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BILATERAL SIMULTANEOUS SAMPLING OF THE CAVERNOUS AND INFERIOR PETROSAL SINUSES IN THE DIFFERENTIAL DIAGNOSIS OF CUSHING'S DISEASE

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Background. Currently, the "gold standard" of differential diagnosis of Cushing's disease is inferior petrosal sinus sampling and measurement of the adenocorticotropic hormone (ACTH) level. The studied literature data indicate a wide variability in the sensitivity and specificity of inferior petrosal sinus sampling in the range of 85–100 and 67–100 %, respectively, which can lead to an erroneous diagnosis of the source of ACTH hyperproduction and, as a consequence, to incorrect and untimely treatment.
Aim. to improve the results of differential diagnosis of Cushing»s disease by using bilateral simultaneous sampling of the cavernous and inferior petrosal sinuses.
Materials and methods. Cohort single-center retro/prospective study of 70 patients with confirmed ACTH-dependent Cushing's syndrome. For the purpose of differential diagnosis, a number of indicators were calculated: central-peripheral ratio, prolactin-normalized ACTH ratio, successful catheterization. Sampling results were evaluated in comparison with contrast-enhanced pituitary magnetic resonance imaging data and intraoperative data.
Results. The study of the central-peripheral ratio showed the need to assess it simultaneously at the level of the cavernous and inferior petrosal sinuses. This approach makes it possible to significantly increase the sensitivity and specificity of the applied gradient to 93.1 and 85.7 %, respectively. Prolactin-normalized ACTH ratio is a second line predictor in the differential diagnosis of Cushing's disease with sensitivity and specificity reaching 94.7 and 28.6 %, respectively. The gradient of successful catheterization is a reflection of possible hemodynamic features of a particular sinus, does not serve as an indicator of the correct positioning of microcatheters in the vascular bed.
Conclusion. Bilateral simultaneous sampling of the cavernous and inferior petrosal sinuses is an effective method of differential diagnosis of Cushing's disease and ectopic ACTH-dependent syndrome.

Keywords: Cushing's disease, central-peripheral ratio, prolactin-normalized adenocorticotropic hormone ratio, successful catheterization, cavernous and inferior petrosal sinuses sampling

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INTRODUCTION

Caused by excessive secretion of adrenocorticotropic hormone (ACTH) hypercortisolism (ACTH-dependent hypercortisolism) is a severe neuroendocrine pathology significantly increasing morbidity, disablement, and mortality among adults of working age [1]. The main cause of endogenic hypercortisolism is ACTH-producing pituitary microadenoma (80–85 % of cases); in 20 % of observations, ectopic tumors are diagnosed, and ectopic corticotropin-releasing hormone-producing tumors account for less than 1 % of cases [2, 3]. Considering very similar clinical manifestations of Cushing»s disease and ectopic syndrome, differential diagnosis of the source of hyperproduction is difficult. Traditionally used lab tests have low sensitivity and specificity varying, according to some data, between 60 and 100 % [1].

Contrast-enhanced magnetic resonance imaging of the pituitary gland can be uninformative in 50 % of cases, but use of additional sequences (SPGR, FLAIR, CISS) can increase diagnostic accuracy by 15–20 % [4–6]. However,

approximately one third or more patients will still have false negative results [7]. Catheterization of the inferior petrosal sinuses with venous blood testing for ACHT level is currently the golden standard of differential diagnosis of ACHT-dependent Cushing's syndrome. However, sensitivity and specificity of the method vary, per different authors, between 85–100 and 67–100 %, respectively [8], which can lead to erroneous diagnosis of the source of ACHT hyperproduction and, subsequently, incorrect and untimely treatment.

The aim of the study is to improve the results of differential diagnosis of Cushing's disease using bilateral simultaneous sampling of the cavernous and inferior petrosal sinuses.

MATERIALS AND METHODS

Analysis of the treatment outcomes of 70 patients with confirmed ACHT-dependent Cushing's syndrome between 2013 and 2019 was performed. The diagnosis of ACHT-dependent hypercortisolism was established according to the international guidelines [1]. The study included patients with absent visualization of pituitary adenoma per magnetic resonance imaging or with pituitary adenoma <8 mm, as well as patients who had discrepancies between lab tests (high-dose dexamethasone suppression test) and contrast-enhanced magnetic resonance imaging. The patients with bilateral adrenalectomy, severe concomitant pathology and complications of the main disease requiring specialized examination and treatment were excluded from the study.

All patients of the treatment group underwent bilateral simultaneous sampling of the cavernous and inferior petrosal sinuses per the original authors' technique (patent for invention No. 2725853 from 06.08.2019) with sampling of venous blood and evaluation of ACHT and prolactin levels. At the same time with the main catheterization stage, blood samples were taken from a peripheral vein for subsequent determination of ACHT and prolactin concentrations.

