CASE REPORT

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Empty sella associated with growth hormone deficiency and polydactyly

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Abstract

Empty sella means the absence of the pituitary gland on cranial computed tomography or magnetic resonance imaging. Empty sella syndrome is the pathological variant of the imaging-described empty sella. We present the case of a male Caucasian child, aged four years and two months, for short stature and diagnosed by imaging procedures as empty sella. The cause of short stature was isolated growth hormone (GH) deficiency. Associated he presented left hand postaxial polydactyly. In connection with this particular case, we propose a review of current knowledge in empty sella syndrome. The particularity of reported case consists of association empty sella with GH deficiency and polydactyly. The association of empty sella with polydactyly is not reported yet in the medical literature and is probably coincidental.

Keywords: empty sella, pituitary gland, growth hormone deficiency.

Introduction

Empty sella (ES) is a relatively new entity, developed with improved imagistic techniques. Empty sella means the absence of the pituitary gland on cranial computed tomography (CT) or magnetic resonance imaging (MRI) [1]. The result is the sella turcica partially or completely filled with cerebrospinal fluid (CSF). ES occurs when CSF enters the sella turcica and compresses the pituitary gland until it lines the sellar floor or wall [2, 3]. This is the result of herniation of the subarachnoid space within the sella, which is often associated with some degree of flattening of the pituitary gland. There are two types of empty sella: primary empty sella (PES), due to endogenous factors (which we are discussing here) and secondary empty sella, due to exogenous factors (*e.g.*, had trauma, radiation, surgery), which usually determines panhypopituitarism [4, 5]. The diagnosis is often made by chance being, usually, recognized incidentally during brain imaging studies performed for different indications. In most cases, this condition is asymptomatic. Empty sella size could be normal or enlarged. The imaging diagnosis is not equivalent to a pathological situation in every instance. The cause, the frequency and the pathogenic mechanisms are not well known. Empty sella syndrome (ESS) is the pathological variant of an empty sella confirmed by imaging [6]. At children, the incidence varies from 1.2% (children without symptoms) to 68% (children with known endocrinopathy) with a male to female ratio of 1.4:1 [7].

The aim of this case report is to contribute to a better knowledge of the primary empty sella syndrome (PESS) by clinical observation of a child who associates empty sella with uncommon congenital condition, namely growth hormone (GH) deficiency and polydactyly.

Case presentation

Patient PE, a five years old boy, was admitted to the Clinical Genetics Service of "Dr. Gavril Curteanu" Municipal Clinical Hospital, Oradea, Romania, for short stature. The boy was the first child of young, healthy and non-consanguineous parents; he had an 18-month-old brother with a normal development. He was born at 40 weeks gestational age by Cesarean section delivery, after an uneventful pregnancy, without perinatal incidents. At birth, his weight was 3600 g, length was 51 cm and Apgar scores were 9 at one minute and 10 at 5 minutes. Breast-feeding initiated at birth. A left hand postaxial polydactyly was observed at birth and for this, a repair surgery was performed at one month of age. Past medical history: increase in subcutaneous thoracic–abdominal fat was observed at approximate six months of age. Also, he presented a moderate psychomotor retardation: he began speaking single words at the age of one year and six months and started walking at approximately 24 months. At physical examination, he presented proportionate short stature. The height was 87 cm (less than 5th percentile); weight was 18 kg (above 95th percentile), body mass index (BMI) was 23.8 kg/m^2 (above percentile 95%). He showed typical puppet faces, down-slanted palpebral fissures, small nose, small mouth, thin lips; fine, thin, soft and pale skin; short and thin fingers; surgical scar seen on the right fifth toe; adipose tissue prominent in thoracic–abdominal region; small penis imbedded in adipose tissue; small testes and no furrow scrotum.

Imagistic investigations

The bone age was delayed (Greulich–Pyle atlas), corresponding to age 2 1/2 years old. Skull radiography showed small sella turcica, 6 mm width (reference value: 8 mm) and 8 mm height (reference value: 11 mm). Cranial CT (Figure 1) showed fluid density at sella turcica, while the pituitary gland was not visualized. To the cranial MRI (Figure 2), sella turcica appeared to be filled by hypodensity T1 and hyperdensity T2, visible only on one coronal image and on two sagittal images; a small zone, 2/3/5 mm, isosignal with white matter, consistent with the pituitary gland with an extremely thin stem was seen on only one cut.

