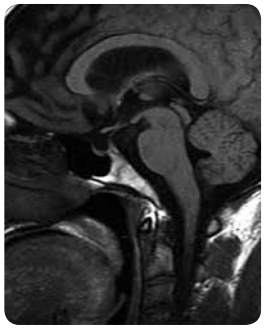

Empty Sella Syndrome Prevalence in a Colombian Population and Its Relation with Age, Sex and Number of Pregnancies

Prevalencia de silla turca vacía en una población colombiana y su relación con la edad, el sexo y el número de gestaciones

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Key words (MeSH)

Sella turcica
Prevalence
Age groups
Parity

Palabras clave (DeCS)

Silla turca
Prevalencia
Grupos de edad
Paridad

Summary

Objective: To determine the prevalence of empty sella syndrome (ESS), evaluated by magnetic resonance (MR), in a Colombian population and its association with the number of pregnancies, age and gender. *Materials and methods:* Descriptive observational cross-sectional study and paired case-control analytical study. *Results:* The prevalence of the finding of empty sella is greater in females, in addition, age was found as a risk factor, which is known as a biological gradient, and there is a statistically significant association with the number of pregnancies, which is summarized in that the greater the number of children, the higher the ESS finding. *Conclusion:* The prevalence of empty sella in the studied population is 24%, which agrees with data from the world literature in which its prevalence in females is described and the relationship is directly proportional with age as a risk factor for ESS.

Resumen

Objetivo: Determinar la prevalencia de silla turca vacía (STV), evaluada por resonancia magnética (RM), en una población colombiana y su asociación con el número de gestaciones, la edad y el sexo. *Materiales y métodos:* Estudio observacional descriptivo de corte transversal y estudio analítico de casos y controles pareado. *Resultados:* La prevalencia del hallazgo de silla turca vacía es mayor en el sexo femenino, adicionalmente, se encontró la edad como factor de riesgo, que se conoce como un gradiente biológico, y que existe una asociación estadísticamente significativa con el número de gestaciones, lo cual se resume en que a mayor cantidad de hijos, mayor es el hallazgo de STV. *Conclusión:* La prevalencia de silla turca vacía en la población estudiada es del 24 %, lo cual concuerda con datos de la literatura mundial en la que se describe su prevalencia en el sexo femenino y la relación directamente proporcional con la edad como factor de riesgo para STV.

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1. Introduction

The empty sella syndrome (ESS) is an anatomical condition characterized by intraselar herniation of the suprasellar subarachnoid space, often resulting in partial or complete compression of the pituitary gland by cerebrospinal fluid (CSF) (1,2). ESS is primary (pESS) in 70 % of cases with an average age of 40,6 ± 9,4 years and is secondary ESS (sESS) in 30 % with an average age of 37± 9,6. Having

These data show that the population most affected by these entities is the middle-aged individuals, with a prevalence rate of 3:1 for the pESS and 2.3:1 for the sESS (3). Based on the above premises, the following general objective was defined: To determine the prevalence of the magnetic resonance imaging (MRI) finding and its association with pregnancy, age and sex.

2. Materials and methods

» Study population: Adult patients who underwent brain MRI in the radiology center to which the authors belong.

» Design: Descriptive observational cross-sectional study and analytical study of cases and paired controls, approved by the institution's ethics committee and conducted over a period of 6 months from November 2016 to April 2017.

» Patient selection: Adult patients who had brain MRI performed over a 6-month period from November 2016 to April 2017 (approximately 660 brain MRIs, 110 monthly).

» Exclusion criteria:

- Patients undergoing emergency brain MRI for cerebrovascular disease in therapeutic window.
- Individuals with cognitive or psychotic disorders.
- Individuals with a current, severe neurological disease, detectable upon medical evaluation

» Brain MRIs: 660 brain MRIs acquired over 6 months were reviewed and evaluated as follows: The Turkish chair was reviewed in the T1 weighted sagittal section, in the T2 weighted coronal section and the criteria defining the tESS (total empty sella syndrome) condition were evaluated.

» Criteria for defining the ESS condition: in the T1 weighted sagittal section and in the T2 weighted coronal section: More than 50% of the Turkish CSF-filled chair and/or pituitary gland < 2 mm in height.

» All patients were evaluated by two radiologists, the first of whom was a resident and the second with over 10 years of experience in brain MRI reading at the facility.

