The pituitary stalk interruption syndrome: Endocrine features and benefits of growth hormone therapy

Le syndrome d’interruption de la tige pituitaire : aspects endocriniens et bénéfices du traitement par l’hormone de croissance

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Résumé

Introduction. – L’insuffisance antehypophysaire de l’enfant est d’origine multifactorielle (malformative, génétique, traumatique, tumorale...). Une entité particulière est individuaisable : le syndrome d’interruption de la tige pituitaire (SITP). L’objectif de notre travail était d’analyser l’évolution à long terme de patients atteints de SITP. Patients et méthodes. – Les dossiers de tous les enfants suivis au CHU de Dijon entre 1990 et 2008, ayant bénéficié d’une évaluation endocrinienne montrant un déficit en hormone de croissance (GH) et d’une imagerie par résonance magnétique (IRM) cérébrale ont été analysés. Nous avons ainsi sélectionné 14 enfants chez qui le diagnostic de SITP a été porté sur la base des résultats de l’IRM cérébrale. Nous avons étudié les caractéristiques périnatales de ces patients, puis l’évolution endocrinienne et auxologique, avant l’initiation du traitement par GH, puis après un et trois ans de traitement et lors de la dernière consultation. Résultats. – Le diagnostic de SITP a été porté chez les 14 enfants à un âge moyen de 3,2 ± 3,5 ans, dont cinq au cours des deux premiers mois de vie. Le suivi de la croissance et des autres déficits antehypophysaires a été fait systématiquement deux à quatre fois par an selon le contexte clinique. Les résultats ont été analysés sur le plan endocrinien chez l’ensemble des 14 enfants et sur le plan auxologique chez les dix enfants qui ont été traités par GH pendant au moins 12 mois, avec une moyenne de 8,3 ± 4,2 ans et une posologie de traitement allant de 0,22 ± 0,02 mg/kg par semaine. Parmi les 14 enfants, 12 avaient un déficit complet en GH et deux un déficit partiel. Neuf avaient un déficit antehypophysaire multiple, diagnostiqué d’emblée ou secondairement chez respectivement cinq et quatre d’entre eux. Les tableaux de panhypopituitarisme ont été observés chez les enfants dont le diagnostic de SITP avait été fait au cours des premiers mois de vie. Chez les dix enfants traités au moins 12 mois, la taille avant traitement était de −3,1 ± 0,8 score de déviation standard (DS). À la dernière visite, le gain de taille total était de +2,5 ± 0,9 DS pour un rattrapage par rapport à la taille cible parentale de +2,7 ± 0,6 DS. Le gain de taille après un an de traitement correspondait à 60 % du gain total. Conclusion. – Chez des enfants atteints de SITP, les autres déficits antehypophysaires sont souvent associés au déficit somatotrope et cela parfois dès le premier mois de vie. Cela impose de suivre précocement, périodiquement et au long cours ces fonctions. La croissance de ces enfants répond particulièrement bien à la GH, en particulier lors de la dernière année.

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Mots clés : Syndrome d’interruption de la tige pituitaire ; Déficit somatotrope ; Déficit antehypophysaire ; Hypoglycémies néonatales ; Syndrome de la ligne médiane

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 analyse the long-term evolution of patients with PSIS. Patients and methods. – The records of all the children followed at Dijon University Hospital between 1990 and 2008 who underwent brain magnetic resonance imaging (MRI) and endocrinological evaluation that revealed a growth hormone (GH) deficiency were analysed. We thus selected 14 children diagnosed with PSIS according to the results of MRI. We studied the perinatal characteristics of these patients, then the endocrinological and the auxological evolutions, before the initiation of GH therapy and then after 1 and 3 years of treatment and during the last evaluation. Results. – Fourteen children were diagnosed with PSIS at a mean ± sd age of 3.2 ± 3.5 years, five of whom being diagnosed during the first 2 months of life. Growth, as well as other anterior-pituitary deficiencies, was systematically followed up two to four times a year depending on the clinical context. The results in terms of endocrinology were analysed in all 14 children, and with regard to auxology in the 10 children who received GH therapy for at

