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# Clinical and hormonal assessment of patients with empty sella on MRI

## Kliniczna i hormonalna ocena pacjentów z obrazem pustego siodła tureckiego w badaniu MR

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**Key words**

primary empty sella, secondary empty sella, magnetic resonance imaging, hyperprolactinemia, pituitary deficiency, diabetes insipidus

**Słowa kluczowe**

pierwotnie puste siodło, wtórnie puste siodło, rezonans magnetyczny, hiperprolaktynemia, niedoczynność przysadki, moczówka prosta

Summary

**Introduction.** Empty sella is caused by the herniation of the subarachnoid space within the sella, which results in compression of pituitary gland. The image of empty sella may be an incidental finding on MRI in asymptomatic patients, but it can be also associated with severe neurological, ophthalmological and endocrine disorders.

**Aim.** The aim of the study was to analyze clinical and hormonal data of patients with empty sella on MRI.

**Material and methods.** We performed a retrospective review of the medical data of patients hospitalized in the Department of Endocrinology in Bielański Hospital during one year searching for those with the diagnosis of empty sella. We collected data on the age, sex, causes of empty sella, results of pituitary function and we analysed the results of MRI of pituitary-hypothalamic region.

**Results.** Among 1724 patients hospitalized in the Department 40 patients (2.3%) had empty sella on MRI. Twenty one (52.5%) patients were diagnosed with primary empty sella (PES) and 19 (47.5%) were diagnosed with secondary empty sella (SES). In patients with PES there were 16 (76.2%) females and 5 (23.8%) (3 to 1 ratio). More than half of PES females (53%) had a history of at least two pregnancies. The mean BMI in PES patients was 27.4 kg/m$^2$. The mean age at diagnosis was 47.8 ± 14.6 years in the whole group. During the hormonal assessment 5 patients (23.8%) with PES were found to have some degree of anterior pituitary deficiency. The most frequent disorder (19%) was hypogonadotropic hypogonadism with symptoms of oligomenorrhoea in females and decreased sexual function in men. In seventeen patients (81%) in PES group MRI revealed partial empty sella (less than 50% of the sella filled with CSF) while in 4 patients (19%) total empty sella (more than 50% of sella filled with CSF).

**Conclusions.** In our study, PES was more common in middle aged, overweight multiparous women. In most cases PES was incidentally discovered by imaging study, but in some it led to diagnosis of anterior pituitary deficiency during the diagnostic evaluation.

Streszczenie

**Wstęp.** Obraz pustego siodła jest wynikiem wgłębiania się opony pajęczej i przestrzeni podpajęczynówkowej w obręb siodła tureckiego. Obraz ten jest najczęściej przypadkowym znaleziskiem u bezobjawowych pacjentów podczas badania MR. Może być jednak związany z poważnymi zaburzeniami neurologicznymi, okulistycznymi i endokrynnymi.

**Cel pracy.** Celem pracy była kliniczna i hormonalna ocena pacjentów z obrazem pustego siodła w badaniu MR.

**Materiał i metody.** W badaniu retrospektywnym przeprowadziliśmy analizę dokumentacji medycznej pacjentów hospitalizowanych w Klinice Endokrynologii CMKP w Szpitalu Bielańskim podczas jednego roku. Wyszukano pacjentów z obrazem pustego siodła w badaniu MR i zebrano dane dotyczące wieku, płci, BMI, przyczyn choroby, czynności przysadki oraz stosowanego leczenia. Analizowano również wyniki badania MR okolicy przysadkowo-podwzgórzowej.

**Wyniki.** U 40 spośród 1724 (2,3%) pacjentów hospitalizowanych w Klinice uwidoczniono obraz pustego siodła w MR, w tym u 21 (52,5%) osób rozpoznano obraz pierwotnie pustego siodła (PES), natomiast u 19 (47,5%) – wtórnie puste siodło (SES). W grupie pacjentów z PES stosunek kobiet do mężczyzn wynosił 3 do 1. Ponad połowa kobiet z PES (53%) była wieloródkami. Wiek w chwili rozpoznania wynosił 47,8 ± 14,6 roku. Średnie BMI u pacjentów z PES wynosiło 27,4 kg/m$^2$. Podczas oceny hormonalnej u 5 pa-

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cjentów (23,8%) z PES rozpoznano niedoczynność przysadki, w tym najczęściej stwierdzano niedoczynność osi gonadotropowej (19%). Hiperprolaktynemia była rzadkim zaburzeniem. U 17 pacjentów (81%) z PES stwierdzono w MR częściowo puste siodło (mniej niż połowa wysokości siodła tureckiego wypełniona płynem mózgowo-rdzeniowym), natomiast u 4 pacjentów (19%) stwierdzono całkowicie puste siodło (więcej niż połowa wysokości siodła tureckiego wypełniona płynem mózgowo-rdzeniowym).

