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Delayed Growth and Puberty Revealing Pituitary Stalk Interruption Syndrome Seen at Befelatanana University Hospital in Antananarivo, Madagascar (Case Report)

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Abstract: Pituitary stalk interruption syndrome (PSIS) is a rare pathology characterized by a triad associating a thin or absent pituitary stalk, small anterior pituitary gland and ectopic posterior pituitary location on pituitary MRI. It is responsible for global or selective impaired production of anterior pituitary hormones. This case concerns a PSIS discovered in 16 years old boy with delayed growth and puberty, bilateral cryptorchidism treated by orchiopexy and asthenia. His personal history was marked by a breech birth with retention of the after-coming head and neonatal asphyxia. The examination revealed a short stature and the lack of signs of puberty, without associated malformation. Biologically, the plasma IGF-1 level was low at 17.6 ng/ml, the plasma total testosterone level was less than 0.4 nmol/l, the plasma FSH level was low at 0.38 mIU/ml, the plasma LH level was less than 0.12 mIU/ml, plasma cortisol level at 8 am was low at 0.6 µg/dl and the plasma TSH and T4L levels were normal. These abnormalities are in favor of somatotropic, gonadotropic and corticotropic insufficiencies. Posterior pituitary's function appears intact. Pituitary MRI shows a pituitary stalk interruption syndrome. Androgen and glucocorticoid supplementation was initiated. Recombinant growth hormone is not available. Thus, any delays in growth and/or puberty must be carefully explored and managed early, with a multidisciplinary approach to improve patient's vital, statural and reproductive prognosis.

Keywords: Anterior Pituitary Hormones, MRI, Growth, Puberty, Pituitary Stalk Interruption Syndrome (PSIS)

1. Introduction

Pituitary stalk interruption syndrome (PSIS) is a rare pathology characterized by a triad associating a thin or absent pituitary stalk, small anterior pituitary gland and ectopic posterior pituitary location on pituitary Magnetic Resonance Imaging (MRI) [1]. Its incidence is estimated at 1 in 200,000 births [2]. This is one of the causes of pituitary insufficiency due to a defect in the stimulation of the pituitary gland by hypophysiotropic factors produced by the hypothalamus. This results from a disruption of functional connections between the hypothalamus and the anterior pituitary [3]. The clinical consequences are those of global pituitary insufficiency affecting the different cell lineages of the anterior pituitary or more selective deficits affecting only a limited number of lineages [4]. No case has been reported in Madagascar. We report a case of PSIS seen in the Endocrinology Department at Befelatanana University Hospital in Antananarivo, Madagascar. Our aim is to report the case by discussing the circumstances of discovery and its therapeutic management.

2. Observation

We report the case of Andr...., a 16-years-old boy, seen in consultation for delayed statural growth and lack of sexual character development in April 2022. He was an only son, born full term in complete breech presentation without instrumental delivery in 2006. The delivery was complicated by retention of the after-coming head, right humeral fracture and neonatal asphyxia. Her birth weight and height were respectively 3100g and 52cm. No particular medical pathology, notably neuromeningeal, had occurred during childhood. The vaccinations were complete and up to date. However, the mother noticed slow-down in statural gain since the age of 2 years and the height stagnated at 125 cm from the age of 14 years old. Furthermore, no signs of puberty had appeared. In addition, his mother noticed bilateral undescended testicles which were found to be intra-abdominal by ultrasound examination. Thus, he had a bilateral orchiopexy in 2020.

He had no headaches, visual or olfactory disturbance. But he complains of fatigue.

No similar family history was reported. The father's height is 155cm and the mother's height 149cm; there was no history of inbreeding in the family.

The examination revealed a height of 125 cm, a weight of 40.7 kg (Body Mass Index: 26 kg/m²), and an abdominal circumference of 77 cm. The appearance was childlike. The limbs were sparse contrasting with the adipose abdomen. Testicles were in intrascrotal location, measuring 1.8 cm x 1 cm and 1.7 cm x 0.9 cm on the left and right, respectively. The penis measured 2 cm in the stretched position. There was no pubic, axillary or facial hair. The stage of genitalia development was then G1 and that of the pubic hair P1 according to Tanner's classification [5]. The 24-hour urinary volume was 1850 ml. No malformation was detectable clinically or on abdominopelvic ultrasound examination.

Biologically, level of basal plasma Growth Hormone (GH) was 0.3 mIU/l (N: 0.2 - 32.4 mIU/l), the plasma Insulin-like Growth Factor type 1 (IGF-1) level was 17.6 ng/ml (N: 119 - 511 ng/ml for corresponding age). Stimulation test is not possible in our country. The level of plasma total testosterone was less than 0.4 nmol/l (N: 3.4 - 29 nmol/l for corresponding age); plasma Follicular Stimulating Hormone (FSH) level was 0.38 mIU/ml (N: 0.95 - 11.95 mIU/ml), plasma Luteinizing Hormone (LH) level <0.12 mIU/ml (N: 0.57 - 12.07 mIU/ml). Plasma cortisol level at 8 am was 0.6 µg/dl (N: 2.7 - 19.4µg/dl), plasma Thyroid Stimulating Hormone (TSH) level was 2.53 µIU/ml (N: 0.35 - 4.94 µIU/ml), plasma free thyroxine (T4L) level was 11.15 pmol/l (N: 9 - 19.04 pmol/l), and plasma prolactin level was 17.98 ng/ml (N: 3,46 – 19,40 ng/ml).