» Classification of patients: The study had two phases.

- *Phase 1:* All patients over 18 years of age with a diagnosis of an empty sella syndrome who underwent brain MRI between November 2016 and April 2017 were included (approximately 660 brain MRIs, 110 per month).
- *Phase 2:* Adult patients who had brain MRI performed at the radiology center over a 2-month period (approximately 220 brain MRIs) were included. This number was contingent upon the losses of patients who did not wish to participate in the study and those who were excluded according to the defined criteria; in total, 49 cases were collected prospectively, and for each case, 1 patient over 18 years of age who did not meet the ESS criteria was included and randomly selected. Subsequently, age and sex parity between cases and controls was performed.

» Comparison between cases and controls according to radiological criteria: Data on the total number of patients with ESS were tabulated and analysed, taking into account that, in the world literature, the number of patients with ESS is lower than the number of patients without ESS. All patients chosen with ESS (cases) were matched by age and sex with patients without ESS (controls).

» Case definition and controls:

- *Cases:* Adult patients undergoing brain MRI who met the criteria for ESS (cases)..
- *Controls:* Adult patients who had brain MRI scans that did not meet the STV criteria (controls).

» Evaluation of the number of gestations of the patients: To evaluate the relationship with the number of pregnancies of women positive for ESS, the data was obtained by telephone.

- Univariate analysis: It made it possible to evaluate the characteristics of each of the two groups. Each variable was described at its level of measurement: mean or median for continuous variables, proportions for categorical or nominal variables. All of their 95% confidence intervals were reported. The comparison between groups was made by Student t-tests, and by $\chi 2$.
- Bivariate analysis: It allowed establishing the association of the explicative variables with the result variable.
- For phase 1, prevalence and prevalence ratio were calculated as measures of frequency and effect.
- For phase 2, the calculation of effect measures such as the odds ratio (OR) and their respective 95% CI was performed, together with the calculation of their p-values. The candidate variables for the adjustment of the ORs were chosen in a multivariate model, whose p-value was less than 0.2.
- Stratified analysis (phase 2 only): A stratified analysis was performed to identify possible confounding variables or effect modifiers.

3. Results and benefits

In Colombia there are no publications on the estimation of the prevalence rates of ESS, so this study was the first to estimate these epidemiological data in the metropolitan area of Bucaramanga and in the country. The results will be divided according to the phases mentioned above

3.1 Phase 1: Descriptive observational cross-sectional study (prevalence). All brain MRIs were reviewed in the period mentioned. A total of 660 patients were found, of which 140 showed the finding of an empty sella syndrome, corresponding to 24% of the population (Figure 1). The prevalence of empty sella syndromes is higher in females. There is a peak increase in this sex in the age group 80-89 years and in the male gender the peak is in the age group 60-69 years (Figure 2, Table 1).

Figure 1. Prevalence of the empty sella syndrome in percentages by age group and sex

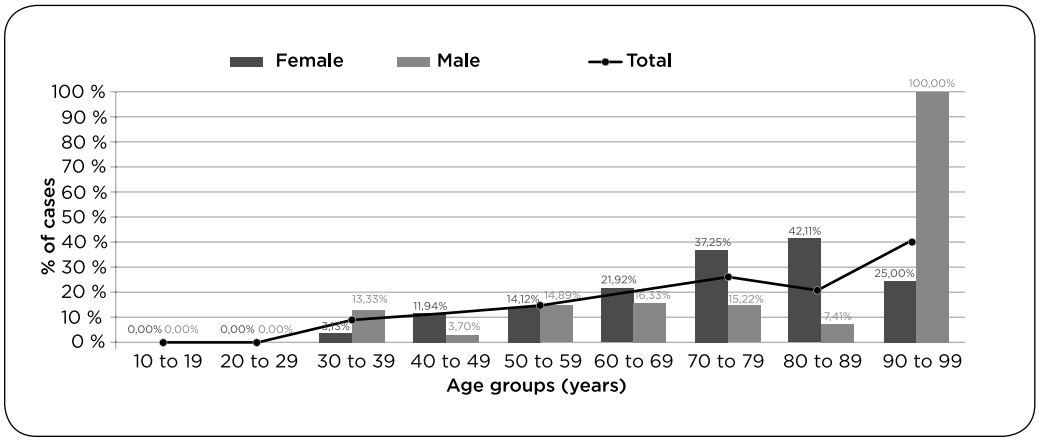

Figure 2. Cases and percentage of empty sella syndrome cases by age group and sex