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least 12 months, with a mean of 8.3 ± 4.2 years and at a mean maintenance posology of 0.22 ± 0.02 mg/kg per week. Among the 14 children, 12 had complete GH deficiency while two had a partial deficiency. Nine had multiple anterior pituitary deficiencies, diagnosed at the same time or later in five and four of them respectively. A clinical picture of panhypopituitarism was found in the infants who were diagnosed with PSIS in their first months of life. In the 10 children who were treated for at least 12 months, the height before treatment was −3.1 ± 0.8 standard deviation score (SDS). At the last consultation, the total gain in height was +2.5 ± 0.9 SDS compared to the distance to target height of +2.7 ± 0.6 SDS. The height gain after 1 year of treatment corresponded to 60% of the total gain. Conclusion. – In children with PSIS, the other anterior pituitary deficiencies are often associated with GH deficiency and sometimes during the first month of life. 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; Growth hormone deficiency; Anterior pituitary deficiency; Neonatal hypoglycaemia; Median line syndrome

1. Introduction

Anterior pituitary insufficiency is a pathological entity with many causes (malformative, genetic, traumatic, tumoral...). Among these, a particular form stands apart: pituitary stalk interruption syndrome (PSIS).

PSIS was first described in 1987 with the introduction of magnetic resonance imaging (MRI) [1,2] which made it possible to identify this entity among idiopathic growth hormone (GH) deficiencies [3]. At MRI, the complete form of PSIS associates, an ectopic hyperintense signal of the posterior pituitary, often located in the infundibulum (median eminence), hypoplasia of the anterior pituitary and invisible pituitary stalk [3–5]. There is a milder form of the condition with a visible but very thin pituitary stalk, requiring gadolinium, a contrast agent, to be injected to make it visible [6,7]. However, with the recent development of ultra thin slices of 0.6 mm (CISS 3D), it is possible to document the disease without this injection. The exact etiopathogenesis of PSIS is still poorly understood. Depending on the patients, there is evidence of antenatal malformation or acquired origin due to perinatal trauma and/or hypoxic-ischemic encephalopathy [2,8,9]. Today, the hypothesis of an antenatal origin seems to be the most likely given the frequent presence of other malformations, notably of the median line, and the fact that around 2/3 of patients with PSIS did not present ischemic events and/or perinatal trauma [4,6,9,10]. Mutations in genes coding for different pituitary transcription factors have only been found in rare cases of PSIS (genes LHX4, HESX1, OTX2, SOX3) [11,12].

PSIS associates a wide range of anterior pituitary endocrine deficiencies; GH deficiency is often at the origin of the diagnosis and always present [4,7,9,13–15]. The diagnosis of PSIS no longer poses any practical problems. Pituitary MRI is systematically performed in any case of pituitary disease, in particular in children presenting with GH deficiency. Most children respond quickly and well to GH therapy [4,13].

The aim of this work was to retrospectively analyse the evolution of growth and the endocrine aspects of 14 children followed in our department for PSIS.

2. Material and methods

The medical records of all the children followed in our University hospital between 1990 and 2008, who underwent an endocrine evaluation that showed a GH deficiency as well as a cerebral MRI, were analysed. We thus selected 14 children in whom the diagnosis of PSIS was based on the results of the brain MRI. We studied the perinatal characteristics of these patients (measurements, term and conditions of birth, associated malformations), and the endocrine and auxological evolution, before the initiation of GH therapy and then after 1 and 3 years of treatment and at the last consultation.

2.1. Imaging

The diagnostic MRI were performed using T1-weighted images (echo time between 20 and 30 ms, repetition time between 450 and 650 ms), with acquisition in the sagittal and coronal planes in thin slices of 3 mm focused on the region of the hypothalamus-pituitary. Supplementary extra-thin 3DT2 slices (CISS sequence) 0.6 mm thick were acquired in the median sagittal plane, with the possibility of reconstruction in different planes to see the presence, absence or discontinuity of the pituitary stalk more clearly. In the oldest patients, gadolinium was injected to see the stalk more clearly when it seemed to be present but very thin. The patients systematically benefited from a complete study of the brain using T2 axial slices (T2 TSE or T2 FLAIR).

2.2. Hormone assays

They were measured using commercial kits by immunoanalysis (radio-immunoassay or more often immuno-radiometric assay).

Levels of serum GH were calibrated according to the preparations. GH peak was measured after two different stimulation tests. The stimulation tests used were as follows: ornithine, glucagon-betaxolol, insulin-arginine, clonidine-betaxolol and growth hormone releasing hormone (GHRH). The GH deficiency was confirmed by a serum peak less than 10 ng/ml in the two stimulation tests; complete deficiency was defined by a peak less than 5 ng/ml in the two tests and a partial deficiency when one peak was less than 5 ng/ml and the other greater or equal to five and less than 10 ng/ml. When expressed in mU/L (the most recent tests), the values were transformed into ng/ml according to international reference 98/574 with an official conversion factor of 3 (1 ng/ml = 3 mU/L) used by the laboratory where the concentrations were measured [14].

