THE CAUCASUS JOURNAL OF MEDICAL & PSYCHOLOGICAL SCIENCES
კავკასიის მედიცინის და ფსიქოლოგიის მეცნიერებათა ჟურნალი
КАВКАЗСКИЙ ЖУРНАЛ МЕДИЦИНСКИХ И ПСИХОЛОГИЧЕСКИХ НАУК
高加索医学和心理科学杂志

2024, Volume 2, Number 1-2
eISSN 2720-8788
pISSN 2720-877X

CENTRAL HYPOTHYROIDISM ASSOCIATED WITH EMPTY SELLA: LITERATURE REVIEW AND CASE REPORT

Meri P. Rekvava[1], Tamar T. Dundua[1,2], Lali V. Javashvili[1,2], Irakli V. Gakhokidze[3,4], Nino T. Meladze[1]

ABSTRACT

Empty Sella Syndrome (ESS) is a rare case of sella turcica malformation, resulting in pituitary gland decrease. It may reveal itself through neurological symptoms, endocrine disorders, visual disturbances or incidental findings during imaging. The urgency of this problem has increased with the widespread use in the diagnosis of the non-invasive method of magnetic resonance imaging (MRI). It can be discovered as part of the investigation of the pituitary disorders, or as an incidental finding when imaging the brain. Practice shows that such patients rarely come with typical complaints thus an extended review of this case is needed to prompt suspicion and aid in the diagnosis of ESS. Few cases of empty sella associated with isolated thyroid-stimulating hormone (TSH) deficiency were published. We report a case of a 46 year-old woman with complaints: edema, dizziness, low blood pressure, hair loss, dry skin. Examinations were performed: ultrasound of the thyroid gland, TSH, FT4 (free thyroxine), FT3 (free triiodothyronine), anti TPO (Antibodies to thyroid peroxidase). Conclusion: patients with TSH, FT4, and FT3 deficiency, should undergo examinations to exclude empty sella as one of the reason of central hypothyroidism. According to the above mentioned the recommendation is to examine all the tropic hormones of the pituitary gland after diagnosing empty sella. Diagnosing central hypothyroidism associated with empty sella helps improving the knowledge and points to different clinical manifestation of empty sella syndrome.

[1]Clinic Cortex, Tbilisi, Georgia; [2]University of Georgia, Tbilisi, Georgia; [3]New Vision University, Tbilisi Georgia; [4]Aversi Clinic Tbilisi, Georgia

KEYWORDS: empty sella; sella turcica; central hypothyroidism; pituitary gland; empty sella syndrome

Cite: Rekvava MP, Dundua TT, Javashvili LV, Gakhokidze IV, Meladze1NT. Central hypothyroidism associated with empty sella. *Cauc J Med &Psychol Sci.* 2024; V.2 (№ 1-2): 98-107; DOI: 10.61699/cjmps-v2-i1-2-p98-107

Sella turcica (L., "Turkish saddle") is a saddle-shaped depression, located in the middle cranial fossa on the upper surface of the sphenoid bone. The term *empty sella* is introduced by W. Busch in 1951 and applied to the appearance of the sella turcica when the diaphragma sellae is incomplete or forms only a small peripheral rim and the pituitary gland is not visible grossly as one views the sella turcica from above at necropsy or at surgery.[4]

Laura De Marinis, Sabrina Chiloiro et al. define empty sella as herniation of subarachnoid space into the sella turcica (arachnoidocele). It is a term for the radiological finding of *empty sellar space* on magnetic resonance imaging (MRI) and computerized tomography (CT) with a flattened pituitary and elongated stalk. It can be partial if less than 50% of sellar space is filled with cerebro-spinal fluid (CSF) (pituitary thickness 3 mm or less), or complete if CSF fills more than 50% of space in the sella (pituitary thickness 2 mm or less). [8]. Empty sella is distinguished in primary and secondary forms. Primary empty sella (PES) excludes any history of previous pituitary pathologies such as previous surgical, pharmacologic, or radiotherapy treatment of the sellar region. PES is considered an idiopathic disease and may be associated with idiopathic intracranial hypertension. Secondary empty sella, however, may occur after the treatment of pituitary tumors through neurosurgery or drugs or radiotherapy, after spontaneous necrosis (ischemia or hemorrhage) of chiefly adenomas, after pituitary infectious processes, pituitary autoimmune diseases, or brain trauma. Empty sella, in the majority of cases, is only a neuroradiological finding, without any clinical implication. However, empty sella syndrome is defined in the presence of pituitary hormonal dysfunction (more frequently hypopituitarism) and/or neurological symptoms due to the possible coexisting of idiopathic intracranial hypertension. Empty sella syndrome represents a peculiar clinical entity, characterized by heterogeneity both in clinical manifestations and in hormonal alterations, sometimes reaching severe extremes. For a proper diagnosis, management, and follow-up of empty sella syndrome, a multidisciplinary approach with the integration of endocrine, neurological, and ophthalmological experts is strongly advocated.[7]

