



BRITISH

MEDICAL JOURNAL



British Medical Journal Volume-2, No 4
10.5281/zenodo.7196611

British Medical Journal
Volume 2, No 4., 2022

Internet address: <http://ejournals.id/index.php/bmj>

E-mail: info@ejournals.id

Published by British Medical Journal

Issued Bimonthly

3 knoll drive. London. N14 5LU United Kingdom

+44 7542 987055

Chief Editor

Dr. Fiona Egea

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British Medical Journal Volume-2, No 4

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STATE OF CORTICOTROPHIC FUNCTION IN PATIENTS WITH CS after TSS

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Abstract: This article presents the results of a test with desmopressin in 38 patients (including the control group -20) with ACTH-DCS. Of the 18 patients, 77,7% (14patients) are women and 22,2% are men (4patients). The average age of women was $38,85 \pm 1,09$ years (from 20 to 51 years), men – $31,5 \pm 0,25$ years (from 31 to 32 years). The duration of the disease was 90,67 months (from 36 to 204 months), the duration before the manifestation was 62,22months (from 6 to 143 months), the duration of the disease from the moment of diagnosis – $29,1 \pm 27,76$ months (9 to 84 months), the age of patients at the time of diagnosis was on average $35,67 \pm 10,49$ years (21 to 51), $37,7 \pm 1,3$ years for women and $28,5 \pm 0,25$ years in men. In the postoperative period, there was a significant decrease in all hormonal indicators of blood and urine (ACTH, cortisol) compared with preoperative ones.

There were significant differences in pre and postoperative mean values of basal ACTH and cortisol levels after the desmopressin test ($p < 0.05$) in all 18 patients. Thus, in the cohort of postoperative patients with remission of ACTH-DCS in our study with a test with desmopressin, 2 (11%) of 18 patients showed an abnormal increase in the level of ACTH and cortisol, i.e. the test was positive, and this indicates the possible risks of tumor growth and relapse of the disease.

Keywords: Cushing's syndrome, relapse, prognosis

ACTH dependent Cushing syndrome (ACTH DCS) is characterized by hypercortisolism, caused by pituitary adenoma, secreting adrenocorticotrophic hormone (ACTH). ACTH-secreting adenomas pituitary gland are most frequent cause endogenous hypercortisolism, on the them share account for 65-70% cases endogenous syndrome Cushing. ACTH DCS causes cognitive violations, obesity, diabetes, high bloody pressure, muscle weakness, osteoporosis and depression, as well as a 5-year risk of cardiovascular mortality up to 50% in untreated patients. In patients with insufficient treatment with ACTH DCS, standardized mortality is five times higher than the norm, which declining before norms patients who reach remissions (normal level cortisol after operations) [21].

Although detailed epidemiological data on CS are limited, the prevalence evaluated about from 1-2 before 40 cases on 1000000 population annually, according to research [18-23]. Medium incidence CS amounted to 2.4 case on

the 1 000 000 residents in year, prevalence -39.1 happening on the 1000 000 residents [18]. How show epidemiological research, conducted on Republic Uzbekistan, on the today, the frequency of CS is 0.68 per 100 thousand of the population (Narimova G.D., 2018) [1-8]. By data Narimova G.D. and et al., probable frequency CS in Republic Uzbekistan should account for 37 new cases annually [5]. From 2002 to 2017 there were fixed total 34 cases of death with CS, from them 31(91.2%) patients ACTH-DCS and 3 (8.8%) with ACTH-NDCS cases, the causes of which were in mainly cardiovascular accidents in 19 (55.9%), purulent complications of diabetes in 9 (26.5%) [7].

