 0.1 | 1.16 | 0.11 |
| 9 | 0.11 | 0.05 | 0.1 | 0.03 | 0.12 | 0.1 | 0.14 | 0.11 | 0.16 | 0.12 |
| 10 | 0.27 | 0.08 | 0.31 | 0.1 | 0.63 | 0.15 | 0.8 | 0.28 | 1.1 | 0.29 |

Notes: GnRH: gonadotropin releasing hormone, FSH: follicle stimulating hormone, LH: luteinizing hormone

posterior pituitary (Fig.1). In Case 2 and 7, partially empty sellar has been found. Moreover, the bone ages are delayed for 2~8 years.

## DISCUSSION

Recently, more understanding of PSIS has been achieved because of the rapid development of MRI. Its MRI results show the absence/slenderness of the pituitary stems and lack of signals of posterior pituitary in the saddle area, while high signal nodules have been discovered in the third ventricular funnel crypt area (Chen *et al.* 1999; Hamilton *et al.* 1998; Wang *et al.* 2014). The PSIS is usually accompanied by the anterior pituitary dysfunction, especially the GH deficiency and hypogonadism. Some patients get a total anterior pituitary dysfunction but a healthy posterior pituitary function without central diabetes insipidus. Previous research (Kyriacou *et al.* 2010) reported that ectopic posterior pituitaries were found in some patients, who were lack of GH.

Currently, the etiology and pathogenesis of PSIS are still unclear despite lots of efforts spent (Wang *et al.* 2017).

**Tab. 5.** Hypoglycemia stimulation test of 10 patients

| No. | 0′Growth hormone (ng/ml) | 15′ Growth hormone (ng/ml) | Growth hormone at hypoglycemia (ng/ml) | 30′ Growth hormone (ng/ml) | 60′ Growth hormone (ng/ml) | 90′ Growth hormone (ng/ml) |
|---|---|---|---|---|---|---|
| 1 | 0.3 | 0.4 | 0.4 (blood sugar-2.2mmol//L) | 0.6 | 0.5 | 0.3 |
| 2 | 0.7 | 0.9 | 1.4 (blood sugar-2.1mmol//L) | 1.2 | 1.3 | 0.6 |
| 3 | <0.05 | <0.05 | <0.05 (blood sugar-2.4mmol//L) | <0.05 | <0.05 | <0.05 |
| 4 | <0.05 | <0.05 | <0.05 (blood sugar-1.8mmol//L) | <0.05 | <0.05 | < 0.05 |
| 5 | <0.05 | <0.05 | <0.05 (blood sugar-2.6mmol//L) | <0.05 | <0.05 | <0.05 |
| 6 | <0.05 | <0.05 | <0.05 (blood sugar-2.3mmol//L) | <0.05 | <0.05 | <0.05 |
| 7 | <0.05 | <0.05 | <0.05 (blood sugar-1.9mmol//L) | <0.05 | <0.05 | <0.05 |
| 8 | 0.3 | 1.2 | 3.0 (blood sugar-2.1mmol//L) | 2.9 | 3.1 | 1.3 |
| 9 | 0.3 | 0.5 | 1.1 (blood sugar-2.2mmol//L) | 1.1 | 0.9 | 0.6 |
| 10 | <0.05 | <0.05 | <0.05 (blood sugar-2.7mmol//L) | <0.05 | <0.05 | <0.05 |

Notes: GnRH: gonadotropin releasing hormone, FSH: follicle stimulating hormone, LH: luteinizing hormone

