Case Report

Pituitary stalk interruption syndrome. Case report and literature study

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Abstract

Growth hormone deficiency is common, with an incidence of 1-3/10.000 live births. In most children, no cause can be identified and it is called idiopathic. Pituitary stalk interruption syndrome is a congenital anomaly characterized by hypoplasia/aplasia of the anterior pituitary, pituitary-stalk dysgenesis, and/or an ectopic pituitary gland. Growth hormone deficiency is always present. Deficiencies of other anterior pituitary hormones may develop gradually and clinicians should be aware of associated problems to initiate appropriate follow-up and treatment. This paper addresses the importance of early diagnosis of pituitary stalk interruption syndrome by highlighting the symptoms and the need of follow-up. Early treatment of pituitary hormone deficiencies can prevent severe morbidity.

Introduction

Short stature is defined as a height more than two standard deviations (SDS) below the mean for age. The initial evaluation of short stature should include a thorough history and physical examination. Accurate serial measurements, determination of growth velocity, midparental height, and bone age are important to study growth. Short stature can be familial or caused by constitutional delay of growth and puberty. Pathologic causes of short stature include chronic diseases, genetic diseases (e.g. Turner syndrome, Noonan syndrome, Silver-Russel syndrome…), or growth hormone deficiency. The term 'idiopathic short stature' was first used in the 1970s and describes non-syndromic short children with undefined etiology (1).

When diagnosing growth hormone deficiency (GHD), which can be congenital or acquired, further radiologic and endocrinologic assessment is necessary (2). Pituitary stalk interruption syndrome (PSIS) is a congenital disorder with a marked phenotypical heterogeneity. The hormonal profile, age, and associated abnormalities determine the patients' clinical picture (3).

PSIS belongs to the spectrum of midline malformations and is often associated with other midline extra-pituitary malformations. Other deficiencies may develop over time and result in panhypopituitarism (4-7).

In this paper, we present a patient with short stature, a stagnating growth curve, and episodes of asthenia, pallor, excessive sweating, somnolence, and abdominal pain. After confirmation of growth hormone deficiency, central imaging was performed and showed an interrupted pituitary stalk, hypoplastic anterior pituitary, and ectopic posterior pituitary. The diagnosis of PSIS was made.

Case report

A 4.2-year-old boy was referred to the general pediatrics outpatient clinic for growth retardation and short stature. He was born at 37+4/7 weeks of gestation after an uncomplicated pregnancy and delivery.

Weight, length, and head circumference at birth were 2950 grams (standard deviation score (SDS) 0.8), 48 cm (SDS -1.1) and 35 cm (SDS 0.0). The neonatal period was uncomplicated except for a period of transient hypothermia (35.5°C). Episodes of pallor, excessive sweating, somnolence, and abdominal pain since the age of 2 were reported.

At the age of 4.2 years, his height was 92 cm (-3.2 SDS), far below the target height (0.5 SDS). His weight was 12.4 kg (-3.2 SDS) and head circumference was 49.8 cm (-0.3SDS). The growth chart showed a growth retardation from the age of 10 months onwards (Fig. 1A). No dysmorphic features nor other abnormalities were noted at clinical examination.

Hormone blood levels showed the following results: undetectable IGF-1 (<35 µg/L), IFGBP-3 1046 g/L (normal value >1177 g/L), thyroid stimulating hormone (TSH) 1.83 mIU/L (0.27- 4.20 mIU/L), free T4 16.7 pmol/L (12.9-23.2 pmol/L), adrenocorticotropic hormone (ACTH) 21.9 ng/L (10.0-60.0 ng/L), morning cortisol 9.3 µg/dL (6.2 – 18.0 µg/dL), LH 0.3 IU/L (1.7 – 8.6 IU/L), FSH 0.3 IU/L (1.2-7.7 IU/L), and prolactin 10.4 µg/L (2.0-18.0 µg/L). The X-ray showed a bone age (according to the Greulich and Pyle method) delayed by 1 year (bone age of 2.84 year for a chronologic age of 3.86 year) (Fig 1B).

A glucagon challenge test was performed. The peak serum GH concentration was 2.5 ng/mL at 90 minutes which was compatible with GHD (normal value >7.5-10 ng/mL) (6). The maximal cortisol response was 14,2 µg/dL. An episode of pallor, excessive sweating, somnolence, and abdominal pain was observed during the challenge test. A hypoglycemia of 39 mg/dL was measured at that moment, for which a bolus of glucose 5% was administered with subsequent normoglycemia.