The serum concentration of Insulin growth factor-1 (IGF-1) was measured at the time of diagnosis and periodically thereafter. It was expressed in SDS according to the age and gender of
the child. The deficiency in other pituitary endocrine functions was evaluated at PSIS symptoms onset and then periodically during follow-up visits conducted two to four times per year. The deficiency in thyrotropin (TSH) was evaluated by measuring plasma levels of TSH and free T4. Corticotropin deficiency was evaluated by baseline plasma levels of cortisol and of ACTH at 8 am. Gonadotropin deficiency was suspected in the presence of clinical signs at birth (in boys, the presence of a microepi-

dard and/or bilateral cryptorchidism), but could not be confirmed until puberty (delay in pubertal development, low plasma levels of sex steroids and gonadotropins). The plasma concentration of prolactin was measured at the time of diagnosis and periodically thereafter. Disorders of post-pituitary function were evaluated at the time of diagnosis by measuring plasma and urinary osmolarity and then according to the clinical context.

2.3. Auxological measurements

The height and weight at birth were expressed in SDS according to the gestational age using Usher and Mac Lean curves [16]. In our study, a growth retardation in utero was defined by height and/or weight at birth less than −2 SDS. Height during growth was expressed in SDS according to the chronological age (CA) according to Sempe tables [17]. Short stature was classically defined by height less than −2 SDS for the CA. The gain in height under GH therapy was analysed after 1 and 3 years and during the last visit and was expressed by the difference from the height before treatment. All of the patients were still under treatment at the time of the last measurement. The total height gain was defined as the difference between the height at the last visit and the height before the start of the treatment.

The parental target height was calculated according to the following formula: ([height of the mother + height of the father] / 2) +6.5 cm for boys and −6.5 cm for girls, and was expressed in SDS using the height at a CA of 18 years. The distance to target height was defined as the difference between the parental target height and the height before treatment.

Bone age (BA) was determined using an X-ray image of the left hand and wrist according to Greulich and Pyle method [18]. Finally, predicted adult height was calculated at the last consultation from BA using Bayley and Pineau tables [19] in patients whose BA was at least 6 years, and expressed in SDS with regard to the CA at the time of measurement.

The body-mass index (BMI) was calculated and expressed as SDS according to Rolland-Cachera et al. tables [20] before treatment and during the last evaluation.

2.4. GH therapy

All of the patients received recombinant GH therapy. Sub-cutaneous injections were given every day or 6 days a week. The mean maintenance dose was 0.22 ± 0.02 mg/kg per week (extremes 0.17 to 0.26 mg/kg per week).

GH was stopped when the height had reached 170 cm in boys and 160 cm in girls and in any case when BA had reached 15 years in boys and 13 years in girls.

2.5. Statistics

The descriptive statistics of the quantitative variables are presented in the form of means ± standard deviations (extreme values), unless otherwise indicated. The relationships between quantitative variables were tested by Pearson’s correlation coefficient. BA and CA at any given evaluation were compared by two-tailed Student t-test for paired series. The threshold of statistical significance was set at 0.05.

3. Results

3.1. Patients characteristics

The characteristics at birth and at the diagnosis of PSIS as well as the endocrinological features were analysed for all 14 patients (nine boys and five girls). The auxological results, however, were only analysed in the 10 patients (five boys and five girls) who had been treated with GH for at least 12 months at the time the data were analysed (20th November 2008).

3.1.1. Neonatal and perinatal characteristics

Mean term was 39.3 ± 1.8 weeks of amenorrhea. One patient was premature (gestational age: 35 weeks of amenor-

hrea + 6 days). Concerning the birth, there were two cases of acute foetal distress (one case of pregnancy toxemia, one case of abnormal cord coiling) and two caesarean sections (one for post-term delivery and one for hydrocephaly and uterine scarring).