**Wnioski.** Obraz pustego siodła był rzadkim rozpoznaniem u pacjentów Kliniki. Wśród pacjentów z pierwotnie pustym siodłem przeważały kobiety, wieloródki z nadwagą. U większości pacjentów rozpoznanie pustego siodła było przypadkowym rozpoznaniem, jednak u 23% prowadziło do rozpoznania niedoczynności przysadki.

## INTRODUCTION

The term empty sella is referred to intrasellar herniation of suprasellar arachnoid and cerebrospinal fluid (CSF) of subarachnoid space, resulting in flattening of the pituitary gland (1). An anatomic defect in the sellar diaphragm has been found in up to 50% of adults and the overall incidence of an empty sella on imaging has been estimated at 12% (2, 3). Empty sella is defined as partial or total when less or more than 50% of the sella is filled with CSF respectively, with the gland thickness being < 2 mm in the latter case (fig. 1) (1). The widespread use of computed tomography (CT) and magnetic resonance imaging (MRI) has made empty sella a common incidental finding. According to data obtained from autopsies and neurological studies, the presence of empty sella ranges from 5.5 to 38% with female to male ratio of 4 to 1 (4). Two types of empty sella should be distinguished. Secondary empty sella (SES) may be caused by pituitary adenomas either undergoing spontaneous shrinkage or more often after medical treatment, surgery or radiation therapy. The image of empty sella may be also a result of a regression of an inflammatory lesions of a pituitary gland such as lymphocytic and granulomatous hypophysitis (4, 5). When no apparent cause of the herniation of subarachnoid space is present (such as surgery, radiotherapy or medical medical treatment for an intrasellar tumor) it is a primary empty sella (PES). Several etiopathogenic hypotheses have been introduced, including a congenital incomplete formation of the sellar diaphragm (1). Moreover, the empty sella has been associated with elevated intracranial pressure (ICP), posteriorly placed optic chiasm and a reduction in pituitary gland volume due to menopause, multiparity, pituitary gland infarction, obesity or dopamine agonists and somatostatin analogs treatment (6). Chronically transmitted CSF pulsations from the herniated subarachnoid space can results in bony expansion and remodeling of the sella turcica. On the other hand the empty sella is the most commonly described imaging sign in the setting of idiopathic intracranial hypertension (also known as pseudotumor cerebri) and presumably there is a correlation between the flattening of the pituitary gland and chronically elevated ICP. On MRI , the empty sella is shown by varying degrees of flatteing of the superior surface of the pituitary gland, elongated pituitary stalk and by CSF-intensity signal within the sella and is often associated with enlargement and remodeling of bony sella (7). Empty sella may be a radiological finding in asymptomatic patients, but it may be also associated with numerous disorders such as neurological, visual and endocrine.

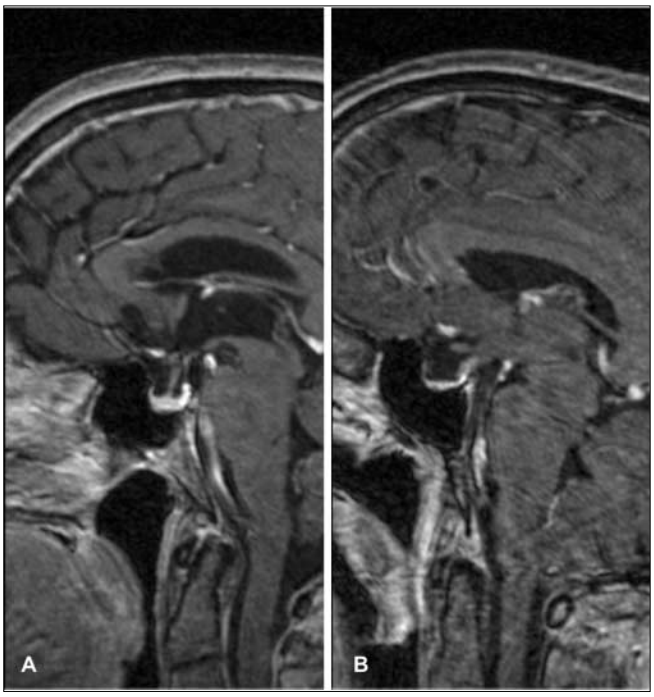


**Fig. 1.** Midsagittal contrast-enhanced T1-weighted MRI image shows A) partial empty sella and B) total empty sella.

## AIM

The aim of the study was to retrospectively review the data of patients with empty sella on MRI hospitalized during one year in the Department of Endocrinology of The Centre of Postgraduate Medical Education in Bielański Hospital. We evaluated clinical characteristics, pituitary function and radiological features, with a detailed analysis of the magnetic resonance imaging of the pituitary-hypothalamic region results.