It is often discovered during imaging tests for pituitary disorders, using MRI of the sellar and suprasellar regions. Over the years, radiologists noticed a similar phenomenon in CT and MRI brain imaging, further refining the term "empty sella". As it was mentioned above, empty sella syndrome, also known as arachnoidocele, is a disorder in which the subarachnoid space herniates into the sella turcica causing compression and flattening of the pituitary gland. Subsequently, the pituitary gland contained in the sella turcica is compressed and flattened, and the pituitary stalk is stretched by the cerebrospinal fluid (CSF), which fills the space, leading to partial or total compression of the pituitary gland, often resulting in hormonal deficiencies. It involves the sella turcica, a bony structure at the base of the brain that surrounds and protects the pituitary gland. [11] Examinations reveal low pituitary hormone levels and lack of

response to stimuli. Most patients suffer from central hypothyroidism as part of pituitary insufficiency. Epidemiology data of empty sella are strongly influenced by collection methods. The first epidemiologic data were derived from an autopsy series and suggested an incidental finding of empty sella in approximately 5.5%–12% of cases [4].

The Empty Sella syndrome (ESS) incidences ranging from 5.5% to 12% of autopsy cases, up to 12% in patients undergoing neuroimaging. Most patients with PES are females affected by obesity, hypertension, headaches, and/or impaired vision with a sex ratio of 4-5:1. [6]. Neuroradiological studies have suggested empty sella is the neuroradiological or pathological finding of an apparently empty sella turcica containing no pituitary tissue. The prevalence of primary empty sella, i.e., empty sella without any discernible cause, is not precisely known; estimates range from 2% to 20%. Technical advances in neuroradiology have made empty sella an increasingly common incidental finding. It remains unclear whether, and to what extent, asymptomatic adult patients with an incidentally discovered empty sella should undergo diagnostic testing for hormonal disturbances.[3] Peter Ucciferro and Catherine Anastasopoulou noted that although empty sella has historically been considered an incidental finding without clinical significance, recent evidence suggests that patients may have associated symptoms, otherwise known as ESS, more frequently than previously believed. Consequently, most experts recommend a thorough evaluation in all patients initially found to have empty sella; reevaluation in asymptomatic patients may be reasonable also. Symptomatic patients with ESS should be managed supportively; the type of treatment indicated can vary from pharmacologic (eg, growth hormone replacement) to surgical (eg, lumbar peritoneal shunt) therapies. Because this condition is being identified more frequently and may be associated with more symptoms than previously believed, clinicians should be familiar with this finding and the variety of potential presentations. This activity will enhance the healthcare professional's competence in diagnosing and managing empty sella syndrome and highlight the critical need for collaboration among multidisciplinary team members such as ophthalmology, neurology, and endocrinology clinicians to improve patient outcomes.[14]

Radiographic studies have gradually become more widely used, leading to an increase in incidental findings. Amongst them is the radiographic appearance of an empty sella.