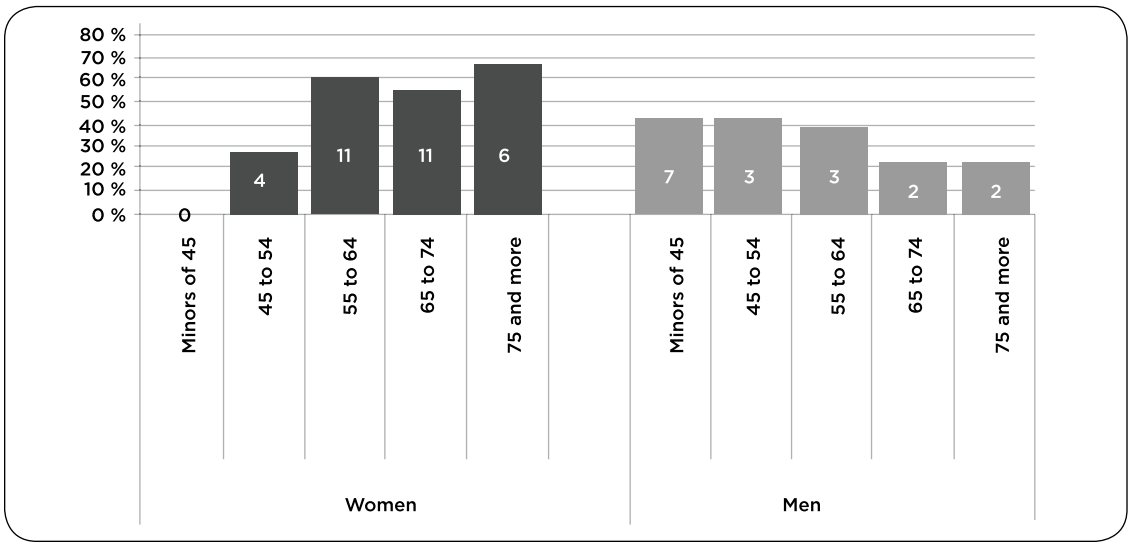

Figure 3. Number and percentage of cases of empty sella syndrome by age group

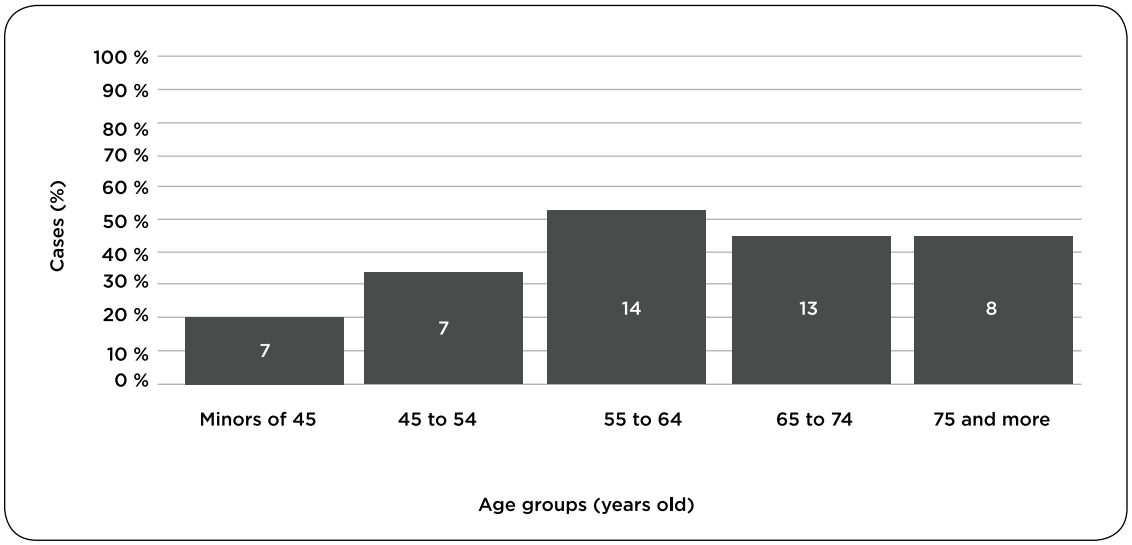

Figure 4. Gestations in cases and controls

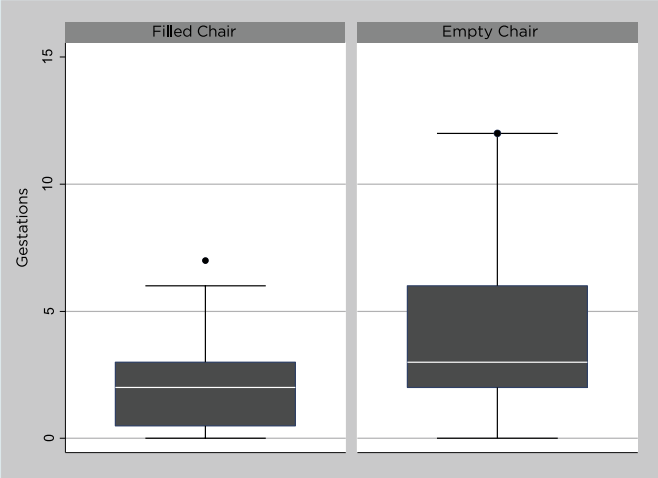

Table 1. Subjects with empty sella syndrome according to sex

Gender variable	Controls (n = 80)	Cases (n = 49)	OR* (IC 95 %)	p
Male	33 (41,25 %)	17 (34,69 %)	0,76 (0,34-1,68)	0,46
Female	47 (58,75 %)	32 (65,31 %)	-	-

*OR: odds ratio.

3.2 Phase 2: 49 cases and 80 controls were included, for a total of 129 patients in this phase.

In the group of cases there were 17 male patients corresponding to 34.69% and 32 female patients corresponding to 65.31%.

In the control group there were 33 male patients corresponding to 41.25% and 47 female patients corresponding to 58.75% (Table 2).

Table 2. Subjects with empty sella syndrome according to age

Variable age grups	Controls (*n* = 80)	Cases (*n* = 9)	OR (95 % CI)	*P*
18-39 years	23 (28,75 %)	4 (8,16 %)	REF	-
40-49 years	11 (13,75 %)	6 (12,24 %)	3,14	0,124
50-59 years	15 (18,75 %)	8 (16,33 %)	3,07	0,108
60-69 years	14 (17,50 %)	17 (34,69 %)	6,98	<0,01
70-79 years	11 (13,75 %)	8 (16,33 %)	4,18	0,04
≥ 80 years	6 (7,50 %)	6 (12,24 %)	5,75	0,03

In the bivariate analysis, age was found to be a risk factor for the empty sella syndrome, which is known as a biological gradient. This study found the greatest risk association in patients in the age group 60-69 years, an OR 6.98, p <0.01. The age groups between 70-79 and 80 and over also reported risk association of empty Turkish saddle with OR 4.18, p < 0.04 and OR 5.75, p 0.03, respectively (Figure 3, Tables 1 and 2).

