

A case of pituitary stalk interruption syndrome with intermittent seizures as the first presentation

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Abstract

Pituitary stalk interruption syndrome (PSIS) is a congenital disease with isolated growth hormone deficiency (GHD) or multiple anterior pituitary hormone deficiencies (MPHD). The typical clinical manifestations of PSIS are growth retardation, hypoglycemia or delayed pubertal development. However, few reports showed cases of PSIS were diagnosed with acute epileptic seizures accompanied by hyponatremia. Here, we report an 18-year-old female presenting with episodes of intermittent seizures for 13 years. The electrolyte examination on many occasions has shown hyponatremia, even as low as 99.9 mmol/L. However, the cause of hyponatremia has not been further discussed. The patient had short stature and no pubertal development. The laboratory tests revealed growth hormone deficiency, secondary adrenal insufficiency, hypothyroidism and hypogonadotropic hypogonadism. MRI showed an ectopic hyperintense signal of the posterior pituitary and no visible anterior pituitary gland or stalk. The hormone replacement therapy helped to raise the sodium concentration to a normal level and in the termination of seizures.

INTRODUCTION

PSIS is typically characterized by a triad of interrupted pituitary stalk, absent or ectopic posterior pituitary and anterior pituitary hypoplasia or aplasia (Pinto *et al.* 1997). It was first reported by Fujisawa *et al.* (1987) in 1987. The estimated incidence of PSIS is approximately 0.5/100,000 births (El *et al.* 2011). PSIS has gained attention especially with the development of magnetic resonance imaging (MRI). Nevertheless, we still lack adequate understanding of this disease. PSIS critically affects the patients' growth and development as well as the quality of life owing to the significantly high

delayed diagnosis rate. The case we are presenting here had frequent seizures with severe hyponatremia and a delay of 13 years have been made in the diagnosis of PSIS.

MATERIAL AND METHODS

History of illness

The patient, a 18-years-old girl, was admitted to our hospital due to repeated seizure attack for 13 years, growth and developmental delay for 11 years. When she was 5 years old, the patient suffered from generalized tonic-clonic seizures accompanied by hyponatremia in the course of

respiratory tract infections. The symptoms relieved after correcting the electrolyte imbalance. Since then the patient experienced similar symptoms intermittently, especially accompanied with infection. The most frequent attacks were at an hour interval lasting from one minute to up to 20 minutes. Although the patient's health improved by correcting the sodium imbalance and with antiepileptic treatment, what exactly was causing the hyponatremia was never further discussed.

Seven years ago, she went to the local hospital presenting with delayed growth and developmental. She was 116 cm in height and weighted 16.5 kg with no signs of sexual maturation as a 11-year-old girl. Laboratory investigations found, serum total triiodothyronine was 0.84 ng/ml (normal range, 0.87–1.78), total thyroxine 2.09 ng/ml (range, 6.09–12.23) and thyroid-stimulating hormone (TSH) 5.76 μ IU/ml (range, 0.34–5.06). Growth hormone (GH) was 0.006 ng/ml (range, 0.82–5.86). With the GH stimulation test, the peak GH value was less than 5 ng/ml. On head MRI, pituitary height was 3 mm and pituitary area was visible along T1 signal. She was diagnosed with hypothyroidism and growth hormone deficiency thus given levothyroxine and growth hormone replacement therapy as the treatment. Three months after the treatment with injections of growth hormone, she developed facial swelling, so the medication was stopped. Levothyroxine was stopped after six months due to patient's unwillingness to take medicine. To date, she still has neither achieved menarche nor developed secondary sexual characteristics. Her intellectual development had fallen behind her peers. The annual increase in height was less than 3 cm and showed no growth spurt.

Twenty days ago, the patient experienced an acute respiratory tract infection along with nausea and vomiting. She was diagnosed with "bacterial infection" which improved slightly after antibiotics treatment. Seven days ago, the patient suffered from an episode of seizure leading to unconsciousness accompanied with eye rolling, frothing and limb stiffness. The symptoms lasted for about one minute and the patient regained consciousness. So she was taken to local emergency department where the laboratory examination showed serum sodium was 105.7 mmol/L. After intravenous sodium supplementation for five days, serum sodium level increased to 127.3 mmol/L. She was referred to our hospital for further diagnosis and treatment.