The relation of hypothyroidism in empty sella has been reported a couple of times.[1]

Incidental radiographic findings of an empty sella are prevalent in up to 35% of the general population. While empty sella was initially considered clinically insignificant, a subset of patients exhibits endocrine or neuro-ophthalmologic manifestations which are diagnostic of empty sella syndrome (ESS). Recent studies suggest that more patients are affected by ESS than previously recognized, necessitating a deeper understanding of this condition. Laura Oleaga et al. studied 11 cases of empty sella with different peripheral pituitary deficiencies. All the patients underwent

MR imaging. MR imaging revealed five cases of partially empty sella with residual pituitary gland on the sella floor and six cases in which the sella was completely empty. It was concluded that MR imaging is the technique of choice in the study of abnormal hypothalamic-pituitary activity. Empty and partially empty sella should be included among the frequent causes of hypopituitarism although there is no clear relationship between the degree of adenohypophyseal insufficiency and the degree of atrophy of this system as viewed in MR images. In some cases, this entity may be the radiological sign of a phase in the development of an autoimmune inflammatory process involving the pituitary gland.[13] Akkus G, Sözütok S, Odabaş F, et al. conducted the study to determine pituitary dysfunction in patients with partial or total primary empty sella, and to evaluate the significance of pituitary volume measurements in these patients. There was not any significant correlation found between the anterior pituitary hormones and volume measurements. Although volume measurement has helped in the diagnosis of pituitary empty sella (partial or total), it does not seem to have any significant correlation with pituitary secretory function. [2] Carosi G, Brunetti A, Mangone A, et al. noted that primary PES represents a frequent finding, but data on hormonal alterations are heterogeneous, and its natural history is still unclear. The evaluation of the pituitary function of patients with neuroradiological confirmed PES and a complete hormonal assessment (between1984-2020) showed that hypopituitarism was frequent (40%) but hormonal deterioration seemed uncommon (3%). It was concluded that patients need to be carefully evaluated at diagnosis, even if PES is incidentally discovered. [5]

Since the December of 2019 there has been an increase in reporting of cerebrovascular events in patients infected with COVID-19. Shubham Nimkar, et al. in the case report noted that Empty Sella syndrome should be explored in any patient who has a persistent headache, blurred vision, obesity, or an endocrine issue. A young, elderly who just complains of a prolonged headache and a small visual aberration and who has a history of COVID-19 infection should be checked for ESS. All clinicians should keep this in mind since it will lead to an earlier diagnosis and better patient care [12] Another very probable cause of an empty sella in Covid-19 is the occurrence of raised intracranial hypertension in Covid-19, which has recently been highlighted in a few case reports. It is suggested that in a patient with a congenitally incompetent diaphragm sella, chronically raised intracranial pressure caused herniation of the subarachnoid space into the sella turcica. Subsequently, sella turcica enlargement and remodeling occur, sometimes with endocrine, visual, and other sequelae. In a few cases, reports of the diaphragm and supra sellar factors such as a stable or intermittent increase in intracranial pressure have also been implicated, but they are a cause of primary empty sella and not infection associated. [12] In this patient, hormonal imbalances like hypothyroidism due to panhypopituitarism can cause clinical manifestations like giddiness, headache, facial puffiness, and edema to rule out the central cause of her symptoms thus specifying pituitary involvement

is the primary goal who has recovered from Covid-19 infection. We may miss the diagnosis or misdiagnose patients presenting with such conditions. In this case, hyponatremia is an important clue for further evaluation of the central cause with a normal kidney function test and liver function test. It was concluded that Empty Sella syndrome should be explored in any patient who has a persistent headache, blurred vision, obesity, or an endocrine issue. A young, elderly who just complains of a prolonged headache and a small visual aberration and who has a history of COVID-19 infection should be checked for ESS. All clinicians should keep this in mind since it will lead to an earlier diagnosis and better patient care. [12] Michelle Lundholm and Divya Yogi-Morren, conducted literature review on etiologies and risk factors associated with primary and secondary empty sella, the radiologic features that differentiate empty sella from other sellar lesions, and the role of clinical history and hormone testing in identifying patients with ESS, as well as treatment modalities. They pointed to the necessity of pituitary function testing for somatotroph, lactotroph, gonadotroph, corticotroph, and thyrotroph abnormalities when suspecting ESS. While an isolated empty sella finding does not require treatment, ESS may require pharmacologic or surgical interventions to address hormone deficits or intracranial hypertension. Targeted hormone replacement as directed by the endocrinologist should align with guidelines and patient-specific needs. Treatment may involve a multidisciplinary collaboration with neurology, neurosurgery, or ophthalmology to address patient symptoms. The review written by Michelle D. Lundholm and Divya Yogi-Morren underscores the evolving understanding of ESS, stressing the significance of accurate diagnosis and tailored management to mitigate potential neurologic and endocrine complications in affected individuals.[9]

It has been reported that 50% of patients are asymptomatic, and others experience symptoms, such as headache, hypertension, or visual field defects. Few cases have an empty sella syndrome, i.e., lacking functional pituitary hormones. Diagnosis is made through NMR or CT.