The risk of suffering from empty sella syndrome increases by 1.08% per year, which means that at the age of 20 there is a 21.6% probability of suffering from this condition, at the age of 40 there is a 43.20% probability, at the age of 60 there is a 64.8% probability and at the age of 80 there is a 86.04% probability.

In the group of cases the number of gestations presents a median of 3 children, with an interquartile range (IQR) (0.5 -2); in the group of controls a median of 2 children with an IQR (2 -6) and a P < 0.01 was found, which implies a statistically significant association with the number of gestations, that is to say that, the greater the number of older children, the greater the finding of an empty sella syndrome is (Table 3, Figure 4).

Table 3. Interquartile range for the gestational variable in cases and controls

	Controls Medium (RIQ)	Cases Medium (RIQ)	*p*
Pregnancies	2 (0,5-3)	3 (2-6)	<0,01

Abbreviations: IQR, Interquartile range.

4. Discussion

In the first phase of the study, the objective of which was to determine the prevalence of ESS in a population in eastern Colombia, 630 brain MRIs were reviewed over a period of 6 months and, in accordance with the defined radiological criteria mentioned in numeral 1.5.1, a total of 140 cases of tESS were found, representing 24% prevalence in the selected population, a data that is also in accordance with the world literature that places the prevalence of this entity between 8 and 35% of the general population (4,5) (Figure 5).

