Pituitary stalk interruption syndrome : Report of 8 pediatric cases

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ABSTRACT

Introduction: Childhood anterior-pituitary insufficiency has many causes (malformative, genetic, traumatic, tumoral...). One particular entity can be clearly identified: pituitary stalk interruption syndrome (PSIS). The aim of our study was to evaluate clinical and paraclinical features of patients with PSIS, and to analyze their growth evolution.

Patients and methods : We selected 8 children diagnosed with PSIS according to the results of MRI. We studied the perinatal characteristics of these patients, then the auxological, the endocrine features, and growth evolution after 1 year of the initiation of GH therapy.

Results : The mean age at diagnosis was 5.3 years. Sex ratio of 0.6. Consanguinity was documented in 50% of cases. Perinatal findings showed: breech delivery in 2 cases and asphyxia in 3 cases. The mean height at diagnosis was -3.32 DS (Range: -1.4 and -5 DS). A facial dysmorphia was found in 3 cases. The mean bone age retardation was 2.5 years. Hormonal assessment showed multiple hypo-pituitarism in all cases. .IGF1 mean level (measured in 6 patients) was 61 ng/ml; Median growth hormone (GH) peak during stimulation test was 0.81 ng/ml with insulin test and 3.98 with glucagon-avlocardyl test. The peaks of GH at stimulation were <0.1ng/ml in the two cases with an anterior pituitary height < 2mm. Central hypocorticism was found in 7 cases with a mean cortisol level range (11-55mg/l). Central hypothyroidism was found in 6 patients with a mean FT4 level=4.95pg/ml (range: 2.1-4.8) and a mean TSH level =2.1 MUI/L (range 0.51-2.7).Growth hormonal treatment was initiated at the dose of 25-35 mcg/kg/day, 7/7 days, 1.5 years after the first medical consultation. The overall height gain after one year of beginning of GH was 0.59 DS (range :0.1-1DS).

Conclusion : In children with PSIS, the other anterior pituitary deficiencies are often associated with GH deficiency. These functions therefore require to be carefully followed early, periodically and in the long term. Growth in these children responds particularly well to GH therapy, in particular during the first year.

Keywords : Pituitary stalk interruption syndrome (PSIS), hypopituitarism, growth retardation, GH therapy

INTRODUCTION

Pituitary stalk interruption syndrome (PSIS) was first described in 1987, soon after magnetic resonance was used. It is characterized by the triad: Ectopic posterior pituitary (EPP), thin or absent pituitary stalk and anterior pituitary hypoplasia, resulting in wide spectrum of pituitary insufficiency. This syndrome belongs to the spectrum of midline abnormalities and is often associated with other midline extra-pituitary malformations (1, 2).

In this study, we aimed to evaluate describe the clinical, radiologic, and hormonal characteristics of 8 children followed in our department for PSIS, and to analyze their growth evolution and endocrine aspects.

MATERIAL & METHODS

We conducted a retrospective study including 8 children diagnosed with (PSIS) who were regularly followed in our department. The diagnosis of PSIS was based on pituitary magnetic resonance imaging (MRI) findings. Family history and perinatal characteristics of patients were collected. A hormonal assessment was realized :

* Growth hormone deficiency (GHD) was defined by GH peak <10 ng/ml after two stimulation tests. Total GHD was defined by GH peak < 5 ng/ml and partial GHD was defined by GH peak between 5-10 ng/ml.

* Central hypothyroidism was defined by FT4 level < 9 pg/ml +/- inappropriate TSH level (normal or <5 MUI/l).

* Central hypocorticism was characterized by cortisol level at 8 am < 70mg/l with inappropriate ACTH level (normal or lower than 60 pg/ml).

* Gonadotropic axis was evaluated in post pubertal age (over 13 years for female and 15 years for males),and was defined by the absence or delayed pubertal development with low oestradiol or testosterone level and blunted LH/FSH response to GNRH stimulation.

* Hyperprolactenimia was defined by a level higher than 25 ng/ml.