[10] If asymptomatic, this condition requires no treatment; otherwise, empty sella syndrome needs hormonal replacement therapy. Benedetta Masserini et al examined the case of asymptomatic empty sella syndrome. A 67-year-old female patient was admitted for dilatative cardiomyopathy. She had a past medical history of arterial hypertension and right ICA endovascular repair. Blood tests demonstrated hypothyroidism, hypoadrenalism, and GH deficiency, without any signs or symptoms. NRM confirmed an empty sella, hence replacement therapy with levothyroxine and cortisone acetate was started. During a follow-up evaluation, we discovered that this biochemical profile of the patient had been known for more than a decade and never treated. Despite being exposed to stress conditions, vascular surgery and angiography, she never developed an adrenal crisis, nor has she ever been symptomatic for severe hypothyroidism. Hormonal replacement therapy was performed. The described clinical scenario is rare, as usually, empty sella syndrome presents with signs of hormone

deficiency, even if asymptomatic cases have been described. Some authors suggest considering it as a hypothalamic dysfunction requiring treatment; others identify it as a paraphysiological variant. However, more cases are needed to establish a correct therapeutic strategy for these patients.[10]

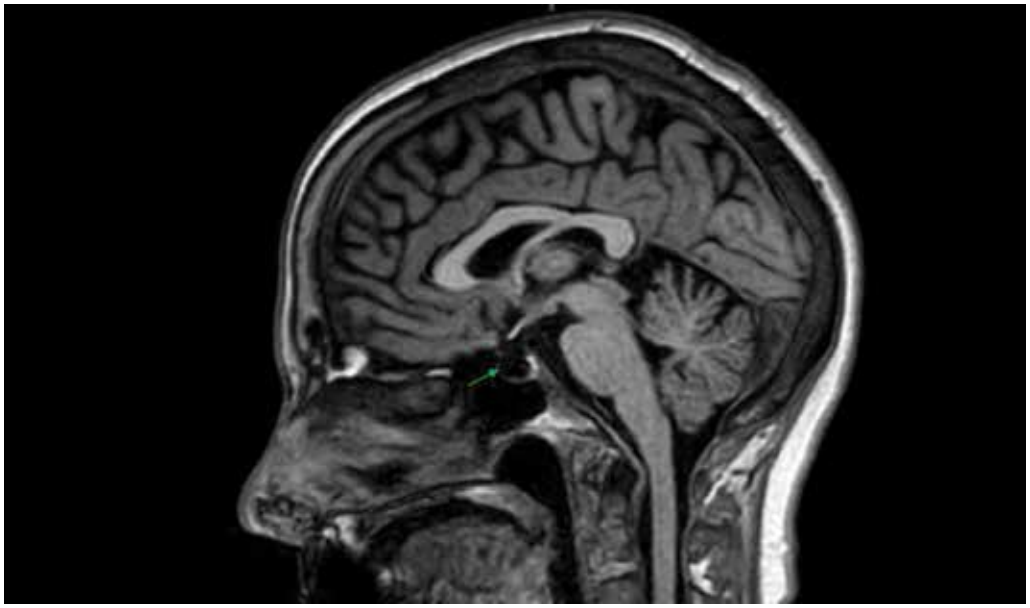

Fig1. Empty sella: T1 sagittal, the pituitary gland is not visible in the sellar region (green arrow)

