Family Multiple Pituitary Deficiencies Associated to Pituitary Process: Which Diagnosis?

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Abstract The hypopituitarism of children, partial or absolute, stems from many causes. Tumor cause, such as craniopharyngioma, is predominant and must always be sought. The presence of a “tumor” pituitary lesion in a child with a GH deficiency, especially in family forms, should not overlook the possibility of a concomitant genetic disorder, in particular mutation of Prop 1. Surgical abstention in this case, with morphological and ophthalmologic monitoring are shown because the spontaneous regression of the hyperplasia pseudo tumor. We report two cases in this clinical regard.

Keywords Pituitary insufficiency, GH deficiency, Pituitary hyperplasia, Mutation of Prop. 1.

1 Introduction
The hypopituitarism in the child involves several etiologies. Tumor causes are predominant and must be systematically sought. There are however, pseudo tumor forms: Infiltrative (autoimmune, neurosarcoïdosis) or genetic disorder which may be confused with authentic pituitary process. These lesions are then recognized late in the pathological study after an abuse surgery of pituitary tumor with all the risks of this one.

2 Clinical presentations
Both BN14 and AS10 years old are two girls from intermarriage of the first degree. They have consulted for delay of stature. The examination revealed the presence of similar cases in the respective brothers BK 08 years and AH 12 years old. Clinical examination in 04 patients revealed severe growth retardation and a characteristic morphotype of GH deficiency (chubby face, nasal bridge, acromicrie and abdominal adiposity). There were signs of discrete hypothyroidism in patients except BK and a micro penis and bilateral cryptorchidism in both boys. The rest of the clinical examination including neuro ophthalmological examination (Table 1) was unremarkable.

Hormonal exploration (Table 2) confirmed the diagnosis of GH deficiency responsible for the short stature. GH deficiency was severe in all the cases with a GH mean peak lower than 1 mIU/L in two Pharmacological stimulation tests (insulin test and glucagon-propranolol test) with collapsed values of IGF1. The evaluation of other pituitary axes confirmed hypothyroidism in three patients and objectified an evident corticotropic deficiency in 01 case and partial one in two other patients. The corticotropic insufficiency was asymptomatic in the 03 cases. However, evaluation of the gonadotropic axis was impossible to realize because of prepubertal bone age. It was being an average 06±1.2 years (5 to 8.5).

The neuroradiological exploration by magnetic resonance imaging revealed two morphological aspects a hyperplasia pseudo tumor in the 02 girls (Figure 1) and pituitary hypoplasia in the brothers.

Because of the familial character and multiple pituitary deficiencies, a molecular biology study has been carried in 04 patients which revealed an homozygous mutation of Prop.1 (Table 3).

The patients underwent a biosynthetic growth hormone substitution subcutaneously due 0.7 μg/week 07 days about 07. This treatment was associated with levothyroxine at 2.5 μg/day orally in case of hypothyroidism.
Table 1 Clinical findings at diagnosis

| Patient (Gender) | Age at first consultation (years) | Phenotypic signs of somatotropic insufficiency | Age of delay stature (years) | Other signs of endocrine insufficiency |
|------------------|----------------------------------|-----------------------------------------------|-----------------------------|--------------------------------------|
| BN (G)           | 14                               | ++                                            | 3                           | Hypothyroidism                        |
| BK (B)           | 08                               | ++                                            | 2                           | Micro pénia                          |
| AS (G)           | 10                               | ++                                            | 3                           | Hypothyroidism                        |
| AH (B)           | 12                               | ++                                            | 2                           | Micro pénia bilatéralCryptorchidism   |
|                  |                                  |                                               |                             | Hypothyroidism                        |

Table 2 Hormonal results

| Patients | IGF1* ng/mL | Glucagon Test/GH (mU/L) | Insulin Test/GH (mU/L) | TSHus (N=0, 2–4) | FT4 (N=11, 5–23) | Cortisol Insulin test (nmol/L) | ACTH Pg/mL |
|----------|-------------|-------------------------|------------------------|------------------|-----------------|-------------------------------|------------|
| BN (F)   | 17          | 0,43–1,02               | 0,2–0,7                | 0,12             | 06              | 80**                          | 10         |
| BK (M)   | 10          | 0,3–1,5                 | 0,1–0,8                | 1,10             | 11              | 160–550                       | 15         |
| AS (F)   | 20          | 0,2–1,2                 | 0,19–0,24              | 0,2              | 08              | 158–240                       | 20         |
| AH (M)   | 16          | 0,18–0,80               | 0,2–0,3                | 0,8              | 04              | 164–230                       | 12         |

