ORIGINAL PAPER

Submitted: 20.11.2023
Accepted: 22.11.2023
Early publication date: 11.12.2023

Endokrynologia Polska
DOI: 10.5603/ep.98271
ISSN 0423–104X, e-ISSN 2299–8306
Volume/Tom 74; Number/Numer 6/2023

The 1 μg Synacthen stimulation test in the diagnosis of secondary adrenal insufficiency in patients with Rathke's cleft cyst and empty sella syndrome

Elżbieta Andrysiak-Mamos[1], *Karol Piotr Sagan*[1], *Łukasz Zwarzany*[2], *Wojciech Poncyljusz*[2], *Anhelli Syrenicz*[1]

[1]*Department of Endocrinology, Metabolic Diseases, and Internal Diseases, Pomeranian Medical University in Szczecin, Szczecin, Poland*
[2]*Diagnostic Imaging and Interventional Radiology Unit, Pomeranian Medical University in Szczecin, Szczecin, Poland*

Abstract

Introduction: Rathke's cleft cyst (RCC) and primary empty sella syndrome (PESS) are usually incidental findings on magnetic resonance imaging (MRI) scans. In most cases, these lesions do not cause mass effect symptoms and do not require surgical intervention. In patients with RCC or PESS, it is important to exclude secondary adrenal insufficiency (SAI), which may be a life-threatening condition.

Material and methods: The incidence of SAI was assessed in patients with RCC or PESS detected by MRI, using the 1 μg Synacthen stimulation test. A total of 38 patients were analysed. Test results were linked to clinical symptoms and the type of cystic lesion.

Results: Assuming that cortisol levels < 14.6 μg/dL in Synacthen test are the criterion of SAI diagnosis, SAI was diagnosed only in 2 patients (5%). Adopting the traditional criterion of cortisol levels < 18 μg/dL, SAI would be diagnosed in 7 patients (18.4 %). Dizziness ($\chi^2 = 3.89$; $p = 0.049$) and apathy ($\chi^2 = 3.87$; $p = 0.049$) were significantly more frequent in the PESS group than in the RCC group.

Conclusions: The incidence of SAI in the general patient population with empty sella syndrome and Rathke's cleft cysts is low. The 1 μg Synacthen test seems to be a valuable tool in the diagnosis of SAI among patients with RCC and PESS. Further studies are necessary to determine the sensitivity and specificity of the 1 μg Synacthen test with the standardization of test protocol and considering the cortisol level at the 20-minute timepoint. PESS patients report dizziness and apathy more frequently than RCC patients, which does not result from the disturbance of the hypothalamic-pituitary–adrenal axis, but probably from the different pathogenesis of these cystic lesions.

(Endokrynol Pol 2023; 74 (6): 631–636)

Key words: *Rathke's cleft cyst; empty sella syndrome; adrenal insufficiency; Synacthen test*

Introduction

Currently, cystic lesions of the sellar region are frequently diagnosed in imaging tests and post-mortem examinations. The most common is Rathke's cleft cyst (RCC); its incidence is estimated at approximately 20% [1]. Despite having a different pathogenesis, RCC requires a differential diagnosis with primary empty sella syndrome (PESS) in imaging studies. The incidence of the latter is determined at 5–12% [2]. Both types of lesions are usually detected incidentally in magnetic resonance imaging (MRI) and rarely require surgical intervention [3]. Rathke's cleft cyst and PESS may, however, cause nonspecific symptoms, such as headache, dizziness, and hypopituitarism.

One of the fundamental issues in the management of RCC and PESS patients is to exclude secondary adrenal insufficiency (SAI) because hypocortisolism may be a life-threatening condition. Studies published so far that analysed the incidence of hypopituitarism in patients with RCC and PESS differ in terms of study populations and testing methods for hormonal insufficiency.

The insulin tolerance test (ITT) is the gold standard in the diagnosis of secondary adrenal insufficiency. However, it poses a risk for patients. In clinical practice, this test is often replaced with the tetracosactide stimulation test (Synacthen, cosyntropin). The classic version of the test uses the 250 μg Synacthen dose. However, some centres use a 1 μg dose because there is evidence for higher test sensitivity. Due to different laboratory methods used to determine cortisol levels, the cut-off value for the test is still disputable.

