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Undescended Testicles and Short Stature as Manifestation of Pituitary Stalk Interruption Syndrome

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Running Title: Pituitary Stalk Interruption Syndrome

Abstract: ***A rare congenital abnormality, Pituitary Stalk Interruption Syndrome (PSIS) is characterized by the deficiency of the isolated growth hormone or multiple deficiencies of the anterior pituitary hormone. In this report, a case of PSIS from Saudi Arabia is presented. On an encouraging note, individuals with this condition have excellent chances of reaching normal height, if they receive treatment before the union of the epiphyses.***

Keywords: Growth hormone, congenital abnormality, pituitary stalk Saud Arabia

1. Introduction

During the development of the pituitary, the embryonic oral and neural ectoderm undergo a complex process in order to form the functional and distinct anterior and posterior lobes. Over the past few decades have a clearer understanding regarding several characteristics of pituitary embryogenesis has been achieved [1]. Pituitary Stalk Interruption Syndrome (PSIS) is an abnormality of the pituitary gland of congenital origin, with the typical triad of features, such as the pituitary stalk which is very thin or interrupted, the posterior pituitary which is either misplaced (ectopic) or absent and the anterior pituitary which is small or completely lacking, and deficiency of the permanent Growth Hormone (GH) [2]. This classic triad of abnormal structures, namely pituitary stalk which is interrupted, posterior pituitary which is either ectopic or absent, and anterior pituitary with hypoplasia or aplasia is typical of PSIS [3]. The age at the time of diagnosis determines the clinical presentation of PSIS. This is evident in neonates, in the form of neonatal hypoglycemia, prolonged neonatal (physiological) jaundice, cryptorchidism, and micropenis. Older children and adults are characterized by the shortness of their stature [3].

Although the frequency of PSIS in the populace is not precise, a recent publication revealed an incidence of approximately 0.5 in every 1, 000, 000 births [3, 4]. During the neonatal stages, patients with PSIS exhibit hypoglycemia, prolonged jaundice, congenital abnormalities, microphallus, and/or cryptorchidism, all of which are indicative of hypothalamic - pituitary deficiencies [5]. The PSIS is also linked to breech presentation, Cesarean section and/or low Apgar scores, in more than the normal prevalence. However, the conditions of birth are more likely a result than the reason for the PSIS. Signs which appear later in childhood indicative of PSIS include stunted stature, lowered growth rate and/or an inconsistency between the target height and actual tallness attained [6].

The indicators of PSIS include the presence of a pituitary stalk, which is either very slender or altogether lacking, as well as hypoplastic adenohypophysis and ectopic neurohypophysis. The occurrence of PSIS is understood to be caused by either mutations of the genes concerned with pituitary embryogenesis (PROP1, LHX3, HEXSX1, PROKR2 and GPR161) or perinatal asphyxia. Besides, PSIS can be expressed as hormone deficiencies of the anterior pituitary (growth hormone, 100 %; gonadotropin, 97.2 %; corticotropin, 88.2 %; and thyrotropin, 70.3 %) [7]. The present report is from Saudi Arabia, regarding a patient with PSIS.

2. Clinical Case

A 16 - year - old Saudi male presented to the endocrine clinic having the characteristics of shortness of stature and undescended testes, status post bilateral orchidopexy. Due to breech presentation and birth asphyxia this boy was delivered via Cesarean section. From a detailed investigation it was evident that his secondary sexual characteristics were underdeveloped, and he had reduced growth of facial and pubic hair. The patient revealed a height of 134 cm, although the bone age was in the range of 9 - 11 years. On pelvic examination, the scrotum with bilateral 1 mL testes was observed, and 3 cm Stretched Penile Length (SPL).

On laboratory investigation, the patient revealed hemoglobin of 13 g/dL, serum sodium of 140 mmol/L, serum potassium of 4.1 mmol/L, serum chloride of 102 mmol/L, calcium of 9.1 mg/dL, random blood sugar of 110 mg/dL and albumin of 3.8 mg/dL. Hypopituitarism with thyroid and adrenal sparing was evident on the pituitary hormone profile. The free T4 was 17.3 pmol/L (9 - 25 pmol/L), while the Siachen test showed the baseline cortisol level (in the morning) of 6.5 go/dL (normal = 4.3 - 22.4 ug/dL) with the adrenocorticotrophic hormone of 9.8 pmol/L (1.1 - 13.2 pmol/L), all of which were recorded for this patient. Besides, the level of the insulin - like growth factor 1 was 50 ng/dL (normal = 193.0 - 731.0 ug/L), follicle - stimulating

hormone was 0.35 µIU/mL (normal, 0.0 - 10.0), and luteinizing hormone was 0.4 µIU/mL (normal = 1.2 - 7.8).