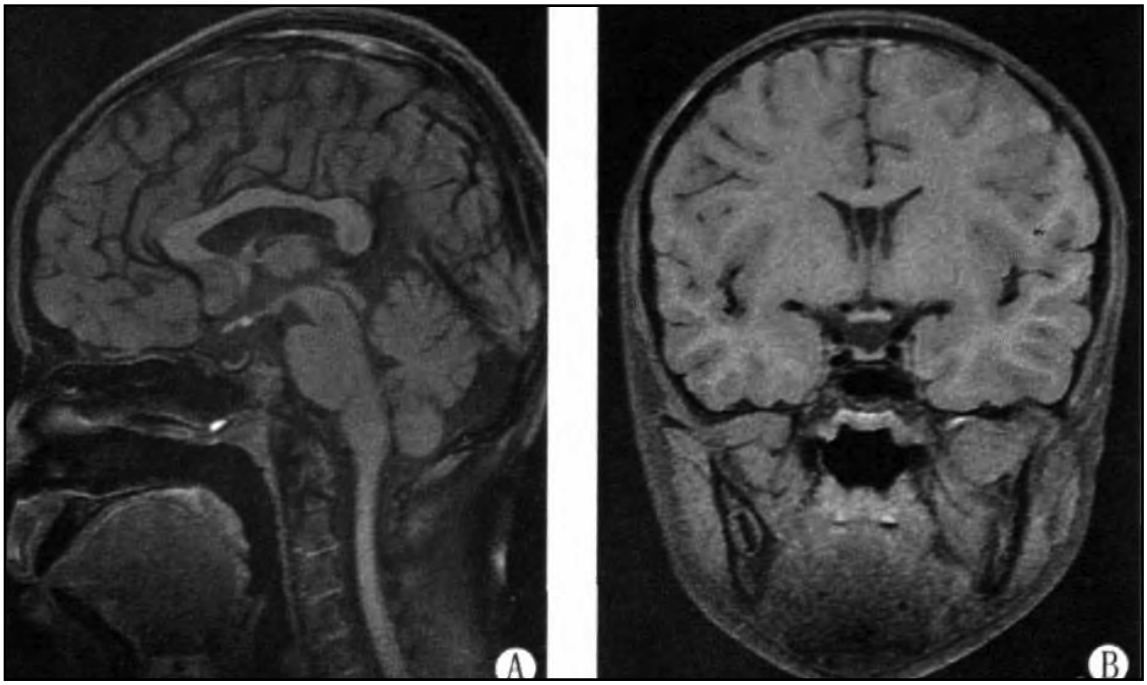


**Fig. 1.** MRI imaging features of pituitary stalk interruption syndrome. On sagittal sequences T1WI plain scan, the hyperintensity of posterior pituitary disappeared, and the ectopic neurohypophysis located in the infundibulum recess of the third ventricle at the bottom of hypothalamus, showing nodular hyperintensity (A). On coronal sequences T1WI, the adenohypophysis became thinner and the pituitary stalk was not shown (B).

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Some researchers thought that there may be a relation between perinatal injuries and PSIS. Some PSIS patients were breech birth. As a result, the probability of dystocia incidence or newborn asphyxia were high. Most of them needed first aid treatments after born. Previous research reported that 70%~80% of infants, who were born with the dystocia due to the beach, had pituitary damage. In our work, 8 of the 10 cases are breach delivery, which is consistent with the findings above.

However, recent studies (Guo *et al.* 2013; Voutetakis *et al.* 2016; Ruszała *et al.* 2019) found that 54% of newborn infants, who had high signals in lateral pituitaries, were born normally. The congenital dysplasia of hypothalamus and pituitaries could lead to unusual motions of fetuses in uteruses, resulting in improper fetal positions. Therefore, this study concluded that PSIS is the reason rather than the result of the breech birth. In other words, gene mutation caused the congenital dysplasia of hypothalamus and pituitaries, which led to the unusual motions of fetuses. Finally breech delivery happened.