## MATERIAL AND METHODS

We retrospectively reviewed the electronic medical records of patients hospitalized in the Department of Endocrinology in Bielański Hospi-

tal between September 2012 and September 2013 searching for the patients with the ICD-10 codes: D35.2 (benign neoplasm of pituitary gland) and E23. That included patients with following codes: E23.0 (hypopituitarism), E23.1 (iatrogenic hypopituitarism), E23.2 (diabetes insipidus), E23.6 (other disorders of pituitary gland). We found of 300 of such and then we searched their electronic and paper documentation to find the cases with the diagnosis of empty sella. The results of current magnetic resonance imaging of pituitary-hypothalamic region were analyzed and 40 patients had empty sella present. We estimated the pituitary height on MRI in all cases. We collected data on the age, sex, BMI, causes of empty sella and results of hormonal and ophthalmological evaluation (if available). Basal endocrine evaluation was performed in most patients: TSH, free T4, ATPO, ACTH, cortisol, LH, FSH, estradiol, testosterone (men), PRL, GH, IGF-1 (age and gender adjusted). Dynamic tests were performed to evaluate the gonadotropic axis if necessary.

## RESULTS

From September 2012 to September 2013 one thousand seven hundred twenty four patients with numerous endocrine disorders were hospitalized in the Department of Endocrinology in Bielański Hospital. Among them we found 40 patients with an empty sella on MRI which constituted 2.3% of all hospitalized patients in the Department of Endocrinology.

Of the 40 patients studied 26 (65%) were females and 14 (35%) were males. Twenty one (52.5%) patients were diagnosed with primary empty sella and 19 (47.5%) were diagnosed with secondary empty sella. In patients with PES there were 16 (76.2%) females and 5 (23.8%) males while in a group of patients with SES there were 10 (52.6%) females and 9 (47.4%) males. In PES group the female to male ratio was 3 to 1. More than half of PES females (53%) had a history of at least two pregnancies. The mean age of diagnosis in the whole group was 47.8 ± 14.6 years. In a group of patients with PES the mean age of diagnosis was 49.4 ± 16.4 while in the group of patients with SES was 47.2 ± 14.1. The mean BMI in PES patients was 27.4 kg/m$^2$ and in SES patients 25.8 kg/m$^2$. In patients with PES MRI was ordered for multiple reasons: headache (57.1%), endocrine disorders (19%), visual disturbances (14.3%), neurological symptoms (4.8%) and others (4.8%). During the hormonal assessment 5 patients (23.8%) with PES were found to have some degree of anterior pituitary deficiency. The most frequent disorder (19%) was hypogonadotropic hypogonadism with symptoms of oligomenorrhoea in females and decreased sexual function in men. In 2 patients (9.5%) low basal GH and IGF-1 below the normal range for gender and age was found. Only one patient had multihormonal pitutary deficiency with secondary thyroid and gonads insufficiency and diabetes insipidus. Biochemical evaluation revealed hyperprolactinemia in one patient (4.8%). The mean prolactin level was 9.7 ± 5.8 ug/L. The mean concentrations of other hormones are presented in table 1. In two male subjects (9.5%), studied for remarkable polyuria (> 4 L/24 hours) and polydipsia, central diabetes insipidus was diagnosed with water deprivation test. These patients showed clinical improvement on DDAVP treatment. In 4 PES patients (19%) positive anti-thyroid peroxidase antibodies (anti-TPO antibodies) were confirmed. In PES group most alterations found during ophthalmological examination (available only in a few cases) were: blurred vision acuity or nonspecific field defects while 26.3% of SES patients had severe field defects. Headache was the most prevalent symptom reported by 81% of patients in our study. Seventeen patients (81%) in PES group had partial empty sella on MRI (less than 50% of the sella filled with CSF; pituitary ≥ 3 mm) while 4 patients (19%) had total empty sella (more than 50% of sella filled with CSF; pituitary height ≤ 2 mm). We performed a careful screening for pituitary adenoma, especially in patients with partial empty sella. All patients with pituitary lesions suspected to be involuted pituitary adenomas were categorized as SES. The degree of empty sella did not seem to strictly correlate with the severity of and/or the nature of clinical picture.