In this study, we prospectively analysed a group of consecutive patients hospitalized at the Department of Endocrinology, Pomeranian Medical University (PUM) in Szczecin from June 2022 to September 2023, who had been diagnosed with RCC or PESS. The aim

Karol Piotr Sagan, Department of Endocrinology, Metabolic Diseases, and Internal Diseases, Pomeranian Medical University in Szczecin, ul. Unii Lubelskiej 1, 71–252 Szczecin, Poland; e-mail: karolsagan@vp.pl

of this analysis was to estimate the incidence of secondary adrenal insufficiency and the correlation between cortisol levels and patient-reported symptoms. The adrenal axis was evaluated with the 1 μg Synacthen test. The symptoms were assessed using a survey prepared by the authors.

Material and methods

The incidence of SAI was assessed in patients with suspected RCC or PESS using the 1 μg Synacthen stimulation test. The study inclusion criterion was suspected RCC or PESS in an adult patient found in computed tomography or MRI. The exclusion criteria were lack of unequivocal radiological signs of RCC or PESS in MRI, current treatment with glucocorticoids, hormonal contraception, and impaired thyroid function, because these factors potentially affect the cortisol-binding globulin levels.

To obtain 1 μg of Synacthen, the following protocol was followed: 1 mL ampoule with 250 μg of Synacthen was diluted in 250 mL of 0.9% NaCl; then, 1 mL of the solution was drawn into a plastic syringe and administered to the patient via intravenous catheter. Special attention was paid to mixing the prepared solution properly before transferring it into the syringe and to flushing the catheter with saline solution using the same transfer syringe. In our opinion, these steps reduce the risk of the active substance being deposited on the plastic layer of medical devices. The cortisol level was measured in all patients 30 and 60 minutes after starting the stimulation. Additionally, in 15 patients, the cortisol level was measured at the 20-minute timepoint. The test was performed in the morning. All patients had their cystic lesion type determined in MRI by a neuroradiologist specializing in the evaluation of the sellar/suprasellar region. The patients filled in the survey prepared by the authors, answering questions about symptoms suggestive of adrenal insufficiency.

A total of 57 patients with suspected RCC or PESS were studied from September 2022 to June 2023. Final statistical analysis was based on the results obtained from 17 patients with PESS (including 8 patients with partially empty sella syndrome) and 21 patients with Rathke's cleft cyst. The remaining patients were excluded due to hyperthyroidism (one patient), equivocal PESS or RCC findings in MRI or contraindications to MRI with contrast administration (12 patients), use of hormonal contraception (3 patients), pre-laboratory error (2 patients), and treatment with glucocorticoids (one patient). The cortisol level was measured with Abbott Architect, Roche Elecsys II. We adopted 2 cortisol level cut-offs suggesting SAI diagnosis: the traditional value <18.0 μg/dL and the value currently proposed in the literature for the reagent used in Roche II, i.e. <14.6 μg/dL.

Statistical analysis

Statistical analysis of the results was done using IBM SPSS 28 (IBM Corp, Redmond, VA, United States). Nominal variables are presented as number (n) and percentage (%), while continuous variables are presented as mean (M) and standard deviation (SD). The normality of the distributions was tested with the Shapiro-Wilk test. The differences between the 2 groups were analysed using the chi-square test for cross-tabulation (2 × 2, for nominal variables) or the independent sample Student's t-test (for continuous variables) with Bonferroni correction. Multivariate logistic regression (backward elimination, the Wald chi-square test) was further performed to identify independent predictors of response to a cortisol stimulation test or clinical symptoms (with the Hosmer-Lemeshow test for evaluating the goodness-of-fit of logistic regression models). Moreover, two-way repeated measures analysis of variance (RM-ANOVA) was used to check the changes of response to a cortisol stimulation test at 3 timepoints (0, 30, and 60 minutes). Cohen's d or η^2 was used to determine the magnitude of effect sizes for Student's t-test or RM-ANOVA, respectively [4]. The alpha criterion level was set at 0.05 for all statistical analyses.