Physical examination

A physical examination showed that her temperature was 35.5°C, pulse 66/min and blood pressure 70/40 mmHg. On anthropometric measurements height was 135 cm, upper body segment to lower body segment 0.93, weight 25 kg and body mass index 13.72 kg/m². She was apathetic and showed poorly developed stature and severely undernourished appearance with a pale complexion. She had sparse eyebrows, absent pubic and axillary hair, hypoplasia of the mammary glands.

Past history

The patient was born by a normal delivery and her birth weight was 3 kg. She had no history of the neonatal hypoxaemia or neonatal jaundice.

Familial history

Her father is 177 cm and weighs 75 kg. He started shaving at age 15. Her mother is 167 cm and weighs 55 kg. She attained menarche at age 18. Her sister is 170 cm and weighs 48 kg. She attained menarche at age 14. The patient had no other significant past medical history including history of trauma.

Laboratory and imaging examination

Laboratory tests showed serum cortisol was 2.16 μ g/dl (range, 5–25) and serum adrenocorticotropic hormone (ACTH) 20.2 pg/ml (range, 0–46). Serum free triiodothyronine (FT3) was 1.74 pmol/l (range, 3.5–6.5), free thyroxine (FT4) 3.95 pmol/l (range, 11.5–23.5) and thyroid-stimulating hormone (TSH) 5.119 μ IU/mL (range, 0.3–5.0). The thyroglobulin antibody and thyroid peroxidase antibody were negative. Serum follicle-stimulating hormone (FSH) was less than 0.30 IU/L (range, 2.5–10.2), luteinizing hormone (LH) less than 0.07 IU/L (range, 1.9–12.5) and the gonadotrophin-releasing hormone (GnRH) stimulation test showed the LH secretion curve was low and flat and the peak median value of LH was less than 0.07 IU/L. The serum GH level was 0.05 ng/ml (range, 0.06–5), IGF-1 26.7 ng/ml (range, 111–996) and IGF-BP3 0.56 μ g/ml (range, 2.4–10). Arginine stimulating GH test revealed all times of GH were less than 0.05 ng/ml and the complete growth hormone deficiency (GHD) was diagnosed. Her 24-hour urine volume was 1,200 ml and serum and urine osmolality were 293 mOsm/(kg.H₂O) (range, 275–305) and 670 mOsm/(kg.H₂O) (range, 600–1,000) respectively. Her skeletal development was delayed by 8.5 years with respect to her chronological age as shown in the X-ray. Pituitary MRI confirmed the diagnosis of PSIS, showing no visible anterior pituitary and pituitary stalk and an ectopic hyperintense signal of the posterior pituitary (Figure 1).

Treatment process

When she came to our department, she still had poor appetite, nausea and vomiting. The emergency laboratory test revealed that serum sodium was 116 mmol/L and blood glucose was 3.4 mmol/l. A congenital hypopituitarism and pituitary crisis were suspected. After the collection of the blood sample, hydrocortisone sodium succinate 50 mg was given intravenously every day. Three days later, the symptoms of nausea and vomiting improved and she got a better appetite. She was retested after three days when serum sodium level was found at 135 mmol/L. In accordance with the clinical features, the results of hormone tests and MRI scan, the diagnosis of PSIS was made. Three days later she was given hydrocortisone 20 mg orally per day. Her over-