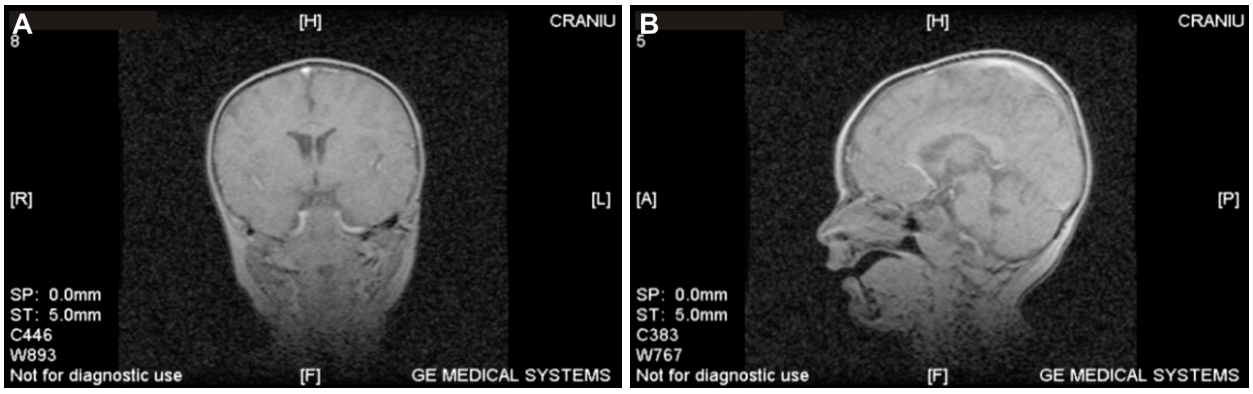

Figure 1 – ***(A and B) Cranial CT scan showed fluid density at sella turcica: the pituitary gland is not visualized.***

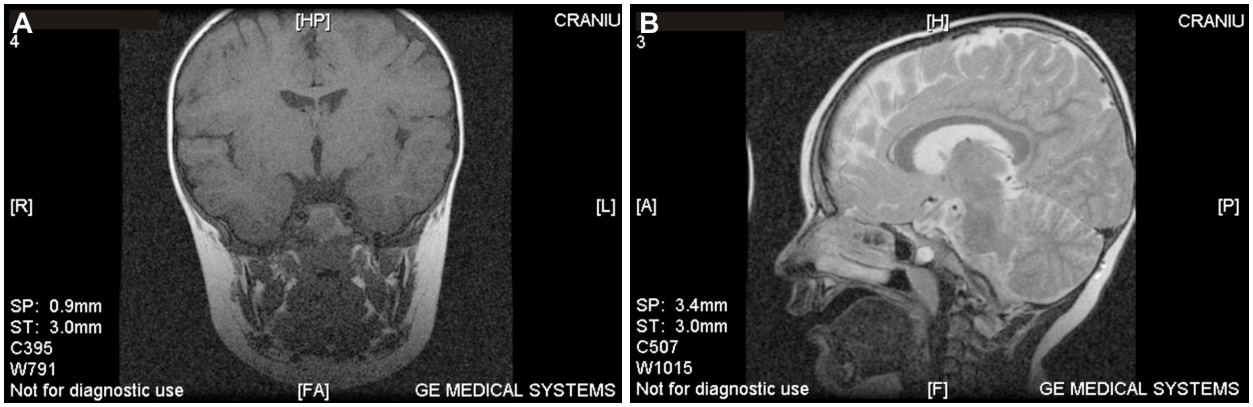

Figure 2 – ***(A and B) Cranial MRI: sella turcica appeared to be filled by hypodensity T1 and hyperdensity T2 visible only on one coronal image and on two sagittal images; a small zone, 2/3/5 mm, isosignal with white matter, consistent with the pituitary gland with an extremely thin stem was seen on only one cut.***

Laboratory investigations

Hematological and biochemical analyses were normal. The metabolic evaluations were performed for serum glycemia, total and fractioned cholesterol, triglycerides, proteins, electrolytes, all at normal values. Dosage of GH, by chemiluminescent immunoassay: *à jeun*, 0.7 μg/mL; after stimulation with insulin, at 30 minutes, 0.75 μg/mL and 1 μg/mL at 60 minutes. Thyroid hormones dosage showed normal values: free triiodothyronine (fT3) 1.08 ng/L; free tetraiodothyronine (fT4) 7.4 μg/dL; thyroid-stimulating hormone (TSH) 3.76 μIU/mL. Insulin-like growth factor-I (IGF-I) concentration was 19 ng/mL (reference values: 30–236 ng/mL). Metabolic screening for inborn errors of metabolism was normal.

Karyotype was performed by culture of peripheral blood lymphocytes and showed normal 46, XY. Fluorescence *in situ* hybridization (FISH) analysis for the detection of the 15q11-q13 deletion seen in Prader–Willi syndrome (PWS) was normal in our patient.

Treatment

A substitution therapy with recombinant GH was initiated. A very good response was noted – height velocity (13 cm) – in the first year of treatment, decreased body fat, normal psychomotor development.