One from most controversial questions cognitive analysis estimates degree postoperative complications states with ACTH-DCS is establishing criteria remission, although definition remissions is preferred because of the possibility of relapse. The ideal definition of remission CS should be available in the early postoperative period and should be associated with changes in clinical characteristics and normalization of biochemical parameters CS. The most recent guidelines for the treatment of CS, published in 2008, define remission how emerging at achieving levels cortisol in range from 55 less than 138nmol/l, in then time how preservation high or only moderately reduced level cortisol and level free cortisol in urine suggests a relapse. Disease remission should be assessed both clinically, as well as from a biochemical point of view. There are two significant factors in the treatment of CS after operations: firstly, condition cure or remissions and potential relapse, and, secondly, recovery hypothalamus-pituitary-adrenal axes, which may take more two years. After operations can be divided into three groups patients: most easily to identify patients with persistent hypercortisolism, then how two other groups are part spectrum, varying from eucortisolism before adrenal insufficiency. The definition of relapse is also not well established because it puts those same problems, what and diagnostics. AT then time how some the authors define relapse as the presence of signs of hypercortisolism, others define it how absence response on the test's suppression or even loss circadian rhythm With eucortisolism, or a combination of several criteria. This should be taken into account when interpretations frequencies relapses, which not comparable between various series, which, in turn differ on observation time and frequency repeated operations [14,15,21]. Risk relapse after successful treatment transsphenoidal surgery at patients with CS good known. Prevalence relapses in different research strongly varies from 0 before 47%. At a recent meta-analysis of the overall relapse rate in CS patients treated with transsphenoidal surgeries, was 10% [95% confidence interval (CI) 6- 16%][10]. Two studies showed a strikingly low recurrence rate of 2% [18,19,20].

The use of TD in the postoperative period makes it possible to detect the presence of residual neoplastic corticotropic cells and thus indicate possible increased risk of relapse. The desmopressin test has been proposed for monitoring of patients with CS. The potential benefit of the desmopressin test was first described fifteen years back at two successfully treated patients with CS. At which later was diagnosed with a relapse after a desmopressin test based on an abnormal increase in

serum cortisol and ACTH, then like any other biochemical anomaly, before surgery, showed hypercortisolism [16]. According to Bou Khalil and colleagues, 85% of patients with relapsing disease had a positive desmopressin test [11]. From them only six had a normal response after operations. Recently Ambrogio et al [10] demonstrated what a reply on the desmopressin disappeared after surgery in all but 13% of patients in remission. Out of 13 patients at which was relapse, at 30% patients was positive early postoperative response to desmopressin and 40% developed a positive response to long observation.

Summing up analysis literature, what existing on the today's data confirm auxiliary role test desmopressin immediately after surgery, when assessing the delayed outcome of the disease and at planning postoperative states persons with ACTH DCS. The loss paradoxical reactions indicates the possibility of a favorable outcome, then how its preservation dictates need careful observations for timely identifying relapse. However, accurate grade positive predictive prices test desmopressin maybe undermined topics fact what general number relapses in published data few and they may occur many years after a successful operation. Therefore, for the final conclusions on this issue, it is necessary to conduct larger studies with more lengthy periods monitoring.

Thus, the desmopressin test currently remains one of the only justified criteria estimates probabilities relapse growth tumors after TSS.

The introduction of this test into clinical practice will allow, firstly, to evaluate the quality of the surgical removal of the formation, and secondly, to establish remission and most main – predict relapse tumor growth.

All the above emphasizes relevance our research.

Aim research - explore significance postoperative samples with desmopressin for estimates efficiency TSS and outcomes on comparison with postoperative level cortisol in group achieved remissions.

Material and research methods:

The object of the study were 60 patients with ACTH - dependent Cushing's syndrome (ACTH-DCS), operated from 2000 to 2020 at the RSSPMCE of the Ministry of Health of the Republic of Uzbekistan named after academician Y. H. Turakulov. Before present time in Uzbekistan desmopressin test generally not carried out both in terms of diagnostics and for prognosis outcomes diseases due to high cost research. For implementation given samples us It was received permission ethical committee at MOH (No. 7/50-1210 from 8.08.2019), also It was received informed agreement on the holding given samples from all patients.

Criteria inclusion were patients, those who have undergone TSS on about ACTH-DCS with transsphenoidal approach.

Exclusion Criteria there were patients with ACTH DCS, treated with medication, radiation therapy, combined therapy and adrenalectomy.