* To rule out diabetes insipidus, we performed regular clinical evaluation (polyuria, polydipsia).If those signs were present; a water restriction test was performed. For follow up: Children were seen every 6 months. Height and weight were obtained at each visit. Evaluation of pituitary function was repeated during follow up visits using clinical evaluation and hormonal measurements.

RESULTS

Eight patients were included. They were aged 5 months to 10 years at the first consultation. The mean age at diagnosis was 5.3 years (Figure 1).

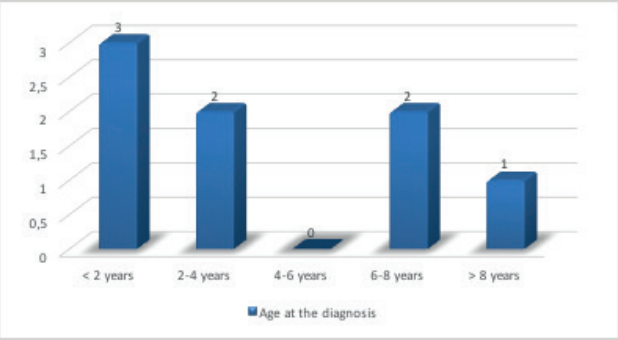

Figure 1 : Age of patients at the moment of diagnosis

There was a female predominance with a sex ratio of 0.6 (3 males /5 females). Familial history of pituitary deficiency was documented in 2 patients: brother and sister. Consanguinity was documented in 50% of cases. Perinatal findings revealed that all children were full term, with breech delivery in 2 cases and asphyxia in 3 cases. Birth weight and length were in the normal range. We characterized some features suggestive for neonatal hormonal deficiencies in all cases: hypoglycemia (4 cases), cryptorchidism and micropenis (4 cases).

Six patients were referred to our department for growth retardation. All of them had multiple previous consultations. A 5-month-old boy was referred for micropenis (1,6 mm) and had also growth retardation at the clinical exam. Once the diagnosis of PSIS done, we summoned his little sister who was "normal" according to parents. The girl consulted at the age of one year and had growth retardation (-3 SD), mental retardation, with MRI findings showing PSIS.

The mean height at diagnosis was -3.32 DS (Range: -1.4 and -5 DS). A facial dysmorphia was found in 3 cases. A severe mental retardation due to an untreated congenital hypothyroidism was found in one-year-old girl. All the other children had a normal mental development. Moderate fatigability and asthenia were reported in two patients. One patient, a three-year-old girl, was diagnosed with solitary median maxillary central incisor (SMMCI) syndrome (figure2).

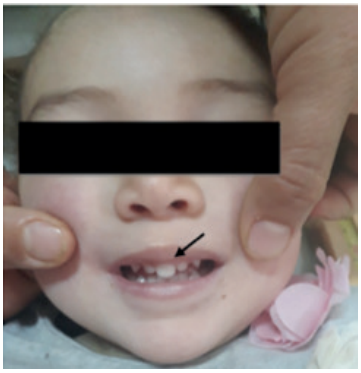

Figure 2 : Three-year-old girl with SMMCI syndrome She had no other malformation, in particular renal, cardiac or vertebral malformation.

The mean bone age retardation was 2.5 years (range 3 months and 5 years). Pituitary MRI was realized in all patients, showing (Figures 3 and 4):

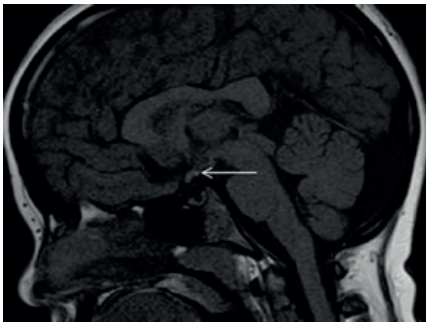

Figure 3 : Sagittal T1-weighted image shows ectopic posterior pituitary.