**Table 1.** Baseline endocrine evaluation in patients with empty sella (mean ± SD).

| Hormone | Normal range | Primary empty sella | Secondary empty sella |
|---|---|---|---|
| ACTH | 5-46 pg/mL | 15.79 ± 9.8 | 19.4 ± 6.53 |
| Cortisol | 5-22 ug/dL | 9.68 ± 5.83 | 8.6 ± 4.05 |
| TSH | 0.35-4 uIU/mL | 1.05 ± 0.61 | 1.06 ± 0.86 |
| fT4 | 10.29-22.7 pmol/L | 14.24 ± 1.9 | 14.17 ± 3.87 |
| PRL | female 1.9-25 ng/mL<br>male 1.9-17 ng/mL | 9.68 ± 5.8 | 15.06 ± 10.23 |
| LH | premenopausal 1.1-9.2 IU/L<br>postmenopausal 15.4-53.3 IU/L<br>male 2.8-6.8 IU/L | 9.45 ± 7.82 | 5.75 ± 3.24 |
| FSH | premenopausal 2.8-10.2 IU/L<br>postmenopausal 13.9-102.1 IU/L<br>male 1.3-11.8 IU/L | 22.94 ± 15.6 | 20.63 ± 11.3 |
| Estradiol | premenopausal 0-112 pg/mL<br>postmenopausal 0-45 pg/mL | 46.53 ± 25.89 | 40 ± 20.5 |
| Testosterone | 1.57-9.23 ng/mL | 3.8 ± 1.96 | 1.87 ± 1.22 |
| IGF-1 | female 43-436 ng/mL<br>male 53-461 ng/mL | 172.5 ± 34.75 | 168.37 ± 22.56 |

Among patients with SES there were 13 patients with macroadenoma (68.4%): 11 of them were previously treated with surgery and two with dopamine agonists; 4 patients with microadenoma (21.1%) after dopamine agonists treatment and 2 patients (10.5%) with lymphocytic hypophysitis. Majority of SES patients presented as a total empty sella with enlarged bony sella. Majority of these patients (84.2%) had multihormonal pituitary deficiency.

## DISCUSSION

Primary empty sella is reported as a common finding in autopsies and neuroradiological exams, ranging from 5.5 to 38% in different series (4, 8). In a large epidemiological study, Foresti et al. detected signs of primary empty sella in 140 out of 500 (38%) consecutive patients, aged 11-82 years, who underwent MR imaging of the brain for a variety of conditions not related to pathologic processes of the sellar or juxtasellar regions. They found 9.6% of cases among subjects under 40 years old and 39.9% of cases among those above 40 (4). In our study the patients with signs of empty sella on MRI constituted only 2.3% of all hospitalized patients in the Department of Endocrinology during one year. Among these patients only 21 patients had primary empty sella. This could mean that not all patients with incidentally visualized on MRI empty sella undergo an endocrine evaluation of pituitary function. It has been proved in many studies that primary empty sella occurs more often in female patients (1, 6). In our study in patients with PES, the female to male ratio was 3 to 1 which is similar to other studies. We did not found such a female gender predominance in a group of patients with SES. Pregnancy is believed to be a trigger factor for PES. The pituitary gland doubles in size during pregnancy, and this is of great importance in the case of multiple pregnancies. The enlargement of a pituitary gland may contribute to the herniation of the subarachnoid space in case of hypoplastic sellar diaphragm and/or CSF hypertension, even if it is moderate or temporary (6). In our study 53% of women were multiparous. PES has been associated with obesity in several reports (9-11). It is believed that obesity can induce hypercapnia, which could be associated with chronically elevated CSF pressure and could induce herniation of suprasellar suparachnoid space (10). Our data suggest a relationship between obesity and empty sella, as the mean BMI in PES patients was 27.4 kg/m$^2$. PES has also been reported in association with various endocrine autoimmune diseases, and the image of empty sella itself has been suggested to be a consequence of lymphocytic hypophysitis (12, 13). However, in our study the patients with known history of lymphocytic hypophysitis were categorized as a SES. Measurements of antipituitary antibodies are not routinely available, so we cannot establish a clear connection between PES and autoimmunity.