Researched us patients (60 patients) in dependencies from level postoperative cortisol blood, according to Clinical Practical Recommendations Society

Endocrinologists (2015), were divided on the 2 groups: I group was patients with level basal cortisol in blood in within ≤ 138 nmol /l, which were regarded, reached remission 18 patients, II group blood cortisol ≥ 138 nmol / l, that is, those who did not achieve remission - 42 patients, group control amounted to 20 healthy persons (ten men and ten women) corresponding age. Total - 80 researched.

Methods research included in myself:

- 1) General clinical (study endocrine, somatic,neurological statuses);
- 2) instrumental (perimetry of visual fields, fundus, visual acuity, ECG, CT/MRI chiasmal-sellar areas and adrenal glands; Magnetic resonant tomography pituitary with contrasting

Everyone patients before operation performed MRI pituitary gland with introduction contrast substances with gadolinium on the apparatus Magnetom Trio A Tim 1.5 Tesla (SIEMENS, Germany). size adenomas considered largest her diameter. Under microadenoma pituitary gland understood education dimensions less ten mm, under macroadenoma - ten mm and more (Hardy J., 1969). invasive growth appreciated on classification degree invasions adenoma pituitary gland in cavity cavernous sinus according to KnospScale: grades 0-2, grades 3-4 were taken for the absence of invasive growth considered invasive growth (Knosp E., 1993). Grade results MRI was carried out specialist MRI, as well as operating neurosurgeon.

- 3) hormonal research:

AT preoperative period: cortisol in serum blood determined method radioimmunoassay (RIA) (Bekhman Coulter, Czech Republic on Gamma-12 and Strantg meters 300). Reference values: morning (8-9.00) - 260 - 720 nmol / l, evening (23-24.00) - less 50 mmol/l. The study of free cortisol in daily urine was determined by the method radioimmunoassay (RIA) (Bekhman Coulter, Czech Republic on Gamma-12 and Strantg meters 300), reference values - 38-208 nmol /day. Study level ACTH in plasma determined by radioimmunoassay (RIA) (BekhmanCoulter , Czech Republic on counters Gamma-12 and Strantg 300), reference values are less than 50 ng / ml (St. Researcher Mukhamedova A.A).

For estimates indicators (ACTH plasma, cortisol serum) in morning fences blood from peripheral veins carried out on an empty stomach in 8-9.00. Samples blood directed in laboratory. For estimates indicators in evening watch (cortisol serum, plasma ACTH) blood sampling was carried out in the evening at 23-24.00, the patient was in state of wakefulness. The tube with ACTH was centrifuged, the plasma was frozen. Samples blood, collected for definitions cortisol in serum placed in fridge. The next morning, blood samples were sent to the laboratory for research.

The collection of daily urine for the determination of free cortisol was started in the morning after awakening patient. A patient emptied uric bubble, fixed time urination, then all portions, starting from the second, collected in special container for collecting urine with a volume of 2 liters; daily urine collection was completed the next day 24 hours after the start - the patient collected the last portion of urine at

this time in capacity. fixed volume urine with accuracy before 50 ml, then urine thoroughly mixed and poured about 50 ml into a container for transport to the laboratory with indicating daily volume urine.

1 mg of dexamethasone was carried out according to the following protocol: at 24.00 the patient took 2 tablets of dexamethasone 0.5 mg each, the next morning at 8.00 a sample was taken blood to determine the level of serum cortisol. Sample with 8 mg dexamethasone (BDP) was carried out according to the protocol: initially, the level of serum cortisol was determined at 8-9.00, the patient then received dexamethasone 2 mg orally every 6 hours for 2 days (the test started at 8.00), on the 3rd day in the morning at 8.00, blood was taken to determine cortisol in serum.

AT postoperative period in progress desmopressin samples method enzyme immunoassay analysis (IFA) (doctor Saidova S.H.)

- 4) Histological research operational material (cabinet histopathology, doctor histologist- Zhuravleva N.S.)
- 5) functional try With desmopressin

Methodology holding samples with desmopressin.

For holding samples used desmopressin acetate four mcg from Ferring Pharmaceuticals Ltd, UK after the conclusion and permission of the Ethics Committee of the MoH Uzbekistan No. №7/50-1210 (from 08/08/2019).