The study did not require the approval of the Ethics Committee (opinion number KB. 006.106.2023)

Results

Secondary adrenal insufficiency

Adopting the cortisol level cut-off 30 minutes after starting the test at 14.6 μg/dL, adrenal insufficiency was diagnosed only in 3 patients, including one RCC patient and 2 PESS patients. In 2 of these 3 patients, the cortisol level at the 20-minute timepoint was also measured, and in one patient, the result of this measurement was >14.6 μg/dL (15.9 μg/dL). This group was too small for statistical analysis. However, adopting the 18 μg/dL cut-off for all measurement (i.e. at 20-, 30-, or 60-minute timepoints), SAI was diagnosed in 7 patients [2 out of 21 (9.5%) patients with RCC and 5 out of 17 (29%) patients with PESS]. Based on clinical assessment and test results, only 2 patients with cortisol levels below 14.6 μg/dL were treated with hydrocortisone.

Type of cystic lesion on MRI and the change in cortisol levels

As shown in Figure 1, the main effect of changes at the 3 timepoints was statistically significant ($F = 114.10$; $p < 0.001$; $\eta^2 = 0.76$) for cortisol levels, while the main effect of the group and the interaction effect was not. Pairwise comparisons showed that the level of cortisol was highest at the 30-minute timepoint and lowest at the zero-minute timepoint ($0.008 > p < 0.001$, respectively).

Type of MRI lesion and response in the Synacthen test

As shown in Table 1, the difference in the frequency of delayed response ($\chi^2 = 0.01$; $p = 0.912$) and correct response ($\chi^2 = 2.47$; $p = 0.116$) to cortisol test between

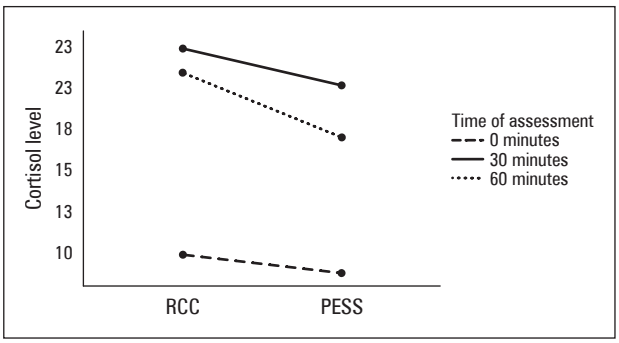

Figure 1. *Type of magnetic resonance imaging (MRI) lesion and the change in cortisol levels at 3 timepoints. RCC — Rathke's cleft cyst; PESS — primary empty sella syndrome*

Table 1. *The frequency of delayed and correct responses to the Synacthen test*

	Delayed response	
	No, n (%)	**Yes, n (%)**
RCC	17 (81.0)	4 (19.0)
PESS	14 (82.4)	3 (17.6)
Total	31	7
	Correct response	
RCC	2 (9.5)	19 (90.5)
PESS	5 (29.4)	12 (70.6)
Total	7	31

RCC — Rathke's cleft cyst; PESS — primary empty sella syndrome

the groups, with respect to the type of MRI lesion was not significant.

Table 2. *The incidence of clinical symptoms*

	Headache	
	No, n (%)	**Yes, n (%)**
RCC	4 (23.5)	13 (76.5)
PESS	3 (30.0)	7 (70.0)
Total	7	20
	Dizziness	
RCC	8 (47.1)	9 (52.9)
PESS	1 (10.0)	9 (90.0)
Total	9	18
	Libido disorders	
RCC	11 (64.7)	6 (35.3)
PESS	5 (50.0)	5 (50.0)
Total	16	11
	Apathy symptoms	
RCC	5 (31.3)	11 (68.7)
PESS	0 (0.0)	10 (100.0)
Total	5	21

RCC — Rathke's cleft cyst; PESS — primary empty sella syndrome

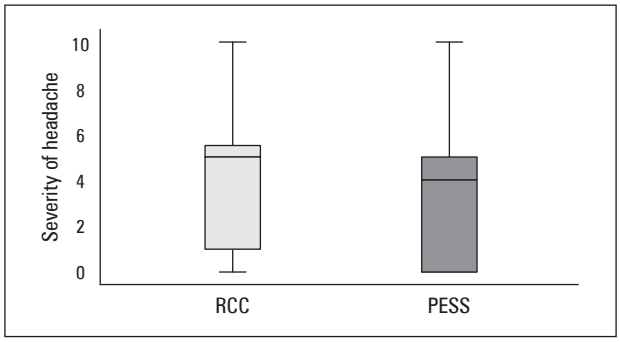

Figure 2. *Type of magnetic resonance imaging (MRI) lesions and the severity of headache. RCC — Rathke's cleft cyst; PESS — primary empty sella syndrome*

