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ORIGINAL ARTICLE

Pituitary morphovolumetric changes in Alström syndrome

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KEYWORDS
Alström syndrome;
ALMS1;
Empty sella;
Pituitary gland;
MRI

Summary
Purpose: Alström syndrome (AS) is a rare monogenic ciliopathy characterized by cone-code dystrophy, leading to early blindness, and obesity. Early endocrinological dysfunctions, especially growth hormone deficiency and hypogonadism, are detected in about half of AS patients. This MRI study investigates the presence of pituitary gland abnormalities in a large cohort of AS patients.
Methods: Pituitary morphological changes (gland flattening with partial or total empty sella) were evaluated on midsagittal high-resolution T1-weighted images of 32 AS patients (mean-age 23.2 ± 9.4 years; range: 6—45, 15 females) and 21 unrelated healthy subjects (mean age 23.2 ± 11.2 years; range: 6—43; 10 females).
Results: Among AS patients, 11/32 (34%) had total empty sella and 6/32 (19%) partial empty sella, while 3/21 (14%) of controls had partial empty sella and none presented with total empty sella ($P < 0.005$). AS patients harboring a total or partial empty sella did not differ from those

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with normal pituitary gland for gender ($P = 0.98$), BMI ($P = 0.10$) or visual impairment ($P = 0.21$), while the presence of empty sella was associated with an older age ($P = 0.007$) being especially frequent above the age of 30.
Conclusions: Total or partial empty sella appears commonly during the course of AS. Pituitary gland flattening might represent the morphological underpinning of subtle endocrinologic dysfunctions and raises the need to further investigate the pituitary function in this rare ciliopathy.

Introduction

Empty sella is a term designating intrasellar herniation of the subarachnoid space resulting in or resulting from a flattening of the pituitary gland. Its incidence on magnetic resonance imaging (MRI) varies from 5.5% to 35% according to age, diagnostic criteria and study population. In most cases, empty sella is considered an incidental finding with little clinical relevance, especially among elderly and female subjects [1]. However, in young people, empty sella might be associated with pituitary dysfunction, particularly increased prolactin levels and growth hormone deficiency [2] or with intracranial hypertension conditions, such as communicating hydrocephalus and idiopathic intracranial hypertension [3]. The latter condition occurs mostly in young obese subjects and presents with headache and impaired vision [4]. It has been suggested that the increased abdominal pressure exerted by the adipose tissue raises the intrathoracic pressure leading to increased cerebral venous pressure, increased intracranial tension and empty sella [5].

Alström syndrome (AS, OMIM 203800) is a rare, autosomal recessive disorder that, in addition to early blindness and progressive deafness, is characterized by obesity and endocrinological dysfunctions, including growth hormone deficiency [6]. AS is caused by mutations in *ALMS1*, a large gene composed of 23 exons and coding for a 4,169-amino acid protein. The localization of ALMS1 to centrosomes, basal bodies, and cytosol predicts ALMS1 to be a ciliary protein and may explain the wide range of AS phenotypes, including brain abnormalities [7]. A few studies have addressed the pituitary function in AS [8—10], but none have focused on the possible concomitant morphological MRI changes of the pituitary gland [11].

The purpose of this study was to investigate the prevalence of pituitary gland MRI abnormalities, especially empty sella, and to correlate these abnormalities with clinical and demographic data in a large cohort of AS patients.

Materials and methods

We retrospectively evaluated sagittal high-resolution T1-weighted images of:

- 32 patients (mean-age 23.22 ± 9.40 years; range: 6—45, 15 females) affected with AS;
- 21 unrelated healthy subjects referred to neuroimaging for headache with no history of prematurity, head trauma, neurological or psychiatric disease and neurosurgery (mean-age 23.24 ± 11.24 years; range: 6—43; 10 females).

AS diagnosis was based on genetic analysis and clinical observations; clinical features of the cohort are presented in Table 1.

MRI scans were performed at 1.5 T (Achieva, Philips Medical Systems, Best, the Netherlands and GE Signa Excite, Milwaukee, WI, USA) with a standard quadrature head coil. The images were obtained with a 3D-T1-weighted sequence acquired in sagittal direction (repetition time/echo time: 20/3.8 ms; flip angle: 20°; voxel size: $0.66 \times 0.66 \times 1$ mm; acquisition-time: about 7 min); multiplanar reconstructions were obtained (slice thickness: 3 mm). On midsagittal T1-weighted images, pituitary findings were categorized as following (Fig. 1):

- total empty sella (pituitary gland height less than one third of the sellar height);
- partial empty sella (pituitary gland height less than two thirds of the sellar height);
- normal pituitary gland (pituitary gland height more than two thirds of the sellar height).

The study was approved by our Ethics Committees. Written informed consent was obtained from patients or their parents.

Statistical analysis

Variance analysis was performed in order to correlate body mass index (BMI), age and sellar MRI findings. Gender, visual acuity, and MRI findings of the sella were correlated by means of Pearson's Chi-squared. Spearman's test was used to verify any linear correlation. Significance was inferred at $P < 0.05$.

Results

Among AS patients, 11/32 (34%) had total empty sella and 6/32 (19%) partial empty sella (Table 1), while among controls, 3/21 (14%) had partial empty sella and none presented with total empty sella ($P < 0.005$). AS patients harboring empty sella did not differ from those with normal pituitary gland for gender ($P = 0.98$), BMI ($P = 0.10$) or visual impairment ($P = 0.21$) (Table 2), while there was a significant association between the presence of empty sella and older age ($P = 0.007$, $r = 0.47$). The high genotypic variability in our sample did not allow the detection of any