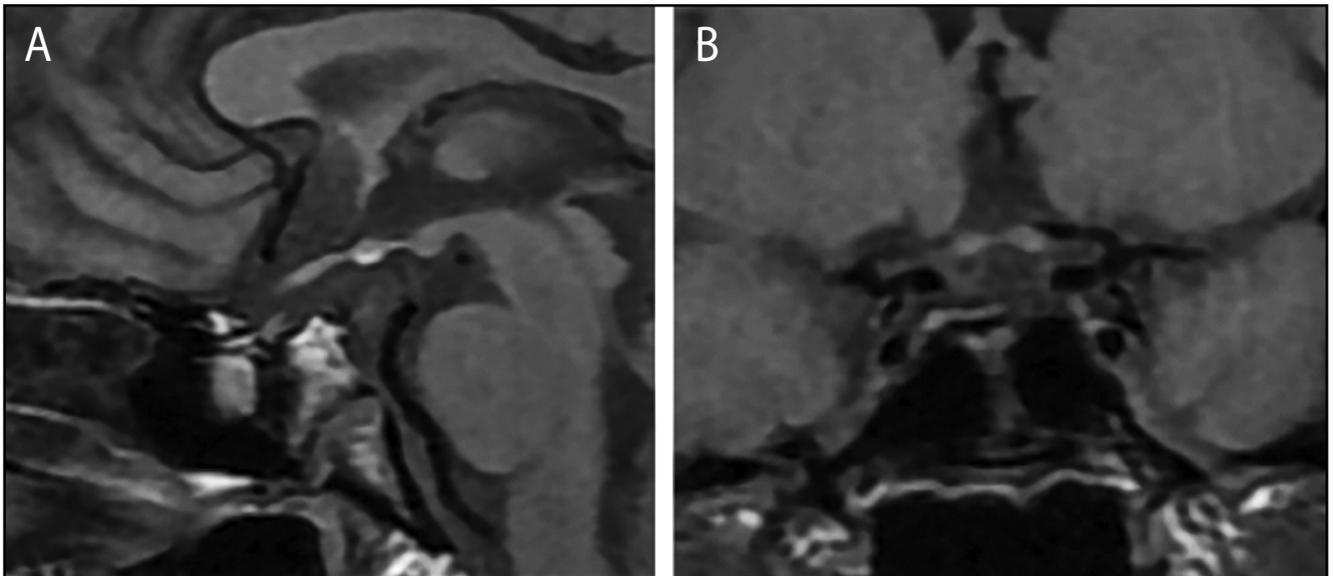


Fig. 1. Pituitary magnetic resonance imaging. A. The sagittal slice shows no visible anterior pituitary. There is an ectopic posterior pituitary at the level of the median eminence with an invisible pituitary stalk. B. The coronal slice shows an invisible pituitary stalk.

all well-being improved and had a good appetite. The blood pressure remained steady at 100/60 mmHg and the sodium level within 142–145 mmol/l. Later, she was treated with levothyroxine replacement therapy and thus her general condition improved. She did not receive growth hormone replacement and no gene testing was done given her low socio-economic status. She received follow-up treatment in our outpatient for the sex hormone replacement therapy.

DISCUSSION

As previously reported, PSIS was a male predominant disease and male-to-female ratio appeared 2.3–6.9:1 (Guo *et al.* 2013). The age for diagnosis of PSIS obviously showed differences among various studies. Wang *et al.* (2015) reported 74 patients of PSIS and the age at diagnosis was on an average 25 years which was apparently more than the age stated in other reports. To some extent, the reason resulting in delayed diagnosis was still the lack of sufficient understanding of this disease.

To date, the underlying mechanisms of PSIS have remained unclear. Classically, it was thought that perinatal injury (such as breech presentation, dystocia and neonatal asphyxia) to the pituitary stalk was the primary cause. Afterwards, some scholars proposed that PSIS was associated with several midline and/or cerebral malformations (Arnold Chiari syndrome, microcephaly and cerebellar or corpus callosum atrophy) and suggested that the disorder in the hypothalamic-pituitary axis during embryonic stage of development may have resulted in malposition of fetus. Therefore, PSIS might be the cause rather than result of delivery modes and/or neonatal hypoxemia (Pinto *et al.* 1997). But approximately half of the patients had no history of

any perinatal injury. Recently, it has been put forward that PSIS was found to be associated with other midline defects during the embryonic period with mutations in critical genes for early pituitary development, such as HESX1, LHX4, SOX3, OTX2 and PROKR2 genes. Although this genetic aetiology is a notable issue, less than 5% of patients with PSIS have been detected with gene mutations until now (Yang *et al.* 2013; Bar *et al.* 2015). On one hand there is a possibility that most of the PSIS patients have not received the gene assessment and on the other hand that most of the genes associated with PSIS have not yet been discovered.