Magnetic resonance imaging (MRI) revealed an interruption of the pituitary stalk, ectopic posterior pituitary, and hypoplastic anterior pituitary, prompting the diagnosis of PSIS (Fig 1C). Additionally, hypoplasia of the optic tract was diagnosed. An additional ophthalmological evaluation was performed but was normal apart from myopia for which glasses were prescribed. Genetic analysis was requested but is still ongoing.

Recombinant GH therapy was initiated with an obvious improvement in both height and weight. The episodes of asthenia, excessive sweating, and somnolence disappeared.

Discussion

PSIS is a congenital pituitary abnormality with a heterogeneous clinical presentation. Due to the low number of reported cases, the exact incidence is difficult to determine. An estimated prevalence of 6.8% PSIS in the population with diagnosed GHD has been reported (n=1019/15043) (7). The etiology of PSIS has not yet been completely elucidated. Molecular defects in genes involved in pathways critical during early embryogenesis might play a role. Pathogenic mutations have been described in the POU1F1, PROP1, HESX1,

LHX3-4, SOX1-3, OTX2-3, POKR2, TGIF, GPR161, CDON, GLI1-2, OTUD4, and ROBO2 genes (1). Novel variants in candidate pathogenic genes of the hedgehog pathway (PTCH1, PTCH2…) have also been proposed (2). A polygenic and multifactorial etiology of PSIS has to be considered, because only 5% of cases can be explained by Mendelian heredity (3). Genetic analysis was requested in our patient but is still ongoing.

The clinical presentation of PSIS is variable and depends on the time of presentation, the hormone profile, and the associated abnormalities. A severe and permanent GHD is always present (3).

Hypoglycemia, prolonged hyperbilirubinemia, cryptorchidism, and/or a micropenis are frequent neonatal presentations of a pituitary disorder. Due to the regular isolated occurrence of these problems in otherwise healthy neonates, the correct diagnosis is often postponed. One clinical study described that in patients diagnosed with PSIS during adolescence, (missed) signs had already been present at neonatal age in 30% of cases (n=14/47) (4). Older patients are usually diagnosed within the context of growth retardation and short stature. Other possible causes of a growth retardation (e.g., disorders in another organ system, allergy, malabsorption, nourishment difficulties, abuse,...) have to be taken into account in the differential diagnosis.

The GH axis is the first pituitary axis to fail. Afterwards, multiple hormonal defects (MHD) and even panhypopituitarism develop while the function of the posterior pituitary is usually preserved. A retrospective longitudinal study following disease progression in 67 patients with PSIS over a period of 20 years (1984-2014) confirmed the regression of residual pituitary function (4). This failure of the various axes does not occur in a set order but some deficiencies are more common: failure of thyroid hormones (70.3-79.8%) is the most prevalent, followed by failure of the gonadotropin hormones (65.1%-97.2%) and ACTH (65.1%-97.2%) (5,8-9). Both hyper- and hypoprolactinemia may occur. The majority of patients have normal levels of antidiuretic hormone. At the age of 4 years, our patient only had an isolated GHD. The diagnosis of growth hormone deficiency (GHD) is a challenge due to the lack of a true gold standard (10). Provocative GH tests continue to play a primary role in the diagnosis of GHD but are invasive, take 2–4 hours in duration, and have potential risks and side effects. A peak stimulated GH of less than 10 µg/L is the usual cut-off for GH deficiency in children in the United States, whereas European countries employ cut-offs as low as 6 µg/L. Two separate growth hormone provocation tests are often advised for a definitive diagnosis. In our patient, only one provocation test was performed as hypoglycemia occurred and an MRI had already confirmed the diagnosis.

MRI is essential for the definite diagnosis of PSIS, to visualize interruption or severe hypoplasia (<1 mm) of the pituitary stalk, hypoplasia/aplasia of the anterior pituitary, and/or an ectopic posterior pituitary. Isolated agenesis or ectopia of the posterior pituitary is not a pathognomonic sign of PSIS.

PSIS can be situated within the spectrum of midline defects, as the genes with pathogenic mutations are described as playing a role in the organogenesis of multiple midline structures. The initial presentation may therefore be based on associated congenital abnormalities such as an unusual facial phenotype (sparse hair, frontal bossing, hypertelorism, broad nasal root, prominent philtrum, cheilo-/palatoschisis, retrognathia, single median incisor) (Fig 2) and central nervous system defects (microcephaly, hydrocephalus, cerebellar atrophy, septo-optic dysplasia, corpus callosum agenesis, cerebellar vermis atrophy, Arnold-Chiari I malformation, aquaeductal stenosis, optic tract hypoplasia, coloboma of the retina). Other syndromes such as CHARGE syndrome and Fanconi anaemia are also associated with PSIS (11). (Table 1) It is unclear whether the presence of associated abnormalities increases the likelihood of developing MHD, (4,9). Clinical follow-up and measurement of hormone levels thus remain of utmost importance.