Blood count, kidney function, blood ionogram test, and inflammatory tests were all normal.

His bone age was approximately 14 to 15 years old on left wrist x-ray.

Pituitary MRI found no pituitary stalk. The anterior pituitary gland was small, with homogeneous signal (Figure 1), withoutabnormality after Gadolinium injectionand the posterior pituitary gland was ectopic and in high signal on T1-weighted imaging (Figure 2). The cavernous loges, diaphragm and floor were normal.

The diagnosis of PSIS was then retained. It was responsible for somatotropic, gonadotropic and corticotropic insufficiencies. Hormone replacement with hydrocortisone and testosterone enanthate was started. Recombinant growth hormone is not available in our country.

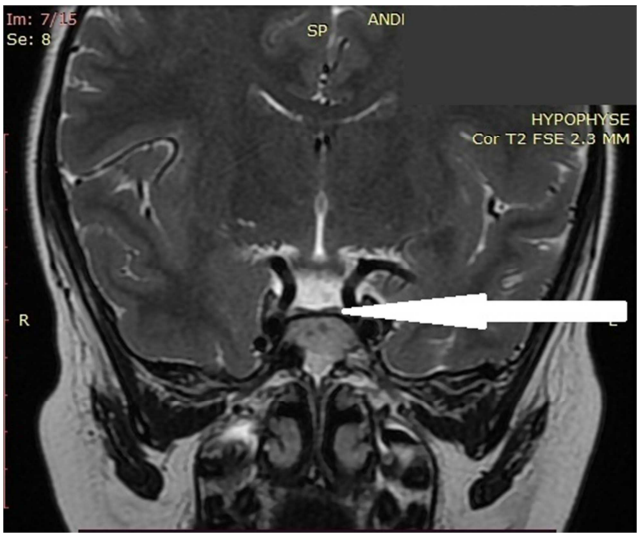

Figure 1. *Coronal T2-weighted image showing lack of stalk and small anterior pituitary with homogeneous signal.*

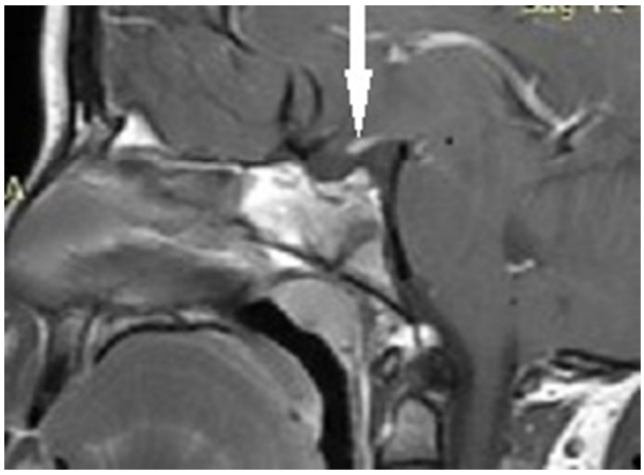

Figure 2. *Sagittal T1- weighted image showing ectopic and high signal posterior pituitary.*

3. Discussion

Delayed growth and puberty are difficult to bear psychologically and impact general well-being and fertility [6]. Etiologies can range from simple constitutional growth delay and/or simple pubertal delay which are diagnoses of elimination to more complex pathologies such as chromosomal or genetic abnormalities and endocrine diseases, accounting for less than 10% of etiologies [7]. Among these endocrine causes is PSIS, first described by Fujisawa et al in 1987 [1]. This is a rare cause of global or

selective pituitary insufficiency, with pathognomonic signs of absent or thin pituitary stalk, hypoplasia of the anterior pituitary and ectopic posterior pituitary on pituitary MRI [1].

We have just reported an observation revealed by statural growth retardation and an impuberism with bilateral cryptorchidism treated by orchyopexy and a micropenis. Indeed, his height is well below -2 standard deviation (SD) below the average height of a boy of the same age as him and no physical manifestation of puberty has yet appeared beyond his 14 years old [6]. In addition, our patient reported asthenia. These clinical manifestations result from somatotropic insufficiency evidenced by low plasma IGF-1, hypogonatropic hypogonadism evidenced by low FSH, LH, and total testosterone levels, and corticotropic insufficiency marked by low plasma level cortisol. In the literature, the clinical manifestations of PSIS are variable. Zhang et al, in 2018, had found in a series of 89 patients with PSIS, somatotropic insufficiency, gonadotropic insufficiency, corticotropic insufficiency, and thyrotropic insufficiency in 100%, 86.52%, 75.28%, and 79.78% of cases respectively [8]. Ioachimescu et al, in 2012, had found thyrotropic and gonadotropic insufficiency in the 4 adult patients they reported, and the association of somatotropic insufficiency in 3 of these 4 patients [3]. For Marmouch et al in 2016, the clinical manifestations were that of panhypopituitarism [9].