Eight patients presented episodes of hypoglycaemia, which were repeated and/or resistant to glucose supplementation. Six of these had concurrent prolonged jaundice (three had neonatal panhypopituitarism and two developed later multiple anterior pituitary deficiencies). Five of the nine boys had a micropenis, one of whom had bilateral cryptorchidism. Seven patients had one or several malformations. Among these seven patients, five had malformations of the median line:

- bilateral choanal atresia (1);
- frontal intraventricular cyst (1);
- Chiari I syndrome (1);
- bilateral labiopalatine cleft (1);
- Binder syndrome (1);
- septo-optic dysplasia – associating agenesis of the septum lucidum, hydrocephaly due to stenosis of the mesencephalic aqueduct, hypoplasia of the chiasma and the optic nerve – (1);
- atypical septum lucidum (1);
- hypoplasia of the corpus callosum (2).

The other malformations were as follows:

- pyloric stenosis (1);
- Ladd’s bands (1);
- facial dysmorphism (3);
- interatrial communication (1);
- bilateral hexadactyly (1);
- grade II vesico-ureteral reflux (1).
Mean height and weight at birth were $-1.5 \pm 0.7$ SDS and $-0.3 \pm 1.4$ SDS, respectively (Fig. 1). Height at birth was normal except in two children in whom it was less than $-2$ SDS (in one case, birth weight was also less than $-2$ SDS).

3.1.2. Characteristics at the time PSIS was diagnosed

Mean age at PSIS diagnosis was $3.2 \pm 3.5$ years (extremes: 8 hours of life to 11.4 years). The symptoms that led to the diagnosis were: episodes of hypoglycaemia repeated and/or resistant to glucose supplementation in six cases, three of which having neonatal panhypopituitarism recorded at 8 hours, 7 and 12 days after birth respectively, and short stature in the eight others. The diagnosis was made during the first 2 months of life in five children and before 5 years in nine children. The diagnosis was not made until the ages of 1.75 years to 6.75 years in three patients with a clinical picture of short stature even though they presented episodes of hypoglycaemia and prolonged jaundice at birth. The height measured in 12 children at the time of diagnosis was $-3.1 \pm 0.8$ SDS (extremes: $-4.3$ to $-2.2$ SDS). In the two children who presented panhypopituitarism at 8 hours and 7 days of life, the severity of the clinical signs (hypoglycaemia) required the immediate initiation of GH therapy, and because of this, short stature was not recorded (moreover the height at birth was normal). The mean delay in BA, evaluated in eight patients was $-1.7 \pm 0.9$ years (extremes: $-0.17$ to $-3$ years); the difference with CA was statistically significant ($p=0.0012$). In five patients, BA was more than 1 year behind CA.

Hypothalamo-pituitary MRI was performed at the time of diagnosis in all of the patients except one; in this patient, the examination was not performed until 7 years after diagnosis. In nine patients, gadolinium was injected; it was not done in the five children of less than 2 months of age, four of whom had inexistential or hypoplastic sella turcica. Moreover, in these five children, the hyperintense signal of the anterior pituitary, which is usually visible before 2 months, was absent.

In all of the patients, we found an ectopic hyperintense signal of the posterior pituitary (Fig. 2). In the 13 patients for whom we have the information, the anterior pituitary was hypoplastic (11 cases) or aplasic (two cases). The pituitary stalk was invisible in nine cases and extremely thin or hypoplasic in four cases. In one case, the information was not available.

With regard to the hormonal status, all the patients had GH deficiency from the beginning. Nine patients underwent two stimulation tests. In four infants aged between 8 hours and 2 months, the stimulation tests were not performed because GH serum concentrations were low (0.01 to 4.7 ng/ml) during spontaneous severe episodes of hypoglycaemia ($\leq 1.65$ mmol/l), which required immediate initiation of GH therapy. Finally, one 5-month-old patient had only one stimulation test; the first stimulated concentration of 1.2 ng/ml associated with an unquantifiable concentration of IGF-1 and hypoglycaemic convulsions made it necessary to initiate GH therapy without waiting for the result of a second test. The mean GH peak during these stimulation tests or measured during spontaneous hypoglycaemia was $3.1 \pm 2.1$ ng/ml (extremes: 0.01 to 8.15 ng/ml). The GH deficiency was considered total in 12 patients, including the five patients who did not undergo the two stimulation tests, and partial in two patients.

The mean serum concentration of IGF-1 was $-2.5 \pm 1.1$ SDS (extremes: $-4.2$ to $-0.1$ SDS). Ten patients had a concentration less than $-2$ SDS for their age.