The common modes of presentations with PSIS were growth retardation, hypoglycemia or delayed pubertal development. However, few reports showed cases similar to this patient presenting with acute epileptic seizures with severe hyponatremia. This patient has been suffering from frequent onset of seizures since childhood. On many occasions the electrolyte examination showed hyponatremia in which the serum sodium had been even as low as 99.9 mmol/L. However, the cause of hyponatremia was never discussed further. The symptoms improved after correction of the sodium imbalance with hypertonic saline and antiepileptic treatment. Recently, Nigro *et al.* (2015) performed a prospective observational multicenter study and they found that acute epileptic seizures appeared in 5% of patients with severe hyponatremia. It implies that acute and severe hyponatremia could lead to seizures, which may be the sole clinical manifestation (Nardone *et al.* 2016). Although hyponatremia is very common and has significant clinical relevance, it still has received little consideration. There are several causes of hyponatremia, such as excessive use of diuretics, vomiting, diarrhea, intake of excessive water and so on. But the most over-

looked reason is adrenocortical insufficiency, which is of grave importance as well as alarming. Our patient experienced frequent seizures from childhood. She was admitted to the hospital where the laboratory examination showed hyponatremia. Sometimes she even experienced serious hypotension leading to shock. However, she never received the adrenal cortex function examination despite the symptoms. This is the first reason of a delayed diagnosis. Hence, as suggested by Wójcik *et al.* (2013), multiple pituitary hormone deficiencies must be considered in the prepubertal patients presenting with severe hyponatremia.

Seven years ago, the patient went to the same hospital for further treatment due to her delayed growth and development. Although the growth hormone test showed GH was below normal level, yet the residual pituitary functions have not been evaluated aptly. This is the second important reason for the delay in diagnosis. It is well established that, GH has a close connection with hypothalamus and pituitary. Whether it is the congenital aplasia or acquired tumors or any inflammatory causes, it could result in GHD. For example, PSIS is one of the causes of the GHD. Kyriacou *et al.* (2010) evaluated 23 patients with idiopathic GHD by cranial MRI and found that 46% of the patients had PSIS. Moreover, several large reports of PSIS had shown that the incidence of growth hormone deficiency was 100% (Pham *et al.* 2013; Guo *et al.* 2013; Wang *et al.* 2015). Therefore, the patients accompanied with short stature or GHD should be considered to take cranial MRI examination to exclude PSIS. Besides, an early diagnosis and treatment of PSIS can prevent the patient from developing a permanent short stature (Tauber *et al.* 2005).

Furthermore, the patient should have been diagnosed with secondary hypothyroidism because there was a very low serum thyroxine with a normal TSH level seven years ago, a slip leading to the third reason for a delayed diagnosis. It puts emphasis on the fact that when hypothyroidism is diagnosed clinically, it is very essential to distinguish its type whether primary or secondary. If it raises suspicion of the secondary causes then the residual pituitary functions should be screened. When insufficiency of adrenal cortical function exists simultaneously with secondary hypothyroidism, the replacement of the adrenocortical hormone should be done prior to the supplementation of thyroid hormone.

The patient presented with hyponatremia, hypothyroidism and growth hormone deficiency. Amongst these, the hypothalamus or pituitary abnormality was the most significant cause for suspicion. The MRI report done 7 years ago showed pituitary height was 3mm, vis-

ible pituitary area along T1 signal and an undescribed the pituitary stalk or neurohypophysis. Nonetheless, this may be another reason for the delay in diagnosis 'of the case' as PSIS. MRI is a gold standard in the diagnosis of PSIS and the ectopic posterior pituitary is the hallmark of the disease (Vijayanand *et al.* 2007).