The final diagnosis was determined based on the results of histological and immunohistochemical examination of the material obtained during surgical intervention.

The study was approved by the local ethical committee of the Almazov National Medical Research Center of the Ministry of Health of Russia. All patients signed voluntary informed consent for participation in the study.

Description of the sampling technique. Sampling of the cavernous and inferior petrosal sinuses (see Figure) included punction and catheterization of the right and left femoral veins under local anesthesia. Then, using introducers installed on both sides, guiding catheters were inserted into the tight and left jugular veins, respectively. Using microtransducers, microcatheters were installed through the inferior petrosal sinuses into the posterior parts of the right and left cavernous sinuses. Control sinusography was performed with evaluation of the correctness of microcatheter tip installation and anatomical structure of the sinuses of the base of the skull with subsequent simultaneous blood sampling from both petrosal sinuses. Then microcatheters were lowered into the inferior petrosal sinus of the corresponding side, rinsed with physiological solution, and the same procedure of blood sampling was performed, and microcatheters and introducers were removed from the blood stream. Additionally, blood was taken from a peripheral vein. Hemostasis was achieved through manual pressure near femoral vein puncture with application of a pressure bandage. During the study, heparinization was performed taking into account patient's body weight (60 U/kg). The obtained blood samples were collected into chilled test tubes containing ethylenediaminetetraacetic acid, and promptly transferred into the lab for determination of ACHT and prolactin levels.

Evaluation of sampling results. For differential diagnosis of Cushing's disease and ectopic syndrome, a number of characteristics were evaluated. The central: peripheral ACHT gradient (CPAG) is a ratio between ACHT levels in blood samples from the cavernous or inferior petrosal sinus and a peripheral vein. According to our protocol, gradient value ≥2 is a predictor of Cushing's disease.

Gradient of successful catheterization (SC) is a ratio between prolactin levels in blood samples from the cavernous or inferior petrosal sinus and a peripheral vein. According to the study protocol, the result ≥1.8 was an indicator of successful sinus sampling on the studied level.

Prolactin-adjusted ACHT ratio (PAAR) is calculated as the ratio between CPAG and SC gradient at the same level. The ratio value ≥0.8 is a predictor of Cushing's disease.

Statistical analysis. Statistical analysis of the data was performed using the Statistica v. 10.0 software. Qualitative

Cavernous and inferior petrosal sinuses sampling (frontal view). 1 – cavernous sinuses, 2 – inferior petrosal sinuses

characteristics are presented as means and standard deviations. Comparison of unrelated groups per quantitative and ordered characteristics was performed using non-parametric ANOVA and Mann–Whitney's U-test; comparison of unrelated groups per qualitative characteristics was performed using t-test. Level of statistical significance of differences was $p < 0.05$. Sensitivity and specificity of the method, as well as other diagnostic characteristics, were calculated taking into account previously determined cutoff points based on the number of false positive and false negative results.

RESULTS

The study included 70 patients (14 men and 56 women) aged between 17 and 74 years. Table 1 presents general characteristics of the patients of the treatment group.

Analysis of the patients' hormonal profile showed more marked abnormalities in the patient group with ectopic syndrome.

Sampling results. During bilateral simultaneous sampling of the cavernous and inferior petrosal sinuses, no complications or lethal outcomes were registered, and no additional neurosurgical and/or resuscitation interventions were needed.

CPAG evaluation. CPAG was calculated in 66 patients at each level (cavernous and inferior petrosal sinuses). Positive gradient (≥2) value was obtained in 50 (75.8 %) of 66 observations at the cavernous sinus level and in 49 (74.2 %) of 66 observation at the inferior petrosal sinus level which supported the diagnosis of Cushing's disease.

Statistical analysis showed significant difference between CPAG at the cavernous and inferior petrosal sinuses' levels (t-test: $p = 0.007$) showing higher gradient values at the cavernous sinuses' level. However, diagnostic accuracy of the gradients did not significantly differ (Table 2).

Complex evaluation of CPAG at 2 levels allowed to confirm a central source of hyperproduction when the gradient value was ≥2 in at least 1 case. This approach allowed to increase the number of observations with positive result to 54 (81.8 %) from 66 increasing diagnostic accuracy of the examination.

SC gradient evaluation. SC gradient evaluation allows to confirm the correctness of blood sampling procedure from the sinuses of the base of the skull. Analysis of this gradient was performed at the levels of the cavernous and inferior petrosal sinuses on the left side in 66 (94.2 %) of 70 patients, on the right side – in 65 (92.8 %) of 70 patients. The values of SC gradient at each level are presented in Table 3.