Five patients had other anterior pituitary deficiencies (thyrotropin and corticotropin) associated with a GH deficiency at the time of diagnosis (Table 1). Indeed, panhypopituitarism was present in the five patients (two girls and three boys) for whom the diagnosis was made during the first 2 months of life.
SDS: standard deviation score; BA: bone age; CA: chronological age.

Table 1
Multiple anterior pituitary deficiencies combined with GH deficiency (N = 9/14).

<table>
<thead>
<tr>
<th>Case No.</th>
<th>gender</th>
<th>Thyrotropin deficiency</th>
<th>Corticotropin deficiency</th>
<th>Gonadotropin deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 F</td>
<td>Primary</td>
<td>0.03</td>
<td>Primary: 0.03</td>
<td></td>
</tr>
<tr>
<td>3 M</td>
<td>Secondary: 2.67 (0.59)</td>
<td>Primary: 0.17</td>
<td>Primary: 0.17</td>
<td></td>
</tr>
<tr>
<td>5 M</td>
<td>Secondary: 13.42 (6.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7 M</td>
<td>Primary: 0.17</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 F</td>
<td>Secondary: 12.25 (10.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 M</td>
<td>Secondary: 5.25 (1.25)</td>
<td>Secondary: 15.50 (11.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 F</td>
<td>Primary: 0.12</td>
<td>Primary: 0.12</td>
<td>Secondary: 11.92 (11.8)</td>
<td></td>
</tr>
<tr>
<td>13 M</td>
<td>Primary: 0.025</td>
<td>Primary: 0.025</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14 M</td>
<td>Primary: 0.003</td>
<td>Primary: 0.003</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AC: chronological age (years).

a AC at deficiency diagnosis.

b (time since GH deficiency diagnosis).

3.2. Evolution of growth in the 10 patients treated with GH for at least 12 months

In the 10 patients analysed, mean age at the start of treatment was 3.6 ± 2.8 years (extremes: 0.3 to 7.3 years). All were still under treatment at the last evaluation. Duration of follow-up was thus the same as that of the treatment and was 8.3 ± 3.0 years (extremes: 1.8 to 12.7 years). The mean CA of these patients at this time was 11.9 ± 4.2 years (extremes: 2.3 to 15.5 years) (Table 2). Only one female patient had reached adulthood at the time of the last visit and her treatment was thus stopped.

Mean height before treatment was −3.1 ± 0.8 SDS (extremes: −4.3 to −2.2 SDS) and parental target height was −0.4 ± 1.0 SDS (extremes: −2.3 to +0.4 SDS). The distance to target height was thus +2.7 ± 0.6 SDS. At the last evaluation, the total height gain was +2.5 ± 0.9 SDS (extremes: +0.7 to +3.4 SDS), which was very close to the distance to target height with a difference of −0.2 ± 1.2 SDS (extremes: −3.0 to +0.8 SDS). Six patients had a total height gain above the target height (Fig. 3).

At the last visit, only two patients had a height less than −2 SDS compared to the CA. The height of the girl who had reached adulthood was −2.5 SDS, for a parental target height of −2.3 SDS. One boy, who, at the beginning of treatment had had a moderate height gain (+0.7 SDS at 1 year and +1.5 SDS at 3 years) spontaneously stopped his treatment between 12.8 and 14.2 years; he did not start again until 1.4 years before the last visit; this patient constituted the only failure of GH therapy; for this case, however, as a delay in pubertal development was recently found, treatment with testosterone enanthate was initiated, which, hopefully, will lead to additional height gain.

The major part of the catch-up growth occurred before 3 years of treatment (Fig. 1 and Table 2). The catch-up growth after 1 year of treatment corresponded to 60% of the total gain and target height gain was +2.5 ± 0.9 SDS (extremes: +0.7 to +3.4 SDS).
after 3 years to 94% of total gain, in the nine children who had at least 3 years of treatment follow-up.

There was a positive correlation between height gain after 1 year of treatment and height gain at the last consultation ($r = 0.703, p = 0.023$) (Fig. 4). We found no statistically significant correlation between height gain at 1 year or at the last consultation and the following parameters: age at the start of treatment, height before treatment and mean GH peak.

The difference between BA and CA at the last consultation was $-0.8 \pm 1.3$ years (extremes: $-3.1$ to $+1.1$ years) (the difference was not statistically significant) with considerable variability between patients. Five patients had a delay greater than 1 year compared to their CA and four patients had a difference between BA and CA that was considered normal according to Bayley and Pineau criteria [19] ($\leq 1$ year). One patient had an advance of more than 1 year.