The Empty sella syndrome (ESS) is an anatomical condition characterized by intrasellar herniation of the suprasellar subarachnoid space, often resulting in partial or complete compression of the pituitary gland by the cerebrospinal fluid (1,2). It can be further divided into primary empty sella syndrome (pESS) and secondary empty sella syndrome (sESS) depending on its aetiology. It should be noted that patients with sESS, with underlying pituitary pathology that explains the empty sella syndrome, were excluded from this study.

Primary ESS is due to congenital weakness due to incomplete formation of the sellar diaphragm causing herniation of the diaphragm and compression of the pituitary gland on the sellar floor; other theories with little evidence indicate that suprasellar factors, such as stable or intermittent increase in intracranial pressure,

may promote herniation of the arachnoid membrane or increase the volume within the pituitary gland, although in most studies patients with a radiological diagnosis of ESS have normal intracranial pressures (6). Generally, pESS is diagnosed in patients without hypothalamic or pituitary disease who have not received radiotherapy, surgery or pharmaceutical treatment for pituitary adenomas (7,8). Some factors are predisposed for the presentation of pESS, such as autoimmune endocrine diseases, lymphocytic hypophysitis (8), and pregnancy, particularly in the case of multiparity, where the pituitary volume doubles (9).

The most accepted theory in the development of sESS results from observing the spontaneous course of some suprasellar tumors, such as pituitary adenomas, which in their growth stage cause an increase in the bone space of the Turkish chair, later on spontaneous necrosis of the adenoma allows the herniation of the subarachnoid space and the appearance of the criteria to be considered ESS (10).

Other general causes of ESS are pathological processes, such as infections, trauma or autoimmune infiltrative inflammation, that affect the pituitary gland or by adverse effects of radiotherapy, chemotherapy, drugs and surgery in the treatment of some intra-selletal tumors (7,11).

The results by age group of the prevalence of ESS show that it increases with age in a progressive and constant manner, which is also in accordance with world literature (Figure 1).

Cortical atrophy is manifested by the widening of the furrows, narrowing of the turns, reduction in the thickness of the grey substance, reduction in the volume of the white substance or the enlargement of the cerebral ventricles and subarachnoid spaces. Normal brain aging is associated with these changes, although age-related atrophy is less rapid and usually less severe than that of neurodegenerative disease-as in Alzheimer's. It is estimated that the brain loses about 0.5% of its volume each year in normal aging, compared to 1-2% in mild cognitive impairment (MCI) (12). As a result, atrophy in structural brain imaging must be interpreted in relation to the patient's age and other factors.

It is well known that as one ages, the CSF/encephalic mass ratio increases, resulting in increased subarachnoid spaces in the pericerebral grooves and silvial valleys, which fill with CSF, and the ventricular system can also increase in size (12) (Figures 6 and 7). The volume of the brain decreases progressively from the age of 65 onwards and affects the frontal and temporal lobes more (13). There is more white matter loss than grey matter loss in cognitively normal older adults (14).

Age-related neuronal loss is prominent in the larger neurons of the cerebellum and in the cerebral cortex. The hypothalamus, the bridge (15) and the medulla (16,17) have modest losses of neurons or volume with normal aging. The deterioration of age-related neurons is probably due to apoptosis (programmed cell death) rather than inflammation, ischemia or other mechanism (18). Age also affects persistent neurons, with loss of dendrites and decreased synapses (19). Such changes may contribute more to age-related loss of brain volume than loss of neurons. In some areas, however, dendritic connections may increase, perhaps as a result of the repopulation of the brain that occurs to compensate for cell reduction. Neurons continue to form new synapses, and new neurons form throughout life, but the rate of loss is higher than the rate of gain (20).

It is therefore appropriate to postulate that in view of the strong evidence of the loss of volume and brain size related to age, the empty sella syndrome is simply the reflection of these ex-vacuum findings due to the increase in the CSF/encephalic mass ratio and, therefore, is only one more of the normal signs of aging.

It was also observed that the prevalence of the ESS finding and the directly proportional relationship is higher in the female sex than in the male sex, which is consistent with the world literature in which a preference of pESS for the female sex is observed, with a ratio of 3:1 for pESS and 2.3:1 for sESS (21).