Headache is one of the most common symptoms in PES, reported in 60-80% of cases (1, 6). Similarly, in our study headache was the main complaint of 81% of patients. Headache was also the main cause for ordering brain imaging in our study, namely in 57.1% of cases. The relationship between headache and PES could be accidental in some patients, since it is a common symptom in general population. Anyway, in patients with PES, headache may be caused hypothetically by the traction on vascular-meningeal structures in the sellar cavity, although there is no conclusive evidence (7).

Visual disturbances have been reported in 1.6-16% of cases in different studies (7, 14). In our study visual disturbances were the reason for brain imaging in 14.3% of patients. During ophthalmological assessment (available only in a few cases) most alterations were: blurred vision aquity or nonspecific visual field defects. Secondary empty sella is most commonly caused by spontaneous or post treatment regression of a pituitary adenoma and it is more likely to cause visual defects than PES. Visual defects may be severe, and usually consists of decreased visual aquity, visual field defects, tunnel vision, bitemporal hemianopsia and quadrantanopia (6). In our study majority of SES patients had various defects in visual field. Visual field defects may occur even without radiological evidence of herniation of the visual system, as reported by Guinto et al. (14).

In several previous studies, pituitary function was reported as normal in patients with PES (15, 16). However, pituitary dysfunction can be explained by chronic compression of the pituitary gland and the pituitary stalk by CSF. The most commonly found pituitary disorders reported in some studies associated with PES are hyperprolactinemia and GH deficiency (17). Different degrees of hypopituitarism ranging from 8 to 60% have been also reported (17, 18). In our study 23.8% of patients had some degree of hypopituitarism. It has been believed that GH deficiency is an early event in patients with PES. Due to the anatomical disposition of somatotrophes within the anterior pituitary lobe, these cells might be more vulnerable to increased intrasellar pressure. However, some authors claim that obesity might play a central role because of its known action in decreasing spontaneous or induced GH secretion (17). In recent study, Poggi et al. found GH/IGF-1 axis dysfunction in 11/28 (39.2%) patients with PES after GHRH plus arginine stimulation test (18). This study supports the need to assess the somatotropic axis in patients with PES, even if they are not affected by other deficiencies. We found low GH and IGF-1 levels in 2 patients (9.5%). IGF-1 is considered as a reliable diagnostic tool for diagnosing GH deficiency in patients with at least 3 pituitary deficiencies. The somatotropic axis was not studied in our patients due to unavailability of stimulation tests in the Department, so the number of patients with growth hormone deficiency may be underestimated. Hyperprolactinemia has been frequently associated with PES with incidence ranging from 10-37.5% according to the literature, and it has been proposed as the most common endocrine abnormality (1, 4, 6). The pathophysiology of hyperprolactinemia in empty sella is related to pituitary stalk compression secondary to increased CSF which results in a decrease in the PRL inhibitory factor, dopamine. Prolactin levels rarely exceed 100 ug/L. In our study hyperprolactinemia was noticed only in one patient with a prolactin level below 50 ug/L. In our study the most common pituitary deficiency was hypogonadotropic hypogonadism presenting with symptoms of oli-

gomenorrhoea in females and decreased sexual function in men. Low levels of FSH and LH were present in 19% of PES patients. In two male subjects (9.5%), studied for remarkable polyuria (> 4 L/24 hours) and polydipsia, central diabetes insipidus was diagnosed with water deprivation test. In previous studies diabetes insipidus is reported to be rarely associated with PES (1, 4, 6). Diabetes insipidus in these two patients may be a result of a regression of lymphocytic hypophysitis. In these two cases the diagnosis of PES is rather presumptive and with a known history of such lesions as lymphocytic hypophysitis they would be classify as SES.

Treatment options for patients with PES include hormone replacement and dopamine agonists in patients with symptomatic hyperprolactinemia. Asymptomatic patients should just remain under observation, although they are unlikely to develop hormonal or radiological changes during follow-up. It is a retrospective study so no follow-up data are available. However, because of the theoretical risk of progression a regular endocrine, neuro-ophthalmological and radiological assessment is recommended in the literature (6).

## CONCLUSIONS

Empty sella is a multifactorial condition ranging from asymptomatic presentation in primary empty sella patients to patients with multiple pituitary deficiency and ophthalmological disorders in secondary empty sella. In our study, primary empty sella was more common in middle aged, overweight, multiparous women. In most cases primary empty sella was incidentally discovered by imaging study, while in some it was found during the diagnostic evaluation of anterior pituitary deficiency or neurological disturbances such as headaches.

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