The forecast adult height, according to Bayley and Pineau tables [19], calculated in eight patients of more than 9 years was $-0.2 \pm 1.4$ SDS (extremes: $-2.4$ to $+2.2$ SDS); it corresponded to the final height in the patient who had reached adulthood.

Mean BMI varied little under treatment (Table 2). Analysis of individual results, however, revealed normalisation in the three patients who had an abnormal BMI before treatment ($-2.7$, $-2.4$ and $+3.6$ SDS respectively). In contrast, one girl developed obesity towards the end of the treatment with a BMI at $+3.2$ SDS, even though it was $+0.3$ SDS before treatment.

3.3. Evolution of endocrine status

At the last evaluation, the mean CA of the 12 patients was $9.4 \pm 6.1$ years. Nine patients had multiple anterior pituitary deficiencies and five (including three who had been followed for $>8$ years since diagnosis) had isolated GH deficiency (Table 1). Eight patients had thryotropin deficiency, which appeared after the original diagnosis for three of them (between 0.6 and 10.5 years after the diagnosis of PSIS), six patients had corticotropin deficiency, which appeared later in one of them (1.25 years after diagnosis of PSIS). All of the thryotropin deficiencies were purely biological. The five cases of initial corticotropin deficiency were diagnosed during the first month of life; these patients had repeated episodes of hypoglycaemia, but they also had total GH deficiency. Patients with thryotropin and corticotropin deficiency all received supplements of L-thyroxine and hydrocortison, respectively from diagnosis onwards.

Two patients (a girl and a boy) had gonadotropin deficiency, diagnosed in the absence of clinical signs of pubertal development associated with very low serum concentrations of sex steroids and/or gonadotropins for the CA. Gonadotropin deficiency was also diagnosed in a boy who, at birth, presented with a micropenis and bilateral cryptorchidism.

Among the seven children who had reached puberty at the time of the last visit, five had spontaneously started to develop at the normal age. In the two other patients described above, who presented pubertal delay, puberty was induced using testosterone enanthate in the boy and estradiol hemihydrate in the girl, who subsequently gained $+0.2$ SDS ($7.8$ cm) in 1 year.

The mean serum concentration of IGF-1 measured in 12 patients $7.0 \pm 3.9$ years after the initiation of treatment was $-0.9 \pm 1.4$ SDS (extremes: $-3.2$ to $+1.9$ SDS). Only two patients had concentrations less than $-2$ SDS, which led to an increase in doses of GH.

We found no cases of diabetes insipidus or prolactin deficiency in our cohort.

4. Discussion

The development of MRI has made it possible to identify PSIS among idiopathic GH deficiencies. This is all the more important since this diagnosis has prognosis and treatment impact for these patients.

The clinical symptoms of anterior pituitary insufficiency can appear very early with repeated episodes of hypoglycaemia that do not respond to glucidic supplementation in the neonatal period or during the first months of life. These are frequently associated with prolonged jaundice and, in boys with a micropenis and/or cryptorchidism. These signs indicate that hypothalamo-pituitary MRI and a complete assessment of pituitary hormones need to be carried out without delay. The diagnosis of PSIS is all the more likely when associated with malformations, notably of the median line. In our series, eight children out of 14 presented a clinical picture suggesting PSIS at birth. In three of these, however, the diagnosis was made only later, when the short stature was noticed. In our series, the earlier the manifestation of PSIS, the more complete the anterior pituitary deficiency was, requiring polyhormonal therapy as early as the first month of life.

This neonatal clinical picture of PSIS has been reported by other authors. Pinto et al. [9] in his series of 51 PSIS, 35 of whom having multiple anterior pituitary deficiencies and 16 having isolated GH deficiency, also described 70% of episodes of hypoglycaemia in multiple anterior pituitary deficiencies, 21 patients with associated malformations and 10 boys with micropenis. Seven out of 27 PSIS reported by Rottembourg [15] had cerebral
malformations of the median line. In a series of 35 patients with PSIS, Tauber et al. [4] found neonatal symptoms in several: prolonged neonatal jaundice with or without hypoglycaemia in 20%, cryptorchidism and microopenis in respectively 39% and 27% of boys and various frequent malformations, in particular of the face or hands (20%). The study of Arrigo et al. [10] compared clinical symptoms at the time of diagnosis, in a series of 49 patients with GH deficiency of apparently idiopathic origin. MRI revealed simple hypoplasia of the pituitary in thirty-two patients (group A), while 17 patients had PSIS (group B). Patients with PSIS presented significantly more episodes of hypoglycaemia (35.3% versus 3.1%, p < 0.005) and a greater prevalence of microopenis (36.4% versus 12.5%) and cryptorchidism (27.3% versus 8.3%) compared with group A. The frequency of difficulties during childbirth and neonatal asphyxia, however, were similar in the two groups. As several authors have suggested, the frequency of early neonatal hypoglycaemia and associated malformations, notably of the median line, as well as the existence of rare family forms seems to support the hypothesis of an antenatal aetiology, most often involving malformation, rather than trauma or a perinatal hypoxic-ischemic event [4,6,9,10,21]. Pinto et al. [9] suggested that the hypoxic phenomena observed in certain patients could be the consequence of antenatal hypothalamo-pituitary lesions rather than their cause.