The results of this study found that there is a peak increase in the female sex in the 80-89 year-old age group, and in the male gender the peak is in the 60-69 year-old age group. No explanation was found in the literature for the age difference of these maximum peaks found in the study.

Some predisposing factors associated with pESS, such as autoimmune endocrine diseases, lymphocytic hypophysitis (8), pregnancy, particularly in the case of multiparity, in which the pituitary volume doubles, morbid obesity with associated hypercapnia may cause chronic CSF pressure elevation, which would contribute to herniation of the subarachnoid space in people with hypoplastic selar diaphragms (9).

It is worth mentioning that a possible explanation for the fact that ESS is prevalent in the female gender is precisely the fact of pregnancy and multiparity, since in the former the size of the pituitary gland is increased considerably (up to twice as much) physiologically or adenomas may grow in it, which would favor its subsequent infarction, herniation of the sellar diaphragm and appearance of ESS. This would be a strong hypothesis that would explain why the STV finding is prevalent in the female gender.

The first study published with the introduction of the term ESS, was conducted by Sheehan and Summers in 1949 (22). Sheehan syndrome (postpartum hypopituitarism) is a rare, but potentially life-threatening complication. The pituitary gland enlarges during pregnancy and is prone to hypovolemic shock infarction. Damage to the pituitary gland may be mild or severe, and may affect the secretion of one, several, or all of its hormones. A common presentation is a combination of lactation failure after delivery and amenorrhea or oligomenorrhea, but any of the manifestations of hypopituitarism (hypotension, hyponatremia, hypothyroidism) can occur at any time from the immediate postpartum period to years after delivery. If the patient remains hypotensive after controlling bleeding and volume replacement, she should be evaluated and treated immediately for adrenal insufficiency. Evaluation of other hormonal deficiencies that are not as emerging may take up to four to six weeks after delivery (23-26). This syndrome, known since before 1950 as the cause of pituitary apoplexy, unique in the female sex, may also help explain why ESS is prevalent in women in countries with sociodemographic conditions such as Colombia where multiparity is common.

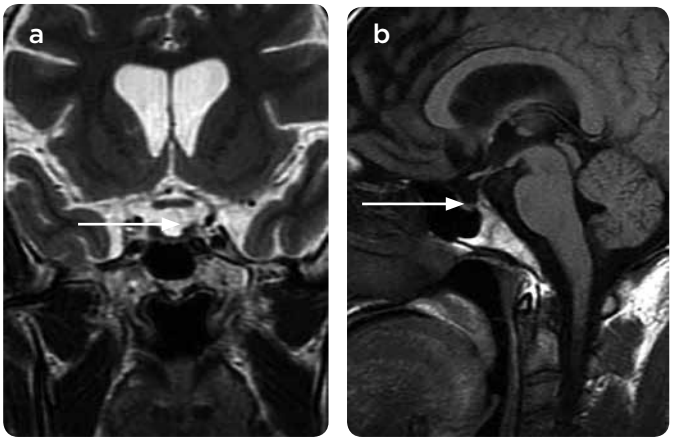

Figure 5. a) Cerebral MRI enhanced in T2, coronal, b) Cerebral MRI enhanced in T1, sagittal, of a 34-year-old man evidencing complete ESS (pituitary height < 2 mm) and sealed space replaced by high signal CSF, and significant changes in cortical atrophy (arrows).