Type of MRI lesion and clinical symptoms

The difference in the incidence of headache ($\chi^2 = 0.14$; $p = 0.711$; Tab. 2) and libido disturbances ($\chi^2 = 0.56$; $p = 0.453$; Tab. 2) was not statistically significant between patients with RCC and PESS. However, dizziness ($\chi^2 = 3.89$; $p = 0.049$) and apathy ($\chi^2 = 3.87$; $p = 0.049$) occurred significantly more often in the PESS group than in the RCC group.

As shown in Figure 2, the difference between headache severity ($t = 0.57$; $p = 0.578$; $d = 0.24$; Fig. 2) was not statistically significant between patients with RCC and PESS.

Additionally, as shown in Table 3, multiple logistic regression was performed to identify the independent factors associated with apathy using a backward elimination process. Neither of the predictors such as the timepoints for cortisol level measurements (0, 30, or 60 minutes) was statistically significant for apathy (analysed models were not well-matched with the analysed data).

Discussion

In this analysis, we assessed the incidence of hypopituitarism within the adrenal axis in consecutive patients with RCC and PESS, regardless of the lesion size or

Table 3. *Multiple analyses of variables independently associated with apathy symptoms*

Model	Variable	Odds ratio	95% confidence interval	p
Model 1	0 minutes	0.92	0.75–1.12	0.399
	30 minutes	1.09	0.76–1.56	0.660
	60 minutes	1.07	0.82–1.41	0.616
Model 2	0 minutes	0.93	0.76–1.13	0.436
	60 minutes	1.12	0.91–1.38	0.274
Model 3	60 minutes	1.08	0.89–1.31	0.422

eligibility for surgery. The function of adrenal axis was assessed with the 1 μg Synacthen stimulation test. We obtained a small number of positive results in our study. Adopting a cortisol level cut-off value at < 14.6 μg/dL or 18 μg/dL, the evidence for SAI was found in 5.3% and 18.4 % patients, respectively. In our group of patients, apathy and dizziness, which might suggest adrenal insufficiency, were not related to the response to the Synacthen test but to the type of lesion observed on MRI scan.

Cystic lesions in the sellar region are usually detected incidentally on imaging scans. They require clinical and hormonal assessment and further follow-up due to the risk of hypopituitarism, coexisting pituitary tumour and the risk of cyst growth. The differentiation between cystic lesions may be difficult and, as well as RCC and PESS, should include craniopharyngioma, cystic pituitary adenoma, pituitary aneurysm, secondary empty sella syndrome, pituitary abscess, intrasellar arachnoid cyst, epidermoid cyst, and xanthogranuloma [1, 5].

Secondary adrenal insufficiency poses a serious threat to patients with focal lesions in the pituitary gland. It may lead to an adrenal crisis, which is a life-threatening condition. Thus, early SAI diagnosis is essential in the management of patients with focal lesions of the sella. However, SAI symptoms and the morning cortisol levels have low specificity and sensitivity. Similarly, predictive factors of pituitary impairment in patients with RCC and PESS are not clear [6]. The diagnosis is therefore established regardless of the type and size of cystic lesion. According to the guidelines of the European Society of Endocrinology, stimulation tests are recommended when morning cortisol levels are between 3.0 and 15.0 μg/dL.