Try was carried out next way:

After night 8 hour starvation in the morning in ⁹⁰⁰ _ established constant catheter in the cubital vein, while the patient remained in the supine position for 120 min, that is, during the entire study period. At 9:00 a.m., 8 ml of blood was taken (0 min) and administered 10 µg of desmopressin as an intravenous bolus injection. Further blood samples for level measurement ACTH and cortisol were received after 30, 60, 90 and 120 minutes. Arterial pressure and frequency cardiac cuts registered in flow Total period research. In overload avoidance _ liquid and hyponatremia (low level sodium in blood), which maybe become serious side effect recommended limitation liquids (not more 1.5-2l.) on the remaining part day.

Statistical methods research. Received data processed with help computer programs Microsoft excel and STATA. quantitative data represented central trends and scattering: average arithmetic (M) and standard deviation (SD) in format M (SD). Comparison two independent groups, having normal distribution, was carried out with help t-test Student. AT this case and at use other criteria zero hypothesis was rejected at $R \leq 0.05$.

Results research:

The object of the study was retrospective data of patients examined and treated in RSSPMEC Uzbekistan with 2000 on 2020, also results created and conducted register of patients with CS and annual monitoring data states patients who are on the accounting in regions RUz.

According to a study from 2000 to April 2020 was registered 308 patients, including those with ACTH-CD amounted to 253 (82.1%), including dead-31. From

the general the number of patients with ACTH-DCS (222) the number of women was 157(70.7%), a men - 65 (29.2%). From decreased (31)-14-men (45.1%), 17 women (54.8%).

An analysis of cases of ACTH DCS in the Republic of Uzbekistan showed that out of 222 patients, 108 (48.6%) were subjected to surgery - TSS and 20 (9%) patients received combination therapy - TSH + adrenalectomy , radiation therapy or electrocoagulation of adrenal vessels. Of 108 patients, 11 patients underwent repeated TSH in connections with relapse.

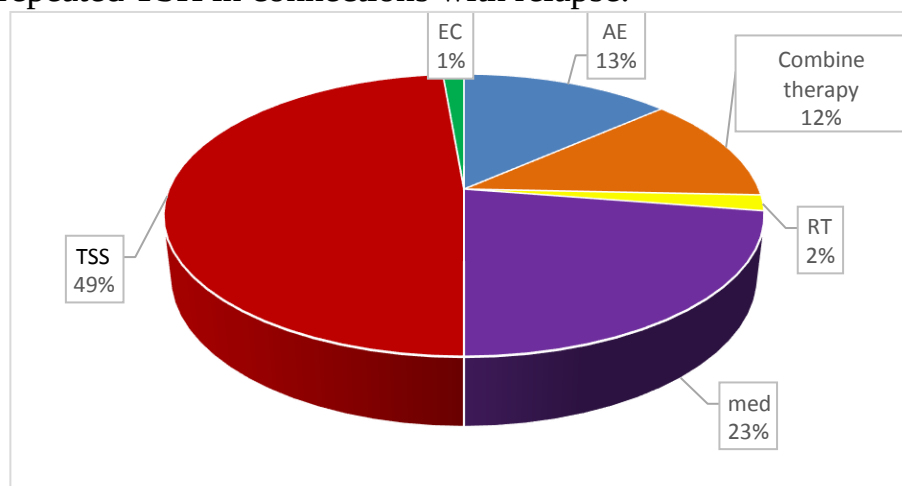


Fig1. Distribution patients with ACTH DCS on the groups on received therapy

As can be seen from Figure 2., half of the patients 49% (108 patients) received highly specialized medical care - were operated on, but due to achievement of target levels of therapy were subjected to additional medication or radiation treatment. Currently, of the operated TSH 81 (75%) patients are in remission and 27 in the active phase (25%). In addition, patients who received combined therapy (20 patients), 17 (85%) - are in remission, 3 (15%) - in active stages.