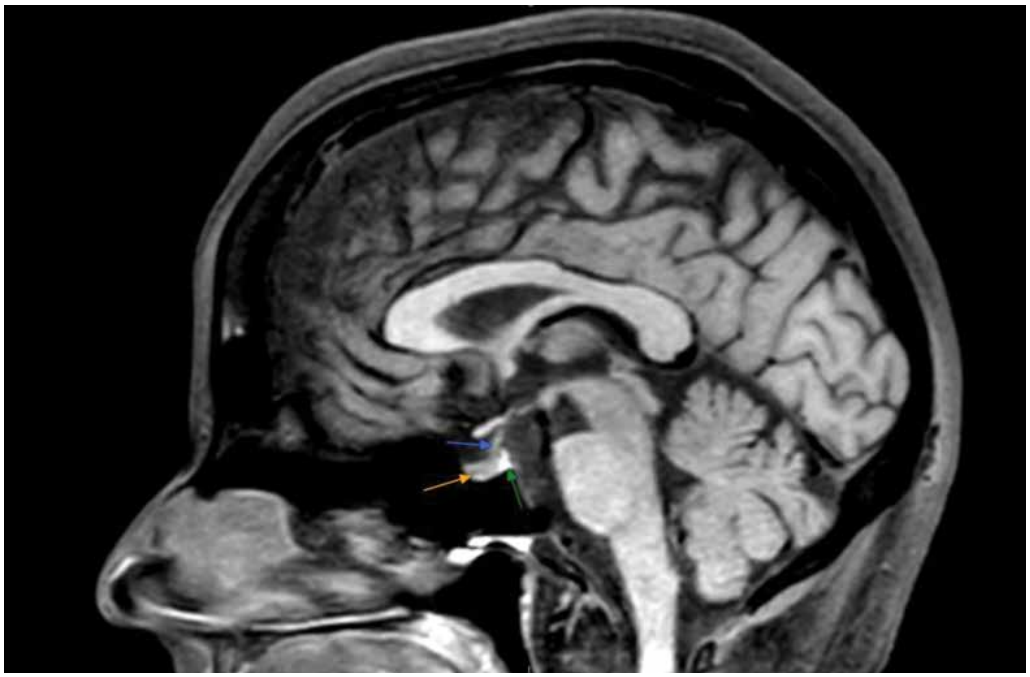

Fig 2. Normal sella: T1 sagittal showing the adenohypophysis (orange arrow), neurohypophysis (green arrow) and infundibulum (blue arrow) in the sellar region

Case presentation

In January of 2022 a women in hers 46s was presented with complaints: edema, dizziness, low blood pressure, hair loss, dry skin. Examinations were performed: ultrasound of the thyroid gland, TSH, FT4 (free thyroxine), FT3 (free triiodothyronine), anti TPO (Antibodies to thyroid peroxidase). Ultrasound of the thyroid gland showed a picture of autoimmune thyroiditis. TSH - 7.82 (N 0.4 - 3.8 MIU/L), FT4 - 11.9 (N12 - 22 pmol/L), FT3 - 3.4 (N 3.10 - 6.80 pmol/L) anti TPO - 334 (N 0 - 34 IU/ml). As a result of investigations, autoimmune thyroiditis and hypothyroidism were diagnosed. Levothyroxine natrium 50 mcg was prescribed.

Results of control studies in 3 months: TSH 3.9 (N 0.4 - 3.8 MIU/L), FT4 - 0.84 (N12 - 22 pmol/L), FT3 - 2.02 (N 3.10 - 6.80 pmol/L).The dose of levothyroxine natrium was increased to 75 mcg and liothyronine sodium 12.5 mg was added.

After 3 months, control studies revealed; TSH - 0.06 (N 0.4 - 3.8 MIU/L), FT4 - 13.73 (N12 -22 pmol/L), FT3 - 4.17 (N 3.10 - 6.80 pmol/L). Prescription: Levothyroxine natrium 62 mcg, liothyronine sodium 12.5 mg.

The patient came for follow-up after 6 months complaining of severe headache. The results of the investigation: TSH - 0.75 (N 0.4 - 3.8 MIU/L) FT4 - 9.02 (N12 - 22 pmol/L), FT3 2.87 (N 3.10 - 6.80 pmol/L). Prolactin - 24.3 (N 2 - 18 ng/ml). Since FT4 and FT3 deficiency was observed on the background of 62 µg of levothyroxine natrium and 12.5 mg of liothyronine sodium and although TSH was decreased, magnetic resonance imaging was prescribed from a diagnostic point of view, as a result of which empty sella was diagnosed.