The insulin tolerance test is the gold standard in SAI diagnosis. Nevertheless, ITT requires hospitalization and poses a risk to the patient. For this reason, the 250 μg Synacthen stimulation test is often used in clinical practice. According to the literature, it correlates well with ITT [7]. During the test, a patient is given 250 μg Synacthen by intravenous (*i.v.*) injection, and serum cortisol levels are measured at baseline, at 30 and 60 minutes of the test. Some authors also emphasize the importance of the measurement at the 20-minute timepoint, although it is not often discussed in the literature. The 1 μg Synacthen stimulation is one of the versions of the test used at some centres. However, the diagnostic superiority of this version remains a subject of discussion. Kazlauskaite et al. pointed to higher sensitivity of the 1 μg dose in their meta-analysis of the diagnostic value of various versions of Synacthen test [8]. Subsequent publications did not confirm this view beyond any doubts. Another meta-analysis conducted by Ospina et al. did not show any benefits of a 1 μg Synacthen dose, indicating that the Synacthen test was useful for confirming SAI but not for excluding it, regardless of the dose used for the test [9]. In a prospective randomized trial, the superiority of the 1 μg Synacthen test over 25 μg and 250 μg doses was not demonstrated [7]. The small number of participants was a limitation of the trial. A literature review published by Birtolo et al. in 2023 seems to indicate a higher value of the 1 μg Synacthen test versus 250 μg [10]. The authors noticed that 14 protocols of the test have been described so far, and their diagnostic value varies [11]. Burgos et al. emphasized the importance of pretest probability for the interpretation of test results, although it cannot be determined in a quantitative manner [12]. It should be assumed that the diagnostic value of the Synacthen test may vary depending on the stimulation dose used, the study group, as well as the test protocol. In our study, special attention was given to proper mixing of the solution before transferring it into a syringe and flushing the venous catheter with saline solution with the syringe used for Synacthen administration. In our study, we obtained a high rate of negative results excluding SAI, which is indirect evidence for the effectiveness of 1 μg Synacthen stimulation. Peak cortisol levels were estimated to occur at the 30-minute timepoint.

Another important aspect for the reliable interpretation of Synacthen test results is the type of reagents used to determine cortisol levels. Li Zha et al. compared the cortisol level results of the Synacthen test obtained with the Roche Elycsys II test with the cortisol level results of tandem mass spectrometry. They adopted 13.2 μg/dL at the 30-minute timepoint and 14.6 μg/dL at the 60-minute timepoint as cut-offs indicating SAI diagnosis [13]. With the same reagent used, Husni H. et al. decided that 15.7 μg/dL and 17.9 μg/dL at the 30- and 60-minute timepoints would be cut-off values for cortisol levels in a retrospective analysis [14]. The largest group was analysed in a retrospective study by Javorsky et al., including 110 patients. Referring to tandem mass spectrometry, the authors demonstrated that Roche II test cortisol levels below 14.6 μg/dL at the 30-minute timepoint in the Synacthen test indicated adrenal insufficiency [15]. However, cortisol levels at the 20-minute timepoint were not measured. In our study, we adopted both the traditional cortisol level cut-off of 18 μg/dL and the 14.6 μg/dL cut-off proposed by Javorski et al. Based on the whole clinical picture, only 2 patients from our study group were treated with hydrocortisone, and their cortisol levels did not exceed 14.6 μg/dL at any timepoint.

Currently available data suggest different SAI incidence in patients with cystic lesions in the sellar area, depending on the group of patients and the tests used in the analysis. In a retrospective study of pa-

tients hospitalized due to RCC, SAI was diagnosed in only 2.3% [16]. However, the diagnosis was not based on stimulation tests. In another retrospective study in RCC patients treated with surgery, SAI was diagnosed in 15.7%, although the diagnosis was also based on the cortisol level only in baseline conditions [17]. In another study including only RCC patients treated with surgery, Langlois et al., who used the 1 μg Synacthen test and considered clinical signs in its interpretation, diagnosed SAI in 24% of patients [18]. Another retrospective analysis of RCC patients with the 1 μg Synacthen test used for the assessment of adrenal axis showed that SAI was diagnosed in 9.7% of patients treated conservatively and in 16.7% of patients treated with surgery [19]. The authors of this paper adopted 18.1 μg/dL as a cut-off for cortisol level. Interestingly, the rate of positive test results obtained by these authors in patients treated conservatively was very similar to the rate obtained by our team (9.7% *vs*. 9.5% of patients). It must be noted, however, that this rate is probably the result of a cut-off that is too high and may lead to SAI overdiagnosis and excessive glucocorticoid therapy. In summary, it may be concluded that the risk of SAI appears to be higher in RCC patients requiring surgical treatment. At the same time, the diagnosis based solely on the morning cortisol levels leads to the underestimation of SAI rates. In PESS patients, there is less evidence and there are more discrepancies. One of the retrospective studies in PESS patients showed SAI in 35%, but the diagnoses were not based on stimulation tests [20]. On the other hand, Giustina A. et al. show that in experts' opinion SAI incidence in PESS patients is 1% [21].