Our series shows that it is possible to make an early diagnosis in a clinical picture of hypoglycaemia that does not respond to supplementation with glucose, prolonged jaundice and reduced growth speed, all the more when there are associated malformations.

Concerning auxological evolution, only two other studies analysed the effect of GH therapy on growth in patients with PSIS [4,13]. In 10 patients in our series, treated for a mean of 8.3 ± 3 years, the difference between the distance to the target height and the total gain at the last consultation was −0.2 ± 1.2 SDS, even though only one patient had reached adulthood. These good results, observed in the growth of patients with PSIS treated with GH, are comparable to those of other authors [4,13]. In 35 patients with PSIS and on GH therapy for an average of 7.5 ± 4.7 years, Tauber et al. [4] reported a total gain of +2.9 ± 1.0 SDS and a difference between final height and parental target height of −0.3 ± 0.1 SDS. Coutant et al. [13] also reported that in such patients who had reached adulthood, total height gain was greater in 15 children with PSIS than in 48 children with non acquired GH deficiency with normal pituitary MRI (+2.7 ± 0.9 in the PSIS group versus +1.3 ± 0.8 SDS, p < 0.01). In the same way, adult height was significantly greater in the PSIS group (−1.1 ± 1.0 versus −1.7 ± 1.0 SDS, p < 0.01). However, the duration of GH therapy was significantly longer in patients with PSIS (7.3 ± 2.2 years versus 4.2 ± 1.9 years, p < 0.01).

There was only one case of failure in our series and this concerned the child who interrupted his treatment for 1 year and 4 months; however, recent induction of his pubertal development may lead to growth gain.

Several studies have evaluated GH secretion after treatment cessation (as growth is considered to have ended) in adolescents or young adults treated for PSIS since infancy. All of these evaluations, combined with measurement of IGF-1 levels show the persistence of severe GH deficiency (GH peak stimulated by hypoglycaemia < 3 ng/ml) in patients with PSIS. This contrasts with other idiopathic GH deficiencies with normal MRI or even isolated post-hypophyseal ectopia in which a certain proportion of patients acquire normal secretion of GH [22–25]. Thus, out of a total of 32 patients with PSIS reassessed in the year following cessation of GH, 31 had a GH peak less than 3 ng/ml while the remaining patient had a peak of 3.4 ng/ml [22–25]. These observations raise the issue of the continuation of GH therapy and treatment modalities during the transition period (between the end of puberty and the end of development/adult maturity) and then in adulthood, for metabolic and functional reasons, according to the Consensus recommendations recently established by the European society for pediatric endocrinology for these two periods of life [26,27].

Regarding the endocrinological concern, three features seem to characterise PSIS: the complete nature and intensity of the GH deficiency as well as the frequency of multiple anterior pituitary deficiencies.

In our series, we only found two partial deficiencies in 14 patients (14%). Tauber et al. [4] reported 77% of complete deficiencies. Arrigo et al. [10] reported a mean peak GH after stimulation of 3.8 ± 2.7 ng/ml versus 1.6 ± 1.7 ng/ml in GH deficiency without PSIS on MRI and in GH deficiency with PSIS, respectively (p < 0.0005). Finally, Coutant et al. [13] observed 15/15 (100%) complete deficiencies in a series of PSIS compared with 8/48 (17%) in patients with non-acquired GH deficiency with a normal MRI.