The absence of diabetes insipidus, in our case, attests to the preserved function of the posterior pituitary, which is reflected in the MRI by the conservation of the signal of the ectopic posterior pituitary gland on MRI. Indeed, most studies seem to show a good correlation between the presence of high signal on MRI and the preserved function of the posterior pituitary [9, 10].

Indeed, the clinico-biological manifestations depend on the failing pituitary cell line. The age of discovery is also variable [8]. But discoveries in adulthood are not rare. For example, in the study by Ioachimescu et al, the age of the patients ranged from 19 to 21 years old [3], for Kulkarni et al, it varies between 10 and 41 years old with 6 out of 12 cases discovered between 4 and 16 years old (mean age = 11.7 ± 4.3 years) [11]. Marmouch's observation was of a 17 years old girl [9]. However, it should be noted that some authors report cases of selective and isolated pituitary hormone deficiency long before the discovery of PTIS [3]. Most patients present in the first decade of life with growth retardation due to somatotropic insufficiency. This may be isolated or associated with other deficits [12]. However, typical features include deficiencies appearing during pediatric age and progressing to panhypopituitarism in adulthood [8].

Typically, for subjects with multiple anterior pituitary hormone deficiencies, the pituitary stalk is not visible on MRI, whereas for subjects with an isolated deficit, the pituitary stalk is detectable but thin [11].

The etiology of PITS remains poorly elucidated. Two pathophysiological hypotheses have been proposed: the first is a genetic mutation [8] affecting the genes PIT1, PROP1, LHX3/LHX4, PROKR2, OTX2, TGIF, HESX1 [13], ROBO1 [14] and GPR161 [15] involved in organogenesis and specifically hypothalamus development and setting of the pituitary structures (sella turcica, pituitary stalk). The presence of associated malformation would be in favor of this hypothesis. The second hypothesis is that of traumatic and vascular causes by lesion of the pituitary stalk caused by an obstetrical trauma during a breech presentation at the time of delivery with perinatal asphyxia [8, 16]. They can be either purely mechanical by stretching or sectioning of the pituitary stalk by the sellar diaphragm, or vascular by anoxia, ischemia, or hemorrhage [1]. In fact, a study carried out in Italy found a notion of breech delivery in 68% of the 27 children suffering from PITS [17]. For our observation, the history of breech delivery with notion of retention of the after-coming head, the neonatal asphyxia and the absence of associated malformation would rather militate in favor of this second hypothesis. Moreover, research on genetic mutations is not yet available in our country.

Treatment is based on long-term hormone-deficient replacement therapy. Early detection of the disease and early initiation of supplementation impact the quality of life and especially the prognosis of patients with PSIS [18, 19].

Our patient suffered from somatotropic, gonadotropic and corticotropic insufficiencies; androgen and hydrocortisone substitution was started. The first one in order to induce puberty and the second one to compensate the glucocorticoid insufficiency and especially to avoid the occurrence of acute adrenal insufficiency. Unfortunately, supplementation with recombinant growth hormone is not possible in our country. This product is not available and the socio-economic conditions of the patient do not allow him to obtain it or to be treated elsewhere. This would certainly compromise its development. Gonadotropins will be used later in the treatment of infertility if available. However, a history of bilateral cryptorchidism, even if it has been operated, is a poor prognostic factor for subsequent fertility [20].

At present, our patient is still free of thyroid insufficiency. However, long-term follow-up is necessary since the development of other pituitary hormone deficiencies may occur over several decades. Most patients present with progressive hormone deficiencies during the first two decades of life evolving to panhypopituitarism in adulthood [21].

The testicles also deserve special attention because of the risk of secondary atrophy or re-expansion and especially degeneration [22] in this patient who had a very long period of cryptorchidism in an intra-abdominal location. This follow-up should continue into adulthood with regular clinical and ultrasound monitoring of the gonads.

4. Conclusion

PSIS is a rare cause of global or selective pituitary insufficiency. The main signs are the delays of growth and puberty, witnesses of somatotropic and gonadotropic deficits as in the case we have just reported. But other hormonal deficits may occur over time. This justifies a long-term follow-up of the patients. The treatment is based on the substitution of the deficient hormones as soon as possible.

Early diagnosis is essential, but in countries with limited resources such as ours, this diagnosis is often late and treatment incomplete. Therefore, meticulous exploration of any delay in growth and/or puberty is essential and a multidisciplinary management of the cases is required.

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