Our study has certain limitations, including missing data on the history of glucocorticoid therapy, the absence of a histopathology report on cystic lesions, small study sample, and a lack of comparison of Synacthen test results with the gold standard, ITT. The strengths of our study include its prospective nature, standard protocol for the preparation of the 1 μg Synacthen solution, the inclusion of consecutive patients in the study regardless of further therapeutic decisions, and the correlation of clinical symptoms with cortisol levels in the stimulation test. We also did not find a similar study in the literature, comparing the incidence of SAI in patients with Rathke's cleft cysts and primary empty sella syndrome.

Conclusions

The incidence of SAI in the general patient population with empty sella syndrome and Rathke's cleft cysts is low. The 1 μg Synacthen test seems to be a valuable tool in the diagnosis of SAI among patients with RCC and PESS. Further studies are necessary to determine the sensitivity and specificity of the 1 μg Synacthen test with the standardization of test protocol and considering the cortisol level at the 20-minute timepoint. PESS patients report dizziness and apathy more frequently than RCC patients, which does not result from the disturbances of hypothalamic-pituitary-adrenal axis, but probably from a different pathogenesis of cystic lesions.

Data availability statement

The data that support the findings of this study are available from the corresponding author, [KS], upon reasonable request.

Ethics statement

The study did not require the approval of Ethics Committee (opinion number KB. 006.106.2023)

Funding

The study received funding from: Fundacja na Rzecz Rozwoju Medycyny w Dziedzinie Endokrynologii i Chorób Metabolicznych

Conflict of interest

Authors have no conflict of interest to declare.

ORIGINAL PAPER

References

1. Andrysiak-Mamos E, Sagan K, Sagan L, et al. Cystic lesions of the sellar-suprasellar region - diagnosis and treatment. Endokrynol Pol. 2018; 69(2): 212–228, doi: 10.5603/EP.2018.0023, indexed in Pubmed: 29952427.
2. Ucciferro P, Anastasopoulou C. Empty Sella. MRI Pituit Gland. StatPearls, Treasure Island 2023: 307–313.
3. Rak B, Maksymowicz M, Grzywa TM, et al. Pituitary tumours - a large retrospective single-centre study of over 2300 cases. Experience of a tertiary reference centre. Endokrynol Pol. 2020; 71(2): 116–125, doi: 10.5603/EP.a2020.0011, indexed in Pubmed: 32154573.
4. Cohen J. A power primer. Psychol Bull. 1992; 112(1): 155–159, doi: 10.1037//0033-2909.112.1.155, indexed in Pubmed: 19565683.
5. Moszczyńska E, Wydra A, Pankowska M, et al. Pituitary abscess in an eight-year-old girl - diagnostic difficulties. Endokrynol Pol. 2022; 73(2): 379–380, doi: 10.5603/EP.a2022.0022, indexed in Pubmed: 35381099.
6. Dadej D, Skraba K, Matyjaszek-Matuszek B, et al. Presenting symptoms and endocrine dysfunction in Rathke cleft cysts - a two-centre experience. Endokrynol Pol. 2021; 72(5): 505–511, doi: 10.5603/EP.a2021.0091, indexed in Pubmed: 34855191.
7. Peechakara S, Bena J, Clarke NJ, et al. Total and free cortisol levels during 1 μg, 25 μg, and 250 μg cosyntropin stimulation tests compared to insulin tolerance test: results of a randomized, prospective, pilot study. Endocrine. 2017; 57(3): 388–393, doi: 10.1007/s12020-017-1371-9, indexed in Pubmed: 28730418.
8. Kazlauskaite R, Evans AT, Villabona CV, et al. Consortium for Evaluation of Corticotropin Test in Hypothalamic-Pituitary Adrenal Insufficiency. Corticotropin tests for hypothalamic-pituitary- adrenal insufficiency: a metaanalysis. J Clin Endocrinol Metab. 2008; 93(11): 4245–4253, doi: 10.1210/jc.2008-0710, indexed in Pubmed: 18697868.
9. Ospina NS, Al Nofal A, Bancos I, et al. ACTH Stimulation Tests for the Diagnosis of Adrenal Insufficiency: Systematic Review and Meta-Analysis. J Clin Endocrinol Metab. 2016; 101(2): 427–434, doi: 10.1210/jc.2015-1700, indexed in Pubmed: 26649617.
10. Birtolo MF, Antonini S, Saladino A, et al. ACTH Stimulation Test for the Diagnosis of Secondary Adrenal Insufficiency: Light and Shadow. Biomedicines. 2023; 11(3), doi: 10.3390/biomedicines11030904, indexed in Pubmed: 36979883.
11. Cross AS, Helen Kemp E, White A, et al. International survey on high- and low-dose synacthen test and assessment of accuracy in preparing low-dose synacthen. Clin Endocrinol (Oxf). 2018; 88(5): 744–751, doi: 10.1111/cen.13559, indexed in Pubmed: 29392744.
12. Burgos N, Ghayee HK, Singh-Ospina N. Pitfalls in the interpretation of the cosyntropin stimulation test for the diagnosis of adrenal insufficiency. Curr Opin Endocrinol Diabetes Obes. 2019; 26(3): 139–145, doi: 10.1097/MED.0000000000000473, indexed in Pubmed: 30855285.
13. Zha Li, Li J, Krishnan SM, et al. New Diagnostic Cutoffs for Adrenal Insufficiency After Cosyntropin Stimulation Using Abbott Architect Cortisol Immunoassay. Endocr Pract. 2022; 28(7): 684–689, doi: 10.1016/j.eprac.2022.04.003, indexed in Pubmed: 35487459.