Discussions

Busch (1951) described for the first time this condition, in a series of 788 autopsies of patients without known pituitary diseases. He found ES in 5.5% of normal patients, introducing the term "empty sella turcica" [8]. ES is an imagistic finding characterized by the herniation of the subarachnoid space within the sella turcica, which is often associated with variable degree of flattening of the pituitary gland. This occurs when CSF enters the sella turcica and compresses the pituitary gland until it lines the sellar floor or wall [9]. Usually, ES is not associated with clinical signs or symptoms. However, if there are associated any clinical manifestations, we talk about ES syndrome [10].

Because our case shows imagistic ES and clinical manifestations (short stature due to GH deficiency and polydactyly), without history for exogenous factors, we consider the diagnosis as a PESS.

The association of ES with GH deficiency is a common condition. In the majority of cases, the reason for presenting to the medical services was the short stature.

Xu *et al.* studied 577 patients with short stature caused by pituitary lesions and identified 68 cases (49 males and 19 females), *i.e.*, 11.8%, with empty sella turcica and CSF signal in most part from [11]. Soliman *et al.*, in a report concluded that children with growth retardation and abnormal hypothalamic pituitary functions have high incidence of empty sella. ES was detected in nine out of 20 children with isolated GH deficiency (45%) [12]. We observed, along 15 years (2001–2016), a series of 44 children with short stature due to isolated GH deficiency. Twelve (27.7%) of them had ES on the MRI. At children, PES is often associated with abnormal pituitary function. Isolated GH deficiency is the most common but other pituitary hormone deficiencies may be present too [13]. Various studies show that 5–58% of somatotropic hormone (STH)-deficient children have PES, while the syndrome occurs in only 2% of children with normal pituitary function. This is the reason why systematic GH testing and GH substitution should be considered in PES. If the symptoms are absents, PES is not requiring any treatment.

The association of ES with polydactyly is not reported yet in the literature. The gene of GH is located on the chromosome 17q23.3, with at least two variants of inheritance: autosomal recessive (AR) [type IA; Mendelian Inheritance in Man (MIM) 262400] and autosomal dominant (AD) (type II; MIM 173100) [14]. The gene for postaxial polydactyly is located on chromosome 7p14.1, with AD inheritance (MIM 174200). There is also a genetic heterogeneity of postaxial polydactyly, including genes located on the chromosomes 13q21, 19p13, 7q22, 13q13, 4p16 [15]. At the current level of knowledge of the human genome, the combination of the two entities described here has to be considered as coincidental.

Other clinical manifestations are described in different studies: amenorrhea, diminished libido, impotence through erectile dysfunction, acromegaly, Cushing's syndrome and diabetes insipidus [16].

Differential diagnosis was made with inborn errors of metabolism that were excluded by specific screening. PWS was excluded by clinical symptoms (no muscular hypotonia, no mental retardation) and cytogenetic studies (normal karyotype, normal FISH). Bardet–Biedl syndrome was excluded by the absence of retinitis pigmentosa. ES has to be distinguished, by imagistic investigations, from other pituitary abnormalities or cystic lesions, as arachnoid and epidermoid cysts and congenital pituitary anomalies. Other entities were excluded by clinical, imagistic or laboratory criteria: septo-optic dysplasia spectrum (optic nerve hypoplasia, pituitary hypoplasia, median brain abnormalities with the absence of the corpus callosum and the septum pellucid, Dandy–Walker malformation), Pallister–Hall syndrome (hypothalamic hamartoblastoma, hypopituitarism, anal imperforation, postaxial polydactyly), Alström syndrome (no ocular abnormalities, no hearing loss, no cardiomyopathy) [17].

Laboratory investigations are particularly directed to the pituitary function. In our case, only isolated GH deficiency was found while other pituitary hormones were normal. In other studies, the following endocrine disorders were identified: panhypopituitarism, hyperprolactinemia, adrenocortical deficiency hypothyroidism [18].

Imagistic examinations (skull radiography, CT, MRI) are the usual investigations for diagnosis. ES may be an accidental discovery in a cranial exam for other disorders or may be required by practitioner, in most cases the reason being the short stature. Skull radiography is not relevant in all cases. In our case, unlike other authors, the size of sella turcica, radiologically evaluated, was under the normal dimensions [19]. More relevant are the cranial CT and cranial MRI examinations, which highlight characteristic changes: the sella turcica occupied by CSF in continuity with overlying subarachnoid spaces the pituitary gland appears to be small or absent, with a semi-lunate aspect, compressed on the sella bottom. The bonny sella is often enlarged [20, 21].

Conclusions

Empty sella is an anatomic variant (non-symptomatic), commonly detected on imaging due to endocrine dysfunction or other disorders. ESS is a pathological condition associating ES with any clinical manifestations. The presented case is a rare ESS associating ES with GH deficiency and postaxial polydactyly. Any GH deficiency could be associated with ES, and any child with ES could have associated GH deficiency. The association of ES with polydactyly is not reported yet in the medical literature and is probably coincidental.

Conflict of interests

The authors declare that they have no conflict of interests.

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