Desmopressin test, after TSH, of which 73.3 % (44 patients) amounted to - women, 26.6% men (16 patients). Average age women was 33.8 ± 0.39 years (from 15 to 54 years), men - 30.75 ± 0.31 (from 26 to 39) of the year. Duration diseases with moment establishing diagnosis amounted to 36.4 ± 0.86 months (from four before 132 months). So how, goal our work came explore significance postoperative test with desmopressin for assessment of the effectiveness of TSH in the group achieved remission (first group), results will be offered in comparison group control. The first group patients amounted to eighteen patients (30%), which according to the clinical Practical Recommendations Society Endocrinologists from 2015, have had level cortisol ≤ 138 nmol / l in first 5-7 days after transsphenoidal adenomectomy pituitary. From them women - fourteen (77.7%), men - 4 (22.2%). The average age of women was 38.85 ± 1.09 years (from 20 to 51 years), men - 31.5 ± 0.25 years (from 31 to 32 years). The duration of the disease was 90.67 ± 58.2 months (from 36 before

204 months), duration before manifestations - 62.22 ± 49.46 months (from 6 before 143 months), duration of the disease from the moment of diagnosis - 29.1 ± 27.76 months (from 9 to 84 months), age patients on the moment productions diagnosis in average was- 35.67 ± 10.49 years (from 21 before 51), 37.7 ± 1.3 years women 28.5 ± 0.25 years -y men. Duration preoperative period disease was in within $1.11 \text{ month} \pm 0.02$ (from one before 2 months), duration postoperative period - 30.67 ± 27.14 month (from 8do 83 months).

Analysis hormonal indicators in preoperative period in I group showed the following: ACTH ranged from 52 to 88 ng / dl and averaged $62.64 \pm 11.21 \text{ ng/ dl}$, exceeding such groups control at 2.88 times ($p \leq 0.001$). Similar trend was observed, in urine free cortisol concentrations - $194.03 \pm 55.27 \text{ nmol / l}$ (range from 122 to 270 nmol /L) and in basal cortisol levels $877.3 \pm 97.1 \text{ nmol /L}$ (range 746 to 1010 nmol / l), which were reliably significantly higher by 1.25 and 1.87 times, respectively on compared to control ($p < 0.01$ ir ≤ 0.001).

Postoperative levels hormones in I group patients were the following: levels ACTH varied in within from 6.5 before 43.1 ng / dl - and in average made up $15.5 \pm 12.5 \text{ ng/ dl}$, UFC- $44.65 \pm 35.6 \text{ nmol/l}$ (range 16 to 115 nmol/l) and basal cortisol $74.23 \pm 30.1 \text{ nmol/l}$ (range 36 to 132 nmol /l). Benchmarking before and postoperative indicators hormones revealed reliably significant decline ACTHv4 times ($p \leq 0.005$), UFC - at 4.34 times ($p \leq 0.001$) and basal cortisol-in 11.8 times ($p \leq 0.001$). How show results, most sensitive and meaningful turned out to be level basal cortisol blood, then UFC and ACTH.