SC analysis showed statistically significant difference between the values in the left inferior petrosal sinus and both cavernous sinuses (t-test: $p < 0.05$) with higher prolactin levels in the latter which reflects reliable venous blood dilution already at the level of inferior petrosal sinuses despite correct installation of microcatheter tips per intraoperative X-ray data.

Analysis of venographies with evaluation of the structure of the inferior petrosal sinuses per the Shiu & Miller classification [9] showed predominance of axial type of petrosal sinuses on 99 (70.7 %) sides of 140; formation of anastomosis with the internal jugular vein through the communicating vein was observed on 22 (15.7 %) sided of 140, discrete type – on 15 (10.7 %) sides, and absence of anastomosis between the inferior petrosal sinuses and internal jugular vein only on 4 (2.9 %) sides.

Dispersion analysis did not show that anatomy of the inferior petrosal sinuses affects the SC gradient (ANOVA: left $p = 0.2$; right $p = 0.9$). *Post hoc* analysis also did not show any differences between patients with different anatomy of the inferior petrosal sinuses ($p > 0.05$).

Table 1. *Characteristic of patients*

Parameter	Cushing's disease	Ectopic syndrome
Gender, %:		
male	19.1	28.6
female	80.9	71.4
Age, M ± SD, year	42 ± 13.5	41.6 ± 16.9
Hormone level, M ± SD:		
cortisol (08:00)	805.4 ± 386.5	1556.8 ± 1163.8
cortisol (23:00)	574.7 ± 243.7	1214.5 ± 744.6
urinary free cortisol	999.2 ± 1214.5	4947.4 ± 4567.5
ACTH (08:00)	63.4 ± 30.2	305.3 ± 433.4
ACTH (23:00)	58.8 ± 33.1	174.7 ± 140.1

Note. *M – mean value; SD – standard deviation; ACTH – adrenocorticotropic hormone.*

Table 2. *Diagnostic indicators of central/peripheral gradient at the level of cavernous and inferior petrosal sinuses*

Sinus	Sensitivity, %	Specificity, %	PPV, %	NPV, %
CS	84.8	85.7	98	40
IPS	83.1	85.7	98	37.5
CS + IPS	93.1	85.7	98.2	60

Note. *Here and in tables 3–5: CS – cavernous sinus; IPS – inferior petrosal sinus. Here and in table 4, 5: PPV – positive predictive value; NPV – negative predictive value.*

Statistical analysis of diagnostic accuracy of SC gradient (Table 4) showed low values with sensitivity equal or below 68.9 % in all observations, and specificity varied significantly between 28.5 and 85.7 %.

PAAR evaluation. PAAR at the cavernous sinuses level ≥0.8 was observed in 44 (68.8 %) of 64 patients, at the inferior petrosal sinuses level – in 46 (73 %) of 63 patients pointing to a central source of ATCH hyperproduction (Table 5).

Complex analysis of the ratio at 2 levels allowed to increase the number of true positive results to 54 (84.4 %) of 64, but the values of sensitivity and specificity changed discordantly.

DISCUSSION

In the performed single-center study, a technique for bilateral simultaneous sampling of the cavernous and inferior petrosal sinuses was examined. This is the largest case series describing simultaneous sampling of the cavernous and inferior petrosal sinuses. The obtained results show that simultaneous evaluation of CPAG at 2 levels allows to significantly increase sensitivity of the used gradient – up to 93.1 % – in differential diagnosis of Cushing»s disease. Specificity for this method is 85.7 % which corresponds to literature data [8, 10, 11].

However, despite positive data, the problem of false negative results in catheterization remains, and the main cause of this are anomalies of the inferior petrosal sinuses draining [8]. In our study, the described problem was solved through simultaneous sampling of the cavernous sinuses. Meanwhile, a second problem has been described in literature: selection of the area of blood sampling from the cavernous sinus. A. Teramoto et al. in their article stated the necessity of blood sampling from the posterior parts of the sinuses because these blood samples had higher ACHT concentration [12]. These data were supported later by Y. Kai et al. who showed high ACHT concentration in blood samples from the middle and posterior parts of the sinus [13], but N. Hayashi et al. demonstrated that drainage of venous blood into the cavernous sinuses can have paradoxical character due to formation of an extensive network of emissary veins entering the pterygoid venous plexus which can cause false negative results of catheterization [14]. Therefore, for selection of the optimal sampling area, it is important to examine anastomoses formed by the cavernous sinuses in addition to evaluation of anatomical characteristics of the inferior petrosal sinuses and their drainage pathways.

Bilateral simultaneous sampling is important for differential diagnosis of ACHT-dependent hypercortisolism which is characterized by typical clinical and biochemical manifestation but unclear source of hyperproduction. Because catheterization verifies the source of ACHT not based on histology but based on functional changes, this diagnostic technique has high sensitivity and specificity.