Pinto et al (Pinto *et al.* 1997) carried out examinations for 51 PSIS patients, where 4 patients are Familial. 10 case shows small penis and 21 cases are combined malformation. Simon et al (Simon *et al.* 2006) reported that 52% of patients had combined pituitary abnormalities, including some defined syndromes (i.e. Fanconi anaemia, Pallister-Hall syndrome, Currarino syndrome, Stilling-Duane syndrome, and other abnormalities in brains, eyes, craniofacial, hearts, skeletal muscle, kidneys, gastrointestinal tracts or skins). Tauber (Tauber *et al.* 2005) found that, in 35 PSIS patients, 5.7% were cleft lips. 8.6% had rectal stenoses. 39% of male patients had cryptorchidism and 27% got small penises. 20% of patients had hand abnormalities (i.e. bend, multiple, connected figures).

All the cases of PSIS were originated prenatally. But the perinatal events could be the consequences of the dysplasia rather than the cause, while gene mutation was regarded as a possible inducement. Genes that regulate pituitary development and differentiation contain POU1F1、PROP1、HESX1、LHX3、LHX4、SOX3 、OTX2 etc (Reynaud *et al.* 2011; Reynaud *et al.* 2006). Their expression in a certain time and spatial order is crucial to the normal development of the pituitary. For example, genes coding GH and GH releasing hormone receptor (GHRHR) play a very important role in GH synthesis and secretion. Therefore, gene mutation could be one possible reason for the PSIS. Although there are no familial disease histories of PSIS or Congenital pituitary disease in our work, the factor of genes cannot be excluded. Further tests of pituitary differentiation genes are necessary and would become the main point of the next step.

Most PSIS patients have GH deficiency (GHD) possibly accompanied by other multiple anterior pituitary hormone deficiencies. The degrees of these deficiencies are different. Mild patients usually have pure GHD (80% are completed GHD and 20% are partially GHD), while more severe patients show anterior pituitary dysfunction (Tauber *et al.* 2005). Despite the high occupation (35%) of GH cells in pituitaries, they are

easiest to be damaged. So multiple deficiencies often contain GHD (Louvel *et al.* 2009).

Compared with other GHD patients without PSIS, there are no obvious differences in sex ratios, body length and weights at birth, target heights and actual height differences, BMI, IGF-1, actual ages and bone ages. PSIS patients have more severe clinical symptoms, earlier diagnoses, and better (easier) treatments. Coutant et al (Coutant *et al.* 2001) compared clinical features between PSIS patients and GHD ones without PSIS. He found that the formers had earlier diagnosis, lower heights and better(easier) treatments. In our work, it is found that patients with earlier onset have clearer manifestations of GHD. For example, the height is not as good as that of peers at the age of 7~8 years old. There is no obvious secondary sexual development after puberty, especially where 6 of 9 male patients have small penises. Hormone tests show that these patients had completed GH and GnH deficiencies. But TSH and ACTH deficiencies don't exist in all cases (There are not obvious TSH deficiencies in Case1, 2, 3, 9 and 10. No ACTH deficiencies are found in Case 1 and 2). Using the replacements of various anterior pituitary hormones is an effective treatment for PSIS. Note that glucocorticoids should be used earlier than thyroid hormones in patients with ACTH and TSH deficiencies.

Premature use of sex hormones would accelerate the closure of the epiphysis and affects the final height. Therefore, the replacement of sex hormones should be comprehensively evaluated according to the age and height of the patients. GH replacements are be applied to GHD (Hilczer *et al.* 2005).

In summary, the pathogenesis of pituitary stalk interruption syndrome is complex with diverse clinical manifestations. But current treatment effects are promising. It is necessary for clinicians to gain a deeper understanding of the disease to treat patients to achieve a better and healthier life.

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## INFORMED CONSENT

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

## FUNDING

None.

## AVAILABILITY OF DATA AND MATERIALS

The analyzed data sets generated during the study are available from the corresponding author on reasonable request. Inquiries for data access may be sent to the following e-mail address: chmw1@163.com.

## COMPETING INTEREST

The authors declare that they have no competing interests.

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study protocol was approved by the Ethics Committee of the First Affiliated Hospital of Anhui Medical University. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

## CONSENT FOR PUBLICATION

Not applicable.

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