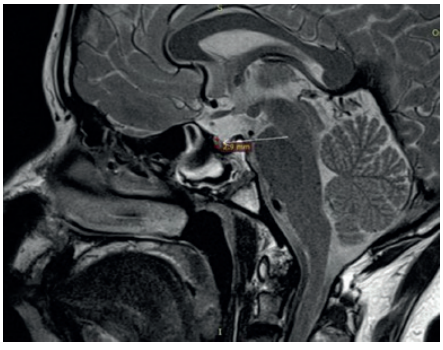

Figure 4 : Sagittal T2-weighted image showing anterior pituitary measuring 2.9mm.

- The pituitary stalk was not visible at the upper third area in 4 cases, and thin in 4 cases.
- The anterior pituitary lobe was hypoplasic in 7 cases and normal in one case, its height was less than 2 mm in 2 children.
- The signal of the posterior pituitary lobe was normal in 87% of patients and absent in only one case.
- Extra-pituitary malformations were found in two patients:

  - Agenesis of corpus callosum and cortical frontal dysplasia in one case.

  - Chiari 1 malformation in one case.

Hormonal assessment showed multiple hypo-pituitarism in all cases (figure 5). Growth hormonal deficiency (GHD) was found in all patients at the time of diagnosis: 7cases of complete GHD and 1 case of partial GHD.IGF1 mean level (measured in 6 patients) was 61 ng/ml; Median growth hormone (GH) peak during stimulation test was 0.81 ng/ml with insulin test and 3.98 with glucagon-avlocardyl test. The peaks of GH at stimulation were <0.1ng/ml in the two cases with an anterior pituitary height < 2mm. Central hypocorticism was found in 7 cases with a mean cortisol level range (11-55mg/l). Central hypothyroidism was found in 6 patients with a mean FT4 level=4.95pg/ml (range: 2.1-4.8) and a mean TSH level =2.1 MUI/L (range 0.51-2.7).

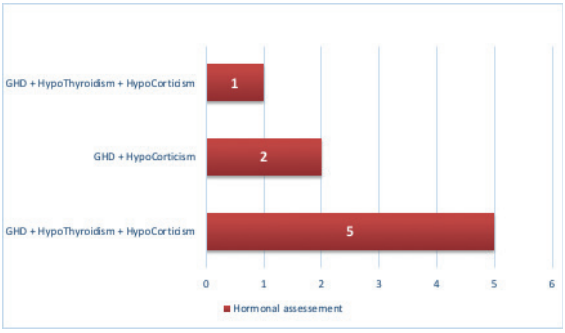

Figure 5 : Distribution of patients according to hormonal deficiencies at diagnosis.

Growth hormonal treatment was initiated at the dose of 25-35 mcg/kg/day, 7/7 days, 1.5 years after the first medical consultation (range 7 months and 2 years). It was received only by 6 patients (one mother refused the injections for one child, the other one could not have access to the treatment). Two types of biosynthetic somatropin were used, depending on availability at the central pharmacy. Despite the cooperation of all parents, multiple interruptions were observed due to lack of availability of the treatment. The overall height gain after one year of beginning of GH was 0.59 DS (range :0.1-1DS). A four-year-old girl developed an undesirable effect after the use of somatotropin (headaches); which regressed after a temporary discontinuation of the treatment and a progressive resumption.
The 6 patients with hypothyroidism were treated by levothyroxin, with regular adjustments according to hormonal assessments and bone age. Seven patients were treated by hydrocortisone (10-15 mg/m2/day) and were provided with therapeutic education and adrenal insufficiency medical alert card.

