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PITUITARY MORPHOVOLUMETRIC CHANGES IN ALSTRÖM SYNDROME

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ETHICAL STANDARDS AND PATIENT CONSENT

We declare that this human study has been approved by the Ethical Committee of the University of Padua and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. We declare that all patients gave informed consent prior to inclusion in this study.

CONFLICT OF INTEREST:

The authors declare that they have no competing interests.

- In the past five years we have not received reimbursements, fees, funding, or salary from any organization that may in any way gain or lose financially from the publication of this manuscript, either now or in the future
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- We do not hold and we are not currently applying for any patents relating to the content of the manuscript. We have not received any reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript.
- We do not have any other financial competing interests.
- There are not any non-financial competing interests (political, personal, religious, ideological, academic, intellectual, commercial or any other) to declare in relation to this manuscript.

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Alström Syndrome; *ALMS1*; empty sella; pituitary gland; MRI

INTRODUCTION

The "empty" sella is the intrasellar herniation of the subarachnoid space resulting in or resulting from the flattening of the pituitary gland. Its incidence on MR imaging varies from 5.5% to 35% according to age, diagnostic criteria and studied population used. In most cases the empty sella is considered an incidental finding with little clinical relevance, especially among elderly and females.[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 present 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 protein of 4,169 amino acids. 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] and none have focused on the possible concomitant morphological MRI changes of the pituitary gland.

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: a) 32 patients (mean-age 23.22 ± 9.40 years; range: 6–45, 15 females) affected with AS; b) 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 I.

MRI scans were performed at 1.5T (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: 20/3.8ms; flip angle: 20°; voxel size: 0.66 × 0.66 × 1mm; acquisition-time: about 7min); multiplanar reconstructions were obtained (slice thickness: 3mm). On midsagittal T1-weighted images, pituitary findings were categorized as following (see also fig 1):

1. total empty sella (pituitary gland height less than one third of the sella height);
2. partial empty sella (pituitary gland height less than two thirds of the sella height);
3. normal pituitary gland (pituitary gland height more than two thirds of the sella 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 sella MRI findings. Gender, visual acuity, and MRI findings of the sella were correlated by means of Pearson's Chi square. The Spearman's test was used for 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 I), 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 ($p = 0.21$) (see table II), 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 association between with the presence and the severity of pituitary abnormalities and the underlying mutations.

DISCUSSION

At MRI, about half of our AS patients disclosed total or partial empty sella. The rate was significantly higher than that observed in age and sex-matched controls. These results point to a common involvement of pituitary gland in AS raising questions about its pathogenesis and clinical implications.

According to our findings, pituitary gland morphovolumetric changes usually appear as the AS patient grows older: in fact, empty sella is rarely detected until the third decade while it becomes very frequent in patients over the age of 30 (5/6 AS patients). This observation

contradicts the hypothesis that underdevelopment of the pituitary gland is due to a direct effect of mutations in the *ALMS1* gene. If this were the case, the pituitary sella would likely be congenitally small and not necessarily empty.

The cause of the progressive pituitary gland atrophy in AS is unclear. Unlike what supposed for pseudotumor cerebri [11], the lack of correlation of AS empty sella with the BMI does not support the hypothesis of increased intracranial pressure due to overweight. The increased frequency of empty sella with age seems to support a degenerative process that could be sustained by defective hypothalamic function or by an accelerated ageing process. A recent study showed the dysfunction of hypothalamic cells in mice with *ALMS1* truncating mutation [12]. As the hypothalamus has trophic effects on the pituitary gland cells, the progressive volume reduction of the pituitary gland might be an epiphenomenon of hypothalamic nuclei disarrangement, that might become evident during and after adolescence. On the other hand, a previous study [7] showed the appearance of vascular-like brain lesions after the age of 30. These changes resemble an accelerated ageing effect on the brain parenchyma, that might also involve the pituitary gland. Both mechanisms, namely a primary hypothalamic involvement and a direct degeneration of the pituitary gland, are not mutually exclusive and might both contribute to the progressive volume reduction of the pituitary gland.

With respect to pituitary gland function in AS, GH functional deficiency has been observed in 50% of AS patients [9]; similarly hypogonadism [10] has been detected in half of male patients, suggesting the presence of a hypothalamic-pituitary-gonadal axis dysfunction. GH/sex hormone and pituitary gland abnormalities could represent the two sides (morphological and functional) of this axis dysfunction. Investigating the correlation between empty sella and the pituitary hormone function will help to address this issue.