In conclusion, patients with TSH, FT4, and FT3 deficiency, should undergo examinations to exclude empty sella as one of the reason of central hypothyroidism. According to the above mentioned the recommendation is to examine all the tropic hormones of the pituitary gland after diagnosing empty sella.

References

1. Acharya S, Shukla S, Kashikar S, Dasarwar S, Mahajan SN. Primary empty sella syndrome presenting as isolated central hypothyroidism. Thyroid Res Pract 2014;11:137–8
2. Akkus G, Sözütok S, Odabaş F, et al. Pituitary Volume in Patients with Primary Empty Sella and Clinical Relevance to Pituitary Hormone Secretion: A Retrospective Single Center Study.Curr Med Imaging. 2021;17(8):1018-1024. doi:10.2174/1573405617666210525111218
3. Auer MK, Stieg MR, Crispin A, Sievers C, Stalla GK, Kopczak A. Primary Empty Sella Syndrome and the Prevalence of Hormonal Dysregulation. Dtsch Arztebl Int. 2018;115(7):99-105. doi:10.3238/arztebl.2018.0099
4. Busch, W. Die Morphologie der Sella turcica und ihre Beziehungen zur Hypophyse.Virchows Arch. path Anat. 1951. 320 (5): 437–458 . https://doi.org/10.1007/BF00957474

5. Carosi G, Brunetti A, Mangone A, et al. A Multicenter Cohort Study in Patients With Primary Empty Sella: Hormonal and Neuroradiological Features Over a Long Follow-Up. Front Endocrinol (Lausanne). 2022;13:925378. doi:10.3389/fendo.2022.925378

6. Chiloiro S, Giampietro A, Bianchi A, Tartaglione T, et al. Diagnosis of endocrine disease: Primary empty sella: a comprehensive review. Eur J Endocrinol. 2017 Dec;177(6):R275-R285. doi: 10.1530/EJE-17-0505

7. Chiloiro S, Giampietro A, Bianchi A, De Marinis L. Empty sella syndrome: Multiple endocrine disorders. Handb Clin Neurol. 2021;181:29-40. doi:10.1016/B978-0-12-820683-6.00003-8

8. De Marinis L, Bonadonna S, Bianchi A, Maira G, Giustina A. Primary empty sella. J Clin Endocrinol Metab. 2005;90(9):5471-5477. doi:10.1210/jc.2005-0288

9. Lundholm MD, Yogi-Morren D. A Comprehensive Review of Empty Sella and Empty Sella Syndrome. Endocr Pract. 2024;30(5):497-502. doi:10.1016/j.eprac.2024.03.00

10. Masserini B, Rivolta B, Bernardi I, et al. Asymptomatic Empty Sella Syndrome: A “New” Hypothalamic Pathology or Paraphysiological Variant. Endocr Metab Immune Disord Drug Targets. Published online July 26, 2024. doi:10.2174/0118715303314951240722093133

11. National Institute of Neurological Disorders and Stroke https://www.ninds.nih.gov/health-information/disorders/empty-sella-syndrome]

12. Nimkar, S, Ahuja, A, Kumar S, Acharya, S. Hyponatremia in Empty Sella Syndrome: Is it a Covid Sequelae? International Journal of Nutrition, Pharmacology, Neurological Diseases 2023; DOI: 10.4103/ijnpnd.ijnpnd_88_22

13. Oleaga L.,Merino M. Delgado A. et al. Empty sella syndrome associated with hormone deficiency in adults. Radiologia. 1999;41(9):625-629

14. Ucciferro P, Anastasopoulou C. Empty Sella Syndrome. [Updated 2023 Oct 26]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK541002/

ABSTRACT

ЦЕНТРАЛЬНЫЙ ГИПОТИРЕОЗ, СВЯЗАННЫЙ С ПУСТЫМ СЕДЛОМ: ОБЗОР ЛИТЕРАТУРЫ И КЛИНИЧЕСКИЙ СЛУЧАЙ

Реквава М. П.[1], Дундуа Т. Т.[1,2],
Джавашвили Л. В.[1,2], Гахокидзе И. В.[3,4], Меладзе Н. Т.[1]

[1] Клиника Кортекс, Тбилиси, Грузия;[2] Грузинский университет, Тбилиси, Грузия; [3] Университет Нью Вижен, Тбилиси, Грузия; [4] Клиника Аверси, Тбилиси, Грузия