DISCUSSION

Eight patients were included. They were aged 5 months to 10 years at the first consultation. The mean age at diagnosis was 5.3 years (Figure 1). PSIS is more prevalent in male and familial in only in 5% of cases. The mean age at diagnosis is about 4 years (3). In an Italian cohort (4), it was revealed in 15 % at neonatal age with severe pituitary deficiency and in 70% of cases in childhood. In our study, there were a female predominance, and the mean age at diagnosis was 5.3 years, almost in agreement with previous reports. We reported familial PSIS with multiple hypopituitarism (somatotrope, thyrotrope and corticotrope deficiency) in a brother and a sister, which is a very rare condition. According to the literature, 70% of breech delivery may result in injury or breaking of pituitary stalk (5), hypoxemia also lead to injury of pituitary gland .In our study, 25% of PSIS children were born from breech delivery and 35% had asphyxia. Thus it's important to predict pituitary deficiency in those patients through regular clinical follow up and hormonal measurement. Genetic factors were also identified to be responsible for PSIS such as mutations or deletions in HESX1, OTX2, and LHX4 (6). Unfortunately, genetic analyses were not available for our patients. Bar and al (3), in a study including 60 children with PSIS, found that about one third had features suggestive for neonatal deficiency. However, we identified those features in 75% of our patients (hypoglycemia in 50% of cases) and micropenis with cryptorchidism in 25 % of cases), which should prompt earlier evaluation of pituitary endocrine. In accordance with other reports (7,8) we demonstrated the presence of extra pituitary malformations, especially in the central nervous system and the craniofacial structures: SMMCI, agenesis of corpus callosum and cortical frontal dysplasia, Chiari 1 malformation). We found that their presence was associated with more severe hormonal deficiency ,which is in agreement with the constatations of Reynaud R and al (9).In fact, for the 2 cases identified, GHD,hypocorticism and hypothyroidism were associated with maximal IGF1level 15ng/ml, GH peak at stimulation =2.4ng/ml, FT4level= 4pg/ml and cortisol level =14mg/l. SCMMI is a complex disorder consisting of multiple, mainly midline defects of development resulting from unknown factors operating in utero. Missense mutation in the SHH gene (I111F) at 7q36 may be associated with SMMCI. The SMMCI tooth differs from the normal central incisor, in that the crown form is symmetric; it develops and erupts precisely in the midline of the maxillary dental arch in both primary and permanent dentitions. SCMMI can be associated with multiple congenital malformations: holoprosencephaly, intellectual disability, congenital heart disease, cleft lip and/or palate, hypopituitarism, esophageal and duodenal atresia, cervical hemivertebrae, absent kidney, micropenis and ambiguous genitalia. Tauber and al (10), in a series of 35 patients, reported

somatotrope, corticotrope and thyreotrope deficiency in 100%, 33.3% and 41.4% of cases respectively. There is an insidious development of hormone deficiency (HD) leading to multiple pituitary hormone deficiencies (MPHD) (8). Thus, once the diagnosis of PSIS is established, children should be carefully followed up for additional HD, especially corticotrope deficiency which may be life threatening .In our series, HD deficiencies were co-existent at time of diagnosis. Diabetes insipidus is not common (4%) as estimated by Bar and al in a cohort study (3). The infrequency of Hyperprolactenimia supports that the reestablishment of vascular connections between hypothalamus and pituitary gland may occur, as reported by Kiyoshi and al (11). A lower anterior pituitary lobe size has been reported to be correlated with the severity of anterior pituitary dysfunction (7). We also found that for children with anterior pituitary height <2 mm, the peak of GH at stimulation test was <0.1 ng/ml. The European Society of Pediatric Endocrinology recommended the continuation of GH therapy during the transition period (between the end of puberty and adult maturity) and than in adulthood (12). The traditional amount of GH prescribed for GHD is 25–50 mcg/kg/day. Side effects of GH replacement therapy in children include rash and pain at injection site, transient fever, prepubertal gynecomastia, arthralgia, edema, benign intracranial hypertension, insulin resistance, progression of scoliosis, and slipped capital femoral epiphysis. Since GH stimulates cell multiplication, development of neoplasms is a concern. Tauber and al (10) evaluated the predictor factors of the response for GH therapy, they found that height gain was not correlated to sex nor to pituitary size, and that was lower in patients with partial GHD or if the treatment was started after 4 years old.

CONCLUSION

Increasing medical awareness on PSIS clinical and endocrine heterogeneity may help an earlier diagnosis. Molecular diagnosis will create premises for genetic counseling and a better patient's management.

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