GHD is treated with daily subcutaneous injections of recombinant GH (0.025 - 0.032 mg/kg/day). The patient's height at the beginning of treatment and the growth rate in the first year after starting treatment are two favorable factors that determine the final height (6,11). Our patient showed an obvious improvement in both height and weight curves. There were no more episodes of asthenia, excessive sweating, and somnolence, which had probably been caused by hypoglycemia. It is known that hypoglycemia can occur in GHD due to increased insulin sensitivity and changes in gluconeogenesis.

Table 1: *Clinical manifestations and hormonal status in patients with PSIS*

Dysmorphic features	Sparse hair, broad forehead with frontal bossing, hypertelorism, broad nasal root, prominent philtrum, cheilo-/palatoschisis, microphthalmia, anophthalmia, single median incisor, bulbous nasal tip, thin upper lip, and retrognathia
Puberty and sexual development	Delayed or absent puberty, micropenis
Hormonal status	GH deficiency, TSH deficiency, LH/FSH deficiency, ACTH deficiency, ADH deficiency, hypoprolactinineamia and hyperprolactinaemia.
Central malformations	Microcephaly, hydrocephalus, cerebellar atrophy, cerebellar dysgenesis, septo-optic dysplasia, corpus callosum agenesis, abnormality of septum pellucidum vermis atrophy, Arnold-Chiari I malformation, septal agenesis, aqueductal stenosis and optic tract hypoplasia, coloboma of the retina, craniopharyngeal canal, holoprosencephaly, bilateral perisylvian polymicrogyria
Other	Cryptorchidism, neonatal hypoglycemia and hyperbilirubinemia, Pallister-Hall syndrome, Stilling Duane syndrome, CHARGE syndrome, Rieger syndrome, Fanconi anemia, epilepsy, intellectual disability, strabismus

If ACTH or TSH deficiency is confirmed, administration of hydrocortisone (8-15 mg/m^2/day) or L-thyroxine (1.5-2.0 µg/kg/day) is required. Glucocorticoids must be substituted first before starting L-thyroxine, because an euthyroid status may destabilize a patient with ACTH deficiency. For dose adjustment, blood tests to determine end-organ and pituitary hormones are carried out at regular intervals, taking diurnal variation into account.

Conclusion

PSIS is a congenital disorder with marked phenotypical heterogeneity. The hormone profile, age, and associated abnormalities determine the clinical picture but the majority of children presents with short stature. Children with GHD are recommended to undergo a thorough neuroradiographic and endocrine evaluation. Characteristic radiological features of PSIS are an interrupted pituitary stalk and a hypoplastic or aplastic anterior pituitary. The posterior pituitary may be absent or ectopic. Several pathogenic and candidate genes have been proposed but polygenic and environmental factors are both likely to play a role in the pathogenesis.

In addition to GHD, other hormone deficiencies may also occur (TSH deficiency, ACTH deficiency, gonadotropin deficiency etc.) in various degrees of severity, but since pituitary function tends to deteriorate in PSIS, rigid follow-up is necessary.

Conflict of interest

The authors of this article declare that they have no conflict of interest. They do not have any affiliation with or involvement in any organization or entity with a financial or non-financial interest in the subject matter or the materials discussed in this case report.

Figure 1 : *Figure 1A. Height and weight curves of the patient. Downward sloping starts from age of 10 months onwards, and height is far below the target height (183.5 cm). Recovery of the downwards slope after administering replacement growth hormone at the age of 4 years and 3 months. B. X-ray of the left hand: delayed bone age of 1 year (according to the Greulich and Pyle method). C. MRI of the pituitary: T1 weighted image with confirmation of PSIS. The yellow arrow indicates an interrupted pituitary stalk, the white arrow the hypoplastic anterior pituitary, and the green arrow the ectopic posterior pituitary.*