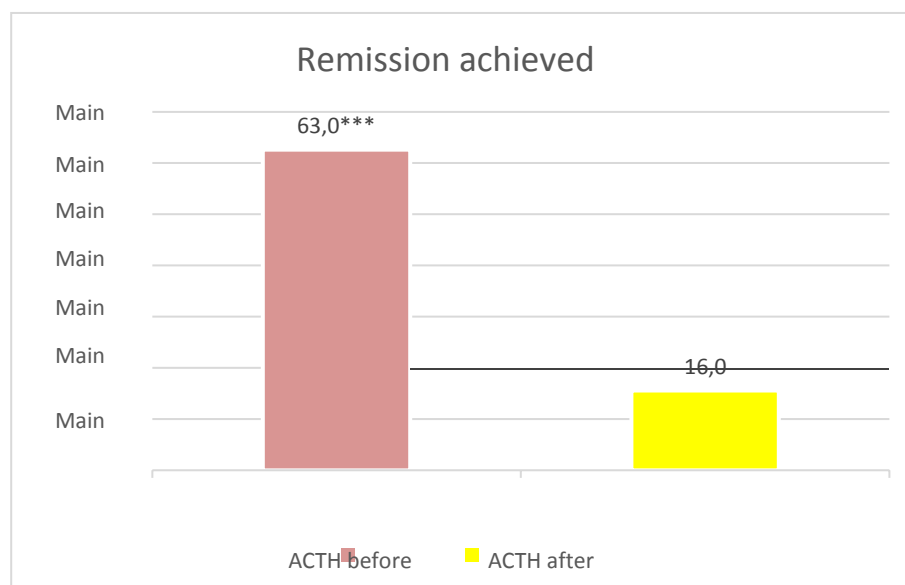


Fig2. Levels ACTH (ng / dl) before and after TSS, *- $p < 0.001$**

Should Mark, what at 2 patients (11.1%) despite on the achievement biochemical remission, clinical signs disease not have had positive dynamics? Objective status patient characterized stability BMI - 45.7 kg/ cm^2 , resistance to blood pressure, which increases against the background of antihypertensive drugs up to 180/100- 150/90 mmHg Detailed analysis data cases showed what Patients have had mean age 34.6 ± 1.6 years, mean duration of illness-100 months and

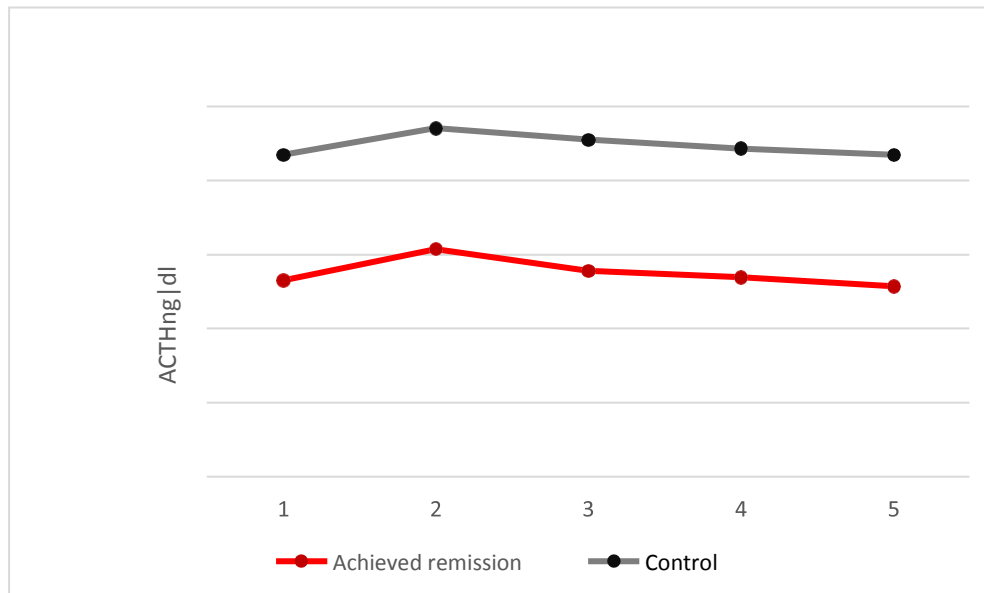
duration before manifestation-50.6 $\pm$ 15.4 months. That is, in general, did not differ from patients of this groups, per except for 2 multiple increase medium duration illness.