The high frequency of multiple anterior pituitary deficiencies in PSIS is reported in every series, whether it is found immediately or develops during the evolution of the condition. In our series, we found 9/14 (64%) patients with multiple anterior pituitary deficiencies. Coutant et al. [13], in his series of 15 PSIS analysed in adulthood, reported 15/15 cases of multiple anterior pituitary deficiencies compared with one in 48 patients with non-acquired GH deficiency with normal pituitary MRI. In his series of 35 PSIS, Tauber et al. [4] reported 47.1, 33.3 and 41.4% deficiencies in thyrotropin, corticotropin and gonadotropin, respectively, discovered at diagnosis of the disease. At 17 years all had multiple anterior pituitary deficiencies; in the 25 patients aged 11 years and more, respectively 28 and 40% had a deficiency in two and three hormones as well as GH deficiency. Arrigo et al. [10] reported a frequency of 64.7% of multiple anterior pituitary deficiencies in 17 PSIS patients, and 21.9% (p < 0.005) in 32 patients with GH deficiency and only hypoplasia of the anterior pituitary on the MRI. The same trends were found by Marcu et al. [14] and Rottembourg et al. [15].

In the publications that provide details of deficiencies, thyrotropin deficiency appears to be the most frequent, as was the case in our series: 70.3 to 91% [4,7,15,28]. Analysis of gonadotropin deficiency depends on the pubertal status of patients at the time of the evaluation. In patients diagnosed in infancy and then re-evaluated at the end of their growth, or at a stage of physiological pubertal development, the frequency of gonadotropin deficiency varied between 43 and 86% [4,14,15,28].
This finding underlines the importance of periodic follow-up of pituitary hormone status as well as pubertal development in these children, at least until they have reached their adult height.

To date and to our knowledge, the outcome of these patients in adulthood is not documented in the literature. The main series published on PSIS between 2005 and 2008 assessed the patients in adolescence when GH, that was prescribed for short stature, was discontinued [4,14,15]. GH deficiency persisting in the big majority of PSIS patients when treatment is discontinued [4,22–25], International Consensus recommends to start again the treatment in adulthood and to continue it throughout all life. However, there is lack of long term follow-up on this point. GH dosage recommended in France for the treatment of GH deficiency in adults is 2.5 to five times lower (0.04–0.08 mg/kg per week) than that administered in children [29]. Tauber series, as well as ours in a lesser extent, have shown that anterior pituitary deficiencies may develop tardily hence requiring long term monitoring and if required, treatment. This notion is reinforced by Gotyo et al. [30] publication: indeed, an anterior pituitary deficiency related to neonatal PSIS was evidenced in a patient only at the age of 38 years. The reproductive ability of these patients whether or not they have a spontaneous and normal or induced puberty is unknown.

Like Tauber et al. [4], Marcu et al. [14] and Chen et al. [7], we found no case of diabetes insipidus.

The main limit of our study is the small number of patients. This prevented us from identifying possible predictors of the response to GH therapy, such as age at the start of treatment, as did Tauber et al. [4] in his series of 35 PSIS and other authors in idiopathic GH deficiency [31,32], who underlined the importance of early diagnosis. We did, however, despite the small number of patients, find a correlation between the response to GH therapy, such as age at the start of treatment, as well as ours in a lesser extent, have shown that anterior pituitary deficiencies may develop tardily hence requiring long term monitoring and if required, treatment. This notion is reinforced by Gotyo et al. [30] publication: indeed, an anterior pituitary deficiency related to neonatal PSIS was evidenced in a patient only at the age of 38 years. The reproductive ability of these patients whether or not they have a spontaneous and normal or induced puberty is unknown.

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Conversely, we did not evidence a statistically significant correlation between the height before treatment and the total height gain ($r = -0.572, p = 0.12$), as it was evidenced in the previous study, in spite of a similar 8 years duration of treatment ($r = -0.521, p < 0.0001$) [33]. The most probable explanation for that is, in addition to the moderate correlation between both factors, the smallest number of patients treated for 3 years (9 versus 59); this is again more probable since we have shown in the present series that 94% of the total height was obtained during the 3 first years of treatment.

5. Conclusion

Despite its limitations, our series underlines the frequency of neonatal symptoms in infants with PSIS. This clinical picture, whether or not associated with malformations, should lead to the suspicion of the condition and MRI must be performed before growth delay evidence. Given that multiple anterior pituitary deficiencies are observed in PSIS, sometimes in the first month of life, these functions must be monitored from the very beginning of life, periodically and in the long term. Growth in these children responds particularly well to GH therapy. More than half of the catch-up growth is obtained during the first year of treatment.

Conflicts of interest

None.

References