14. Husni H, Abusamaan MS, Dinparastisaleh R, et al. Cortisol values during the standard-dose cosyntropin stimulation test: Personal experience with Elecsys cortisol II assay. Front Endocrinol (Lausanne). 2022; 13: 978238, doi: 10.3389/fendo.2022.978238, indexed in Pubmed: 36060940.
15. Javorsky BR, Raff H, Carroll TyB, et al. New Cutoffs for the Biochemical Diagnosis of Adrenal Insufficiency after ACTH Stimulation using Specific Cortisol Assays. J Endocr Soc. 2021; 5(4): bvab022, doi: 10.1210/jendso/bvab022, indexed in Pubmed: 33768189.
16. Zhang L, Li X, Li C, et al. Analysis of the Clinical Characteristics and Pituitary Function of Patients in Central China With Rathke's Cleft Cysts. Front Endocrinol (Lausanne). 2022; 13: 800135, doi: 10.3389/fendo.2022.800135, indexed in Pubmed: 35295993.
17. Wang HK, Lee CC, Wang YuC, et al. Rathke's cleft cyst classification and outcomes after endoscopic endonasal approach. Clin Neurol Neurosurg. 2023; 233: 107882, doi: 10.1016/j.clineuro.2023.107882, indexed in Pubmed: 37517273.
18. Langlois F, Manea A, Lim DS, et al. High prevalence of adrenal insufficiency at diagnosis and headache recovery in surgically resected Rathke's cleft cysts-a large retrospective single center study. Endocrine. 2019; 63(3): 463–469, doi: 10.1007/s12020-018-1784-0, indexed in Pubmed: 30338480.
19. Chong GYC, Tan KCB, Lau EYF, et al. A study on clinical outcomes of Rathke's cleft cyst in patients managed conservatively. Pituitary. 2022; 25(2): 258–266, doi: 10.1007/s11102-021-01194-9, indexed in Pubmed: 34807360.
20. Lu M, Ye J, Gao F. Analysis of clinical features of primary empty sella. Ann Endocrinol (Paris). 2023; 84(2): 249–253, doi: 10.1016/j.ando.2023.01.003, indexed in Pubmed: 36642370.
21. Giustina A, Aimaretti G, Bondanelli M, et al. Primary empty sella: Why and when to investigate hypothalamic-pituitary function. J Endocrinol Invest. 2010; 33(5): 343–346, doi: 10.1007/BF03346597, indexed in Pubmed: 20208457.