The morning testosterone level of the patient was 8 ng/dL (normal = 280 - 800 ng/dL) and prolactin 116 mIU/L (normal = 86 - 324 mIU/L). No symptoms implying posterior pituitary involvement such as polyuria - polydipsia syndrome, or urine and serum osmolality were noted. From an examination of the MRI, neither could the pituitary gland be observed in the sella turcica, nor was there evidence of a clear pituitary stalk. Just posterior to the optic chiasma the T1 hyperintense focus was clearly identified through post - contrast enhancement, indicating the presence of an ectopic posterior pituitary gland. To the patient's medical therapy, additional therapies were included in terms of growth hormone and testosterone therapies, and neither thyroid or nor hydrocortisone replacement therapy was provided.

3. Discussion

This genetic disease, PSIS, is related either to the isolated Growth Hormone Deficiency (GHD) or Multiple Anterior Pituitary Hormone Deficiencies (MPHD) –the Growth Hormone Deficiency linked to this abnormality involves at least one or another of the hormones of the anterior pituitary, but with normal functioning of the hormones of the posterior pituitary [8]. There is a two - fold significance in diagnosing the pituitary hormone deficiencies, well in time. First, if left untreated there is high risk of mortality and morbidity. Second, inadequate height during the onset of puberty will result in shortness of the final height. Therefore, early diagnosis and treatment of the GHD is crucial in the promotion of growth to achieve normal height prior to attaining puberty [4, 9]. In this context, we include a report on a PSIS case from Saudi Arabia.

As the reported PSIS cases are rather few in number, the clinical expressions of this disease are both complex and diverse. In neonates, the commonest presentations include prolonged neonatal jaundice, hypoglycemia, cryptorchidism, and micropenis. However, growth retardation is the most frequent presentation in older children and adults. Most patients lack sexual development [8]. Investigation of the patient revealed underdeveloped secondary sexual characteristics, with decreased facial and pubic hair growth. Earlier studies stated that treatment was based on the replacement of deficient hormones, particularly GH, thyroxine, hydrocortisone and, at puberty, sex steroids. If the diagnosis of PSIS can be done at birth, hypoglycemia and secondary adrenal deficiency and other related cerebral and vital risks can be avoided [3].

At the time of diagnosis, the age of the patient, shows variation in the literature [4]. In this study, the patient at the time of diagnosis was 16 years old, which exceeds the 3.6 years, the mean age reported by Gascoin - Lachambre et al., [10], the 4.0 years stated by Pinto et al., [11] and the 9.6 years cited by Reynaud et al. [12]. If timely diagnosis and treatment are started, the prognosis is good. However, any setback in the diagnosis and treatment may cause seizures in the patient due to hypoglycemia and/or hypotension induced by cortisol deficiency, and/or intellectual delays because of thyroid deficiency. These risk factors raise the mortality and morbidity in patients with PSIS to a greater extent than in the general populace, most often occurring before two years of age is reached [13].

From earlier studies it is evident that the ACTH values and cortisol levels post the stimulation tests show significant reduction in individuals with PSIS, when compared with CPHD patients possessing a visible pituitary stalk [14]. To date, the etiology continues to remain unknown. However, gene - environment interaction is most likely responsible for this disease. The GH has a vital part to play in the growth stage. However, several other hormones too can influence the growth [3]. According to Zhang, individuals with PSIS revealed symptoms caused by the deficiency of the anterior pituitary hormones, like the growth hormone (GH; 100%), gonadotropin (86.52%), corticotropin (75.28%), and thyrotropin (79.78%). These deficiencies produced the characteristic features of short stature, cryptorchidism, micropenis, delayed puberty, hypoglycemia, and central hypothyroidism [15]. In the present case, the adrenocorticotrophic hormone level of the patient was 9.8 pmol/L (1.1 - 13.2 pmol/L); the insulin - like growth factor 1 was 50 ng/dL (normal = 193.0 - 731.0 ug/L); the follicle - stimulating hormone was 0.35 µIU/mL (normal, 0.0 - 10.0), and the luteinizing hormone was 0.4 µIU/mL (normal = 1.2 - 7.8). The morning testosterone level of the patient was 8 ng/dL (normal = 280 - 800 ng/dL), while the prolactin was 116 mIU/L (normal = 86 - 324 mIU/L).

4. Conclusion

Although PSIS is a rare genetic disorder, it must always be included in the differential diagnosis of a patient who is short in stature. However, individuals with this disease have excellent chances of achieving normal height if they present to the hospital prior to the union of the epiphyses. Besides, when health care professionals, patients, and caregivers are educated regarding this rather uncommon condition, it raises the possibility of early diagnosis and immediate intervention, which can go along way in minimizing the mortality risks.

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