Results desmopressin test in I group

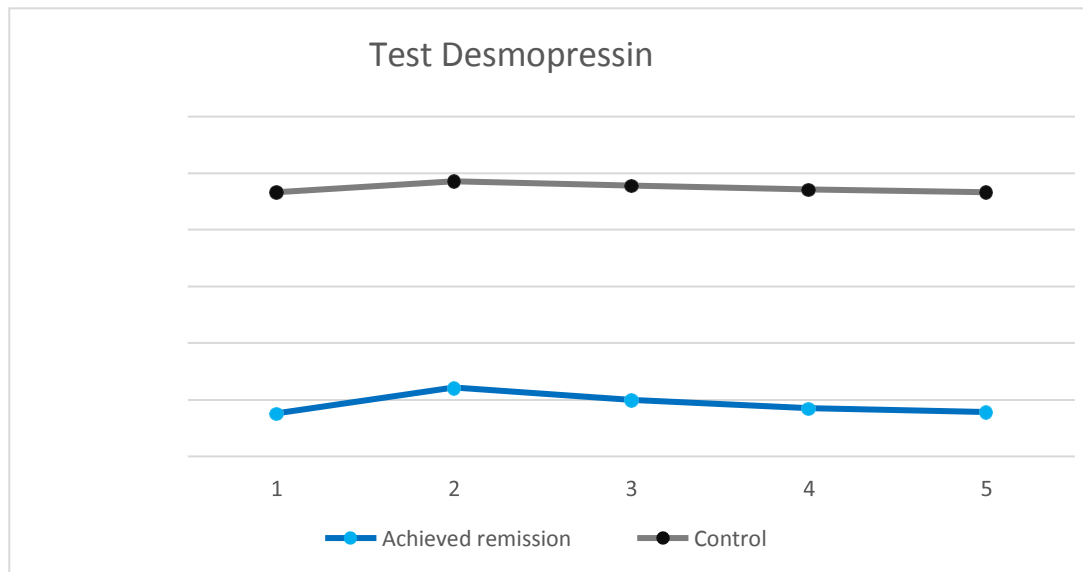
Early postoperative cortisol at patients I groups was fixed in within 74.2 ± 30.18 nmol / l and varied in within from 36 before 132nmol/l. On the day the test, the level of cortisol at 0 min was 76.02 ± 58.62 nmol / l and was 6 times lower than in the control group ($p \leq 0.0005$), and the cortisol response peaked at the period between 30 and 60 minutes, averaging 121.7 ± 95.76 nmol / l, that is, 4 times lower, how in group control ($p \leq 0.001$), Δ Cort 45.74 ± 55.78 nmol/l , growth cortisol- 57.32 ± 79.6 nmol/l, what in 2.4 times above, how in group control. ($p \leq 0.005$)

Level ACTH 0 made up 13.25 ± 14.09 ng/dl peak ACTH accounted for on the period between 30 and 60 min 15.37 ± 14 ng/ dL , and these figures were 1.5 times lower ($p \leq 0.5$) groups control. More Togo, how Δ ACTH (2.11 ± 2.63 ng/ dl), So and growth ACTH (31.71 ± 47.4 ng/ dl) were above control in 1.17 and 3.85 times ($p \leq 0.5$) respectively. Data given in form Rice 5;6.

Pic. 1. The results of the dynamics of ACTH in the blood during the test with desmopressin in the studied groups



Pic. 2. Results of cortisol dynamics in the blood during the test with desmopressin in researched groups



In this way, a thorough analysis of the data in the study groups showed that TD is a sensitive tool in determining the reactivity of corticotropic pituitary cells. Judging by the level of ACTH and cortisol during TD and carefully comparing with clinical, biochemical, hormonal parameters and risk factors can be evaluate the effectiveness and radicalness of the surgical intervention. So, according to the results of our research, it is clear that TD clearly shows facet remissions and Availability relapse, about how testify significant high reactivity corticotropes (Maybe residual or recurrent again) With sharp hyperproduction ACTH and cortisol after them stimulation at sick with dubious outcomes disease or with subclinical cushingoid after conducted by TAG. Moreover, TD can help to identify cases, i.e. a group risk among patients with objective indicators of remission according to the latest clinical recommendations [7]. So, in the study us a cohort of postoperative sick with remission ACTH-DCS on the background samples with desmopressin at 2 (11%) of eighteen patients revealed an abnormal increase in the level of both ACTH and cortisol, i.e., the test was positive and this is indicating on the Availability possible risks growth tumors and relapse illness.