Синдром «пустого» турецкого седла (ПТС) является одной из малоизученных проблем нейроэндокринологии. Характеризуется пролабированием супраселлярной цистерны в полость турецкого седла с распластыванием гипофиза по дну и стенкам турецкого седла, сопровождающееся эндокринными, неврологическими и зрительными нарушениями. Диагностируется с помощью магнитно-резонансной томографии (МРТ) селлярной и супраселлярной областей. Мы представляем 46-летнюю пациентку страдающую аутоиммунным тиреоидитом и гипотиреозом. Несмотря на лечение левотироксином натрия и лиотиронином натрия, уровень гормонов щитовидной железы: ТТГ, FT4 и FT3 был снижен. С диагностической точки зрения была назначена магнитно-резонансная томография, в результате которой было диагностировано пустое седло. Диагностика центрального гипотиреоза, связанного с пустым седлом, помогает расширить знания и указывает на различные клинические проявления синдрома пустого седла.

Ключевые слова: центральный гипотиреоз, гипофиз, Синдром «пустого» турецкого седла

რეზიუმე

ცენტრალური ჰიპოთირეოზი დაკავშირებული „ცარიელი“ თურქული კეხის სინდრომთან: ლიტერატურის მიმოხილვა და კლინიკური შემთხვევა

რეკვავა მ.პ.[1], დუნდუა თ.თ[1,2],
ჯავაშვილი ლ.ვ.[1,2], გახოკიძე ი.ვ.[3,4], მელაძე ნ.თ. [1]

1 კლინიკა კორტექსი, თბილისი, საქართველო 2 საქართველოს უნივერსიტეტი, თბილისი, საქართველო; 3 ნიუ ვიჟენ უნივერსიტეტი, თბილისი, საქართველო; 4 ავერსის კლინიკა, თბილისი, საქართველო

„ცარიელი“ თურქული კეხის სინდრომის დროს თურქული კეხის დიაფრაგმის ხვრელი ივსება ცერებრო-სპინალური სითხით, რაც იწვევს ჰიპოფიზის ჯირკვლის ნაწილობრივ ან სრულ შეკუმშვას, რაც ხშირად იწვევს ჰორმონალურ დეფიციტს. „ცარიელი“ თურქული კეხის დიაგნოზის დასმა ხდება მაგნიტურ-რეზონანსული ტომოგრაფიის (MRI) გამოყენებით. ზოგად პოპულაციაში ნეირორადიოლოგიური კვლევისას „ცარიელი“ თურქული კეხის სინდრომი საკმაოდ ხშირად ვლინდება და იგი შეიძლება ასოცირებული იყოს ჰიპოპიტუიტარიზმთან. გამოკვლევების შედეგად გამოვლინდა ჰიპოფიზის ჰორმონების დაბალი დონე და სტიმულებზე რეაგირების ნაკლებობა. პაციენტების უმეტესობას აწუხებს ცენტრალური ჰიპოთირეოზი, როგორც ჰიპოფიზის უკმარისობის ნაწილი. ცენტრალურმა ჰიპოთირეოზმა შეიძლება მნიშვნელოვნად იმოქმედოს ცხოვრების ხარისხზე ყველა ასაკში. ჩვენს მიერ გამოკვლეული იქნა 46 წლის ქალბატონი - აუტოიმუნური თირეოიდიტით და ჰიპოთირეოზით. ლევოთიროქსინ ნატრიუმით და ლიოთირონინ ნატრიუმით მკურნალობის მიუხედავად, ფარისებრი ჯირკვლის ჰორმონების (TSH, FT4 და FT3) დონე დაქვეითდა. დიაგნოზის დასაზუსტებლად დაენიშნა თავის ტვინის მაგნიტურ-რეზონანსული ტომოგრაფია, რის შედეგადაც დაუდგინდა „ცარიელი“ თურქული კეხი. აქედან გამომდინარე „ცარიელი“ თურქული კეხის დროს საჭიროა ჰიპოფიზის ჰორმონების კვლევა.

საკვანძო სიტყვები: ცენტრალური ჰიპოთირეოზი, ცარიელი თურქული კეხის სინდრომი, თურქული კეხი, ჰიპოფიზი.