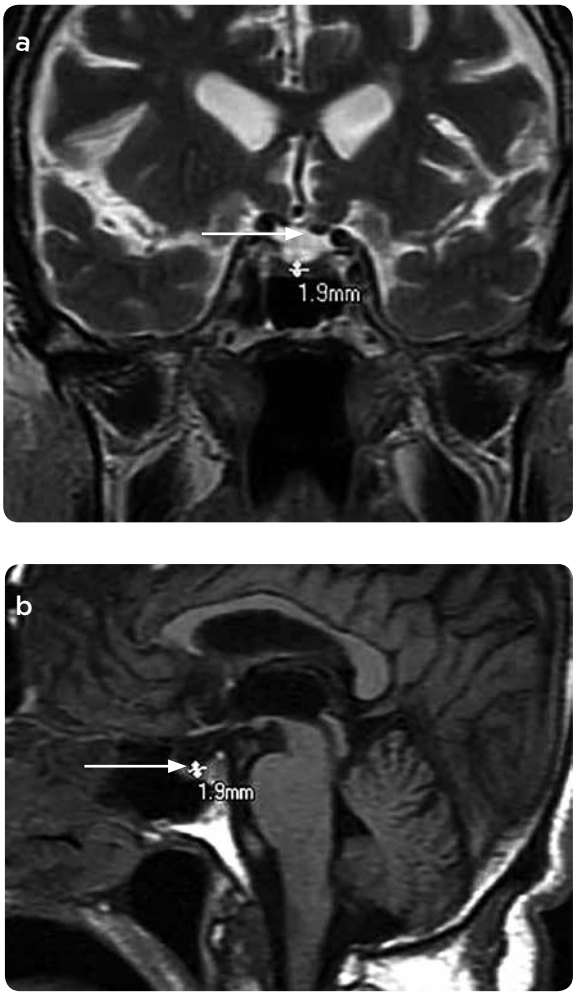

Figure 6. a) Cerebral MRI enhanced in T2, coronal, b) Cerebral MRI enhanced in T1, sagittal, of a 78 year old man evidencing complete ESS (pituitary height < 2 mm) and sealed space replaced by high signal CSF and significant changes in cortical atrophy (arrows).

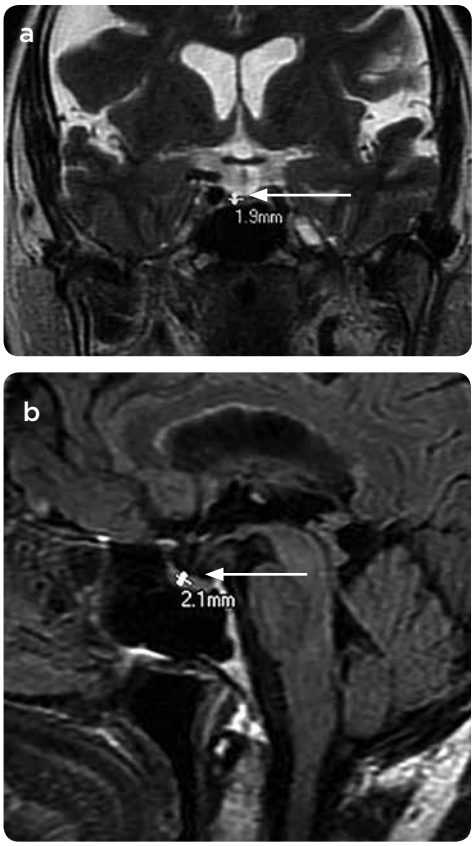

Figure 7. a) Cerebral MRI enhanced in T2, coronal, and b) Cerebral MRI enhanced in T1, sagittal, of a 70-year-old woman evidencing complete ESS (pituitary height < 2 mm) and replaced sellar space by high signal CSF and important changes (arrows).

In the second phase of the study (cases and controls) and following the collection of patients undergoing brain MRI for a period of 2 months, 49 cases and 84 controls were collected prospectively and compared for further analysis.

In the bivariate analysis, age was found to be a risk factor for ESS, which is known as a biological gradient. This study found the greatest risk association in patients in the age group 60-69 years. The age groups 70-79 and 80 and above also showed an association of ESS risk.

The study found that the risk of ESS increases by 1.08% per year.

Considering that the pituitary gland and hypothalamus are responsible for the structural and functional integrity of the systemic endocrine glands, control of processes such as sexual function, fertility, linear and organ growth, lactation, stress responses, energy, appetite, temperature regulation and secondary regulation of mineral metabolism and carbohydrates, i.e. hormonal homeostasis (3), it would be very interesting to carry out a second part of this study, which takes into account the possible relationship between the finding of ESS with endocrine disruption, measured both clinically and paraclinically.

5. Limitations

In this study, the lack of a patient's medical history to determine the reason for the examination was found to be a limitation. Howe-

ver, it was identified that the request for review did not mention the exclusion criteria

6. Conclusion

The prevalence of ESS in the study population is 24%, which is consistent with data from the world literature: the highest incidence in the female sex. In addition, it is directly related to age as a risk factor for this entity.

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Received for assessment: August 30, 2017
Accepted for publication: April 11, 2018