Discussion results research

Colombo et al. [14] examined 19 patients with ACTH DCS in the postoperative remissions with repeated tests desmopressin in time observations. They are not observed changes in susceptibility to desmopressin over time; At 14 patients which considered "healed" postoperative TD was negative, but remained negative, and none of them had relapses, whereas in 5 patients with "normalization" of cortisol levels,

positive TD was in the first postoperative month and remained positive throughout the period, 2 of them recurred. However, the duration of observation was rather short (up to 36 months). Ambrosietal [10] described three patients in whom TD became negative after "cure" but again appeared in time observation, and, what important, this is preceded clinical and hormonal documentation of relapse by 4–39 months. BouKhaliletal [12] also reported that 17 out of 20 patients with recurrent ACTH in final eventually have had positive answer on the stimulation analogue vasopressin (Including desmopressin in 17 patients) and that it preceded the midnight increase cortisol (in serum or saliva) or

UFC in 71% patients. Recently Ambrogioetal [ten] reported about 43 patients With ACTH DCS (including four with negative preoperative TD) in stages remissions after TSH, which was subjected to TD for 20 years after surgery. A positive response was defined as an increase in ACTH levels of at least 27 pg /mL. All but 6 patients did not respond to TD after surgery; TD continued to be negative in the majority (he became positive at 9) patients with long remission then how answer on the desmopressin reappeared in patients who subsequently relapsed, even years before overt hypercriticism. In the study VassiliadiDA et al. [24] one patient relapsed despite an apparently negative postoperative TD. This patient had repeated TD and tested positive 3 years after operations, preceded documented relapse through 21 month. Among biochemical markers, increase level cortisol in saliva late nights, how reported to be one of the earliest anomalies indicative of ACTH recurrence after operations, With reservation, what he suffering from significant variability inside the patient, which requires the collection of three or four samples in successive days [17].

Comparison data about postoperative TD and cortisol saliva late nights [12, 13] and future studies comparing these two markers are of particular interest. AT Overall, the available data, although limited, indicate that positive response may appear during long-term follow-up, earlier than other markers relapse, affirming role repeated TD how parts longitudinal estimates successfully operated patients with ACTH DCS. We postulate that the reappearance TD positivity represents a relapse, while early postoperative positivity indicates the persistence of pathological corticotropes, which can progress over time and lead to clinical reappearance of ACTH DCS.

By data our research, in postoperative period noted reliable decline hormonal indicators blood and urine (ACTH, cortisol) on compared with preoperative data in patients of the study groups. Comparative analysis before and postoperative indicators hormones revealed reliably significant decrease in ACTH by 4 times ($p \leq 0.005$) UFC - by 4.34 times ($p \leq 0.001$) and basal cortisol-b 11.8 times ($p \leq 0.001$). As the results show, the most sensitive and significant turned out to be level basal cortisol blood, then UFC and ACTH.

Holding samples With desmopressin revealed what in all fences blood after loads at PATIENTS I groups levels ACTH and cortisol blood were reliably above, how at sick groups control. Level ACTH 0 made up 13.25 ± 14.09 ng /dl peak ACTH accounted for on the period between 30 and 60 min -15.37 ± 14 ng/ dl, and data indicators were below in 1.5 times ($p \leq 0.5$) groups control. More Togo, how Δ ACTH

(2.11 ± 2.63 ng/ dl), So and growth ACTH (31.71 ± 47.4 ng/ dl) were above control in 1.17 and 3.85 times ($p \leq 0.5$) respectively.

For accurate answers on the questions needed further monitoring quality life sick With ACTH-DCS in postoperative period.

Conclusions

1. Cognitive analysis estimates recurrence ACTH- DCSs application desmopressin test at patients who achieved postoperative remission showed that TD is a sensitive tool in determining the reactivity of corticotropic pituitary cells.

2. Mapping clinical, biochemical, hormonal indicators and factors risk in progress TD will allow estimate efficiency and radicalism conducted surgical intervention. Beside this, TD clearly shows facet remissions and having a relapse about what testify significant high reactivity corticotropes (Maybe residual or recurrent again) With sharp hyperproduction of ACTH and cortisol after their stimulation in patients with doubtful outcomes disease or with subclinical cushingoid after the TSH.

3. Usage TD in combinations basal cortisol blood after TSH at ACTH-DCS maybe promote identification groups risk among patients having objective indicators of remission according to the latest clinical guidelines. AT researched us cohort postoperative 18 patients With remission ACTH-DCS on the background TD in 11% patients have had positive reaction on the desmopressin, about how testified promotion level cortisol and maybe serve positive predictive ACTH-DCS marker probabilities recant exodus disease

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