Note: * Interpretation according to pubertal stage and age; ** Insulin test not realized

Table 3 Neuro radiological and genetic results

| Patient (Gender) | Pituitary MRI | Mutation |
|------------------|---------------|----------|
| BK (B) hypoplasia| hypoplasia    | Prop. 1 R 120 c homozygous |
| BN (G)           | Hyperplasia   | Prop. 1 R 120 c homozygous |
| AS (G)           | Hyperplasia   | Prop. 1 R 73 c homozygous |
| AH (B)           | Hypoplasia    | Prop. 1 R 73 c homozygous |

The evolution was marked by the appearance of thyrotropic deficit in the patient BK, by emergence of corticotropin deficiency in patients AS and AH as well as spontaneous regression of the pituitary volume to hypoplasia after a follow up of 2.5 years on average (Table 4).

3 Discussion
The presence of endocrine disorders associated with pituitary tumor lesion is immediately evocative of an organic lesion. Its exploration by magnetic resonance must be systematic to eliminate expansive intracranial process. craniopharyngioma is considered as the most common in children. Other acquired diseases as infectious ore infiltrative diseases are rarer at this age (Calzada et al., 1978; Castinetti et al., 2008; Levine et al., 1988). A new entity reported during the last decade

Figure 1 A: Sagittal MRI: Pituitary expansive process with homogeneous appearance; B: Coronal MRI: Homogeneous pituitary bulging diaphragm process and 5–10 mg/m2/d of hydrocortisone in case of corticotropin deficiency.
is the pseudo tumoral aspect related to a mutation of the gene encoding the transcription factor of ontogenesis pituitary Prop 1 (Berenice et al., 1999; Delodoey et al., 1999; Riepe et al., 2001; Teinturier et al., 2002). In fact, since twenty years, molecular studies have found genetic alterations responsible for congenital pituitary deficits in humans (Brue et al., 2004). However, despite the discovery of several genes associated the GH deficiency in humans, the molecular mechanisms behind the vast majority of deficiencies defects remain to be elucidated (Parks et al., 1993). In humans, mutations of Prop1 are currently the leading cause of multiple pituitary deficits (Delodoey et al., 1999; Enjalbert, 2002; Reynaud et al., 2006). All patients with this mutation in the homozygous state have hypopituitarism characterized by progressive installation and variable of different hypothalamic-pituitary deficits (Botttner et al., 2004). The constant and complete GH deficiency is responsible for severe growth retardation and a characteristic phenotype. The age at diagnosis is between 06 and 07 years (Delodoey et al., 1999). Ages of our two patients was advanced because of delayed diagnosis. The thyroid stimulating deficit, missing at first, appeared secondarily as well as a constant deficiency of the gonadotropin axis (Delodoey et al., 1999). The corticotropic deficit is the only one considered unstable in the literature (Botttner et al., 2004). Individuals with such a deficit still asymptomatic and the severity of possible acute decompensation require, as for other injuries, potential regular reassessments.

The study of pituitary morphology in patients with a mutation of Prop1 shows different aspects: Anterior pituitary hypoplasia, hyperplasia or normal size. The increase of pituitary size can lead to problems of differential diagnosis with an authentic tumor process and lead to a radical treatment. The consequences can be severe. In fact, evolution is marked in all cases with spontaneous regression of pituitary hyperplasia. These findings were verified in our patients. The possibility of visual disturbances secondary to pituitary hyperplasia indicates to repeated radiological controls and visual fields. It should also be noted that there is no genotype-phenotype correlation for this mutation. Indeed, the respective brothers of the two patients studied carry the same mutation but had a different biological and radiological phenotype.

The pathogenesis of this hyperplasia remains unknown. It appears that the process causing the pseudo-tumoral aspect of the pituitary gland would be to the intermediate lobe whose physiological regression at birth is late due to the loss of functional Prop 1.

4 Conclusion

The presence of a “tumor” injury on MRI in children with a family multiple hypopituitarism must consider genetic hyperplasia. The adequate therapeutic in this case is a surgery abstention with hormone replacement. Patients should be monitored by clinical inspection, regular biological, neuro — ophthalmologic and radiological controls.

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