CONCLUSION

Total or partial empty sella is a common feature of AS that feature might represent the morphological underpinning of subtle pituitary dysfunction. Further studies, addressing the pituitary function of this rare ciliopathy are required.

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Fig.1.

Magnified midsagittal T1-weighted images through the sella turcica show the three categories of pituitary tissue height in three different AS patients:

A, Normal.

B, Partial empty sella (pituitary gland thickness less than two thirds of pituitary sella height)

C, Total empty sella ((pituitary gland thickness less than one third of pituitary sella height)

Table 1
Epidemiological, clinical and neuroradiological pituitary gland features in our AS patients cohort.

AS Patient #	Age (years)	Gender	Genotype Allele 1	Genotype Allele 2	Empty Sella	BMI	Visual deficit
1	6	M	p.Arg3611Glnfs*	p.Arg1007Lysfs*	N	26	N
2	9	M	p.Arg3611Glnfs*	p.Arg1007Lysfs*	N	27	N
3	11	F	p.Ser1142*	p.Leu590*	N	27	R
4	12	F	p.Ser1142*	p.Gln3127*	N	27	R
5	12	M	p.Ser1142*	p.Leu590*	Total	26	R
6	13	F	p.Arg2928*	p.Ser3301Leufs*7	N	36	R
7	14	M	p.Arg3659*	p.Glu2435Valfs*7	Partial	31	B
8	17	M	p.Ser1142*	p.Ser1142*	N	23	B
9	17	F	p.Ser1142*	p.Ser1142*	N	28	B
10	18	M	p.Gln2980*	p.Gln2980*	N	20	R
11	19	M	p.Asp3771Gluufs*20	p.Glu3773Trpfs*18	Total	39	R
12	19	F	p.Gln2648*	p.Lys3055*	Total	25	B
13	19	F	p.Gln2648*	p.Lys3055*	N	30	B
14	20	M	p.Ser3873Tyfs*19	p.Asn3885Leufs*9	N	26	B
15	20	F	p.Ser979fs	p.Pro3422Glnfs*2	N	30	B
16	23	M	p.Arg3806*	unknown	N	25	R
17	23	F	p.Arg720Lysfs*60	p.Gly893Aspfs*41	Total	32	B
18	25	F	p.Tyr1051*	p.Phe3795Leufs*38	Partial	47	B
19	26	F	deletion Ex 17	p.Tyr1715*	Partial	41	B
20	27	F	p.Asp2459Alafs*18	p.Asp2459Alafs*18	Total	29	B
21	28	M	p.Lys3545Asnfs*18	p.Lys3545Asnfs*18	Total	31	B
22	28	M	p.Gln1769*	p.Gln1769*	N	40	B
23	29	F	p.Phe3795Leufs*38	unknown	Partial	25	B
24	30	M	p.Gln635*	p.Tyr1193*	Partial	36	B
25	30	F	p.Arg3772Trpfs*10	unknown	Total	45	R
26	30	F	p.Gln3495*	p.Glu3617*	N	26	B

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AS Patient #	Age (years)	Gender	Genotype Allele 1	Genotype Allele 2	Empty Sella	BMI	Visual deficit
27	31	M	p.Gln1394*	p.Gln1394*	Total	27	B
28	31	M	p.Ser3301Leufs*7	p.Asn3885Leufs*9	Partial	38	B
29	32	M	p.Thr3592Lysfs*6	unknown	N	38	B
30	36	M	p.Glu3773Trpfs*18	IVS16-G>A	Total	32	B
31	43	M	p.Asn3885Leufs*9	p.Lys1608Argfs*9	Total	29	B
32	45	F	p.Ser2102*	p.Thr3592Lysfs*6	Total	21	B

BMI=Body Mass Index; M: male; F: female; N=normal; I= reduced visual acuity; B=blindness.

Epidemiological and clinical features of our sample of AS patients according to pituitary gland findings. Age (years) and Body Mass Index are reported as mean±standard deviation.

Table II

Empty Sella	# (%)	Age	Gender	BMI	VISUS		
					Normal (%)	Reduced (%)	Blindness (%)
No	15 (47%)	18.3±7.6	8M/7F	29±5.7	2 (13%)	5 (33%)	8 (53%)
Partial	6 (19%)	25.8±6.2	3M/3F	36±7.7	0	0	6 (100%)
Total	11 (34%)	28.5±10.2	6M/5F	31±7.0	0	3 (27%)	8 (73%)
Whole sample	32	23.2±9.4	17M/15F	30.7±7.0	2	8	22

BMI=Body Mass Index; M: male; F: female