Bar *et al.* (2015) followed 21 PSIS patients with growth retardation ranging from 7.3 to 16.6 years and documented a progressive worsening of the endocrine impairment. Therefore, the regular assessment of pituitary function and long-term follow-up for PSIS patients are very essential.

REFERENCES

- 1 Bar C, Zadro C, Diene G, Oliver I, Pienkowski C, Jouret B, *et al.* (2015). Pituitary stalk interruption syndrome from infancy to adulthood: Clinical, hormonal, and radiological assessment according to the initial presentation. *PLoS ONE*. **10**: e142354.
- 2 El CS, Callier P, Masurel-Paulet A, Bensignor C, Mejean N, Payet M, *et al.* (2011). 17Q21.31 microdeletion in a patient with pituitary stalk interruption syndrome. *European journal of medical genetics*. **54**: 369–373.
- 3 Fujisawa I, Kikuchi K, Nishimura K, Togashi K, Itoh K, Noma S, *et al.* (1987). Transection of the pituitary stalk: Development of an ectopic posterior lobe assessed with MR imaging. **165**: 487–489.
- 4 Guo Q, Yang Y, Mu Y, Lu J, Pan C, Dou J, *et al.* (2013). Pituitary stalk interruption syndrome in Chinese people: Clinical characteristic analysis of 55 cases. *PLoS one*. **8**: e53579.
- 5 Kyriacou V, Mavridou C, Bintoudi A, Tzikos F, Kotziamani N, Tsiouridis I (2010). Pituitary stalk interruption syndrome: The role of MRI and review of the literature. *The neuroradiology journal*. **23**: 607–612.
- 6 Nardone R, Brigo F, Trinka E (2016). Acute symptomatic seizures caused by electrolyte disturbances. *J Clin Neurol*. **12**: 21.
- 7 Nigro N, Winzeler B, Suter-Widmer I, Schuetz P, Arici B, Bally M, *et al.* (2015). Symptoms and characteristics of individuals with profound hyponatremia: A prospective multicenter observational study. *J Am Geriatr Soc*. **63**: 470–475.
- 8 Pham LL, Lemaire P, Harroche A, Souberbielle JC, Brauner R (2013). Pituitary stalk interruption syndrome in 53 postpubertal patients: Factors influencing the heterogeneity of its presentation. *PLoS one*. **8**: e53189.
- 9 Pinto G, Netchine I, Sobrier ML, Brunelle F, Souberbielle JC, Brauner R (1997). Pituitary stalk interruption syndrome: A clinical-biological-genetic assessment of its pathogenesis. *The Journal of clinical endocrinology and metabolism*. **82**: 3450–3454.
- 10 Tauber M, Chevrel J, Diene G, Moulin P, Jouret B, Oliver I, *et al.* (2005). Long-term evolution of endocrine disorders and effect of GH therapy in 35 patients with pituitary stalk interruption syndrome. *Hormone research*. **64**: 266–273.
- 11 Vijayanand P, Mahadevan S, So S, Reddy N, Ramdoss N (2007). Pituitary stalk interruption syndrome (PSIS). *Indian journal of pediatrics*. **74**: 874–875.
- 12 Wang W, Wang S, Jiang Y, Yan F, Su T, Zhou W, *et al.* (2015). Relationship between pituitary stalk (PS) visibility and the severity of hormone deficiencies: PS interruption syndrome revisited. *Clinical endocrinology*. **83**: 369–376.
- 13 Wójcik M, Janus D, Herman-Sucharska I, Starzyk JB (2013). Generalized seizures as the first manifestation of multihormonal pituitary hormone deficiency causing normovolemic hyponatremia. *Am J Case Rep*. **14**: 507–510.
- 14 Yang Y, Guo QH, Wang BA, Dou JT, Lv ZH, Ba JM, *et al.* (2013). Pituitary stalk interruption syndrome in 58 Chinese patients: Clinical features and genetic analysis. *Clinical endocrinology*. **79**: 86–92.