Table 3. *The results of successful catheterization of the cavernous and inferior petrosal sinuses*

Parameter	Left CS	Right CS	Left IPS	Right IPS
M ± SD	13.8 ± 20.6	11.3 ± 16.3	5.2 ± 9.4	8.2 ± 11.1
Median	3.3	4.3	2	2.8

Note. *M – mean value; SD – standard deviation.*

Table 4. *Diagnostic values of successful catheterization of the cavernous and inferior petrosal sinuses*

Sinus	Sensitivity, %	Specificity, %	PPV, %	NPV, %
Left CS	64.3	71.4	94.7	20
Right CS	61.8	28.6	87.1	8.7
Left IPS	59.3	85.7	97.2	20
Right IPS	68.9	28.5	88.9	10

Table 5. *Diagnostic values of prolactin-normalized adrenocorticotropic hormone ratio of the cavernous and inferior petrosal sinuses*

Sinus	Sensitivity, %	Specificity, %	PPV, %	NPV, %
CS	77.2	71.4	95.7	27.8
IPS	82.1	28.6	90.2	16.7
CS + IPS	94.7	28.6	91.5	40

Hypercortisolism does not affect the level of prolactin secretion in the anterior pituitary, therefore the level of this hormone can be used as an independent SC factor [15–17]. However, incorrect interpretation of this gradient as "control of catheter position during selective blood sampling from the inferior petrosal sinuses" can be found in literature which is not accurate [17].

Complex study of SC gradient showed that this value reflects possible hemodynamic characteristics of a specific sinus, i. e. normality of venous draining from the pituitary gland [8]. Ability of the surgeon to use intraoperative X-ray control of microcatheter tips positioning in the veins excluded interpretation of the gradient as a criterion for microinstrument positioning. This conclusion finds confirmation in the recent studies [18]: correct position of the microcatheters according to X-ray is not always accompanied by adequate blood sampling. Therefore, in these observations, non-optimal blood sampling is a more correct interpretation.

In our study 15 (22.7 %) of 66 patients with negative SC results received the diagnosis of Cushing's disease through CPAG analysis, and similar observation was described by G.B. Mulligan et al. [18].

Currently, evaluation of SC gradient is necessary in cases of negative CPAG results and abnormal structure of the inferior petrosal sinuses for confirmation of blood sampling correctness and subsequent calculation of PAAR. The study by G.B. Mulligan et al. showed that SC evaluation does not affect CPAG interpretation in case of its positive result [18].

Prolactin-adjusted ACHT ratio is a 2nd line criterion in differential diagnosis of Cushing's disease and ectopic syndrome [18, 19]. In the analyzed patient cohort, PAAR showed high sensitivity of 94.7 %, but specificity was considerably lower: 28.6 % which can be caused by 2 main factors: 1) small number of observations with ectopic ACHT-dependent syndrome; 2) selection of diagnostic value of the gradient. In our opinion, the main cause is the second factor. Currently, there is no consensus on the optimal cutoff point. In the literature, the value of ≥0.8 [19] is the most common, but H. Akbari et al. showed high diagnostic accuracy of the gradient with the value of ≥0.33 (sensitivity 100 %, specificity 80 %), however their sample contained only 20 observations [20]. Other authors used diagnostic value of the gradient ≥1.3 with sensitivity and specificity reaching 100 and 91 %, respectively [16]. The above-described problem is characteristics of our study too: PAAR allowed to accurately establish topic diagnosis in 5 patients with falsely negative CPAG results at the levels of the cavernous and inferior petrosal sinuses, but in 5 patients with ectopic syndrome falsely positive results were obtained. Taking into account the wide range of cutoff points, the question of PAAR evaluation remains open and requires further study.

Our study has several limitations: small number of patients with ectopic syndrome and mixed study design (retro-/prospective). Therefore, it should be anticipated that further prospective studies with a larger number of patients will allow to refine current data and receive answers to the outstanding questions.

CONCLUSION

Sampling of the cavernous and inferior petrosal sinuses with evaluation of CPAG and PAAG is characterized by high diagnostic accuracy (92.4 %) for differential diagnosis of Cushing's disease and ectopic syndrome. The evaluation of SC gradient is helpful for subsequent calculation of PAAR in case of negative CPAG result which allows to increase diagnostic accuracy of the method.

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Authors' contribution
I.A. Rudakov: collection and processing of material, statistical data processing, article writing;
A.V. Savello: development of the concept and design of the study, collection and processing of material, statistical data processing, writing and editing of the article;
V.Yu. Cherebillo: development of the concept and design of the study, collection and processing of material, statistical data processing, editing of the article;
A.A. Paltsev: collection and processing of material, article writing;
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