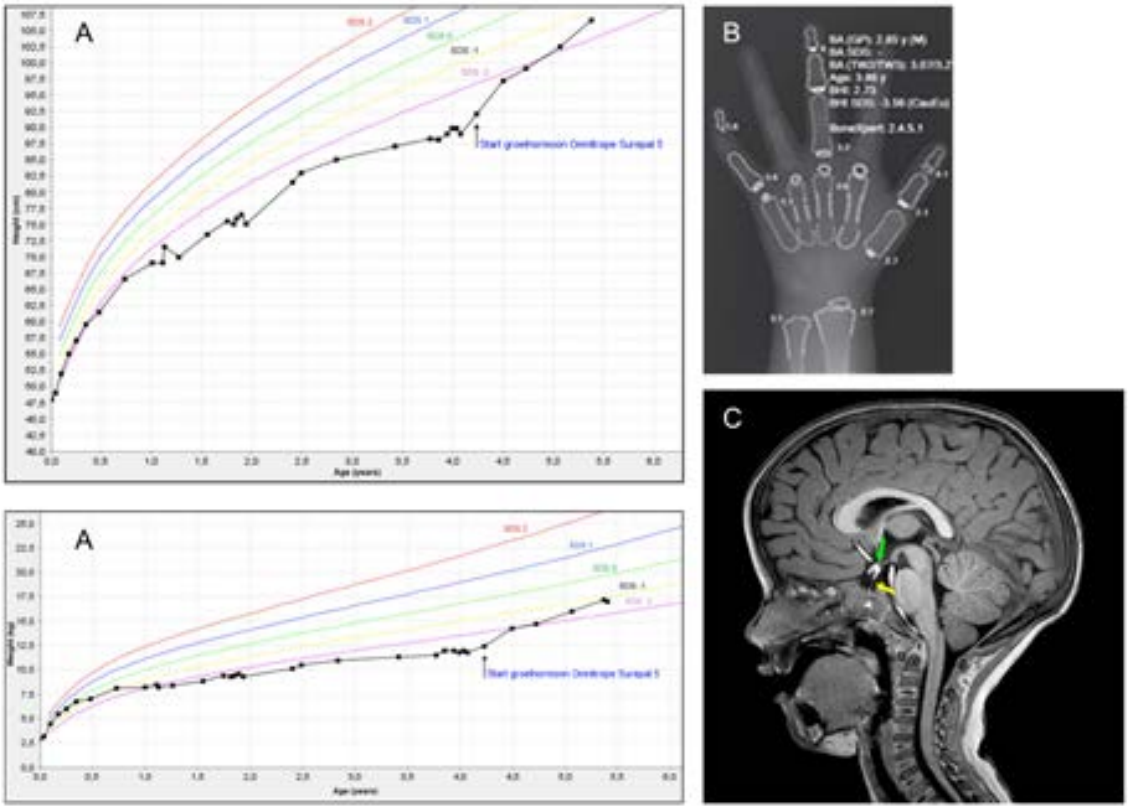
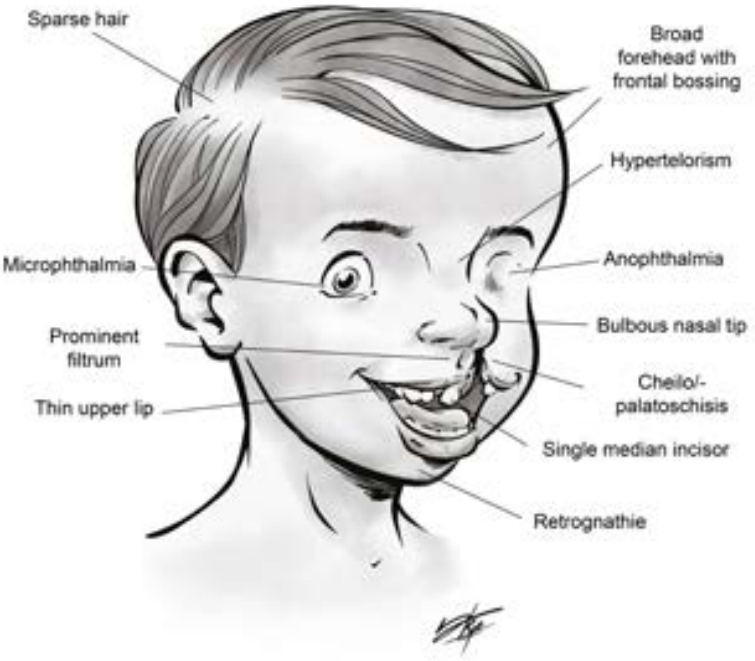


Figure 2 : *Dysmorphic facial features matching PSIS*



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