Visual Function Impairments in Patients with Functioning and Non-Functioning Pituitary Adenoma

G. Slatkevičienė*
B. Glebauskienė*
R. Liutkevičienė**
L. Kriaučiūnienė**
G. Bernotas***
A. Tamašauskas****
D. Žaliūnienė*

**Lithuanian University of Health Sciences, Medical Academy, Department of Ophthalmology, Lithuania*

***Lithuanian University of Health Sciences, Medical Academy, Department of Ophthalmology, Lithuania; Neuroscience Institute, Lithuanian University of Health Sciences, Medical Academy*

****Lithuanian University of Health Sciences, Medical Academy, Department of Neurosurgery, Lithuania*

*****Neuroscience Institute, Lithuanian University of Health Sciences, Medical Academy; Lithuanian University of Health Sciences, Medical Academy, Department of Neurosurgery, Lithuania*

Summary. *Aim.* To evaluate visual functions (visual acuity, maximum color contrast sensitivity, visual field) and optic disc changes in patients with functioning and non-functioning pituitary adenoma (PA).

Methods. Forty one person (82 eyes) with PA and 100 (200 eyes) age and gender matched controls were tested. PA diagnosis was confirmed by magnetic resonance imaging (MRI) scans. Visual acuity (VA) and perimetry tests were estimated. Hormonal dysfunction was tested in patients' blood samples. Computerized Maximum Color Contrast Sensitivity test (MCCST) was used for color discrimination testing. Patients were divided into two groups according to hormonal function of PA. The first group consisted of patients with functioning PA (N 40 eyes) and the second group consisted of patients with non-functioning PA (N 42 eyes). In the MCCST, subject's task was to determine the correct direction of a bar in a circle. A subject had to press a button with a bar matching the direction of a bar in the circle. If the direction was unclear, blank button was pressed.

Results. VA decline was found in 50 (61%) patients eyes. No visual field defects were found in 12 eyes (16%) and 70 eyes (84%) had visual field deficit. VA and visual field were statistically better in the group with functioning PA ($p<0.001$). Optic disc pallor was found in 56 (68%) eyes, compared with normal optic disk appearance, that was found in 26 eyes (32%). The mean error score of the MCCST in healthy persons was 1.4, in patients with PA that produces hormones – 2.5, when in inactive PA group it was 4.2; $p<0.0001$.

Conclusions. Our results show that PA can cause the impairments of VA, perimetry and colour contrast sensitivity. These results depend on the type of PA. In our study patients with non-functioning PA suffered from more severe impairment of visual function than patients with functioning PA. MCCST may be one of the earliest methods to diagnose the damage of chiasm in patients with PA.

Keywords: hypophysis, pituitary adenoma, visual function impairment, MCCS.

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INTRODUCTION

Pituitary tumors are common in the general population. In 16.7% changes in the pituitary gland can be detected [1]. Microadenomas (less than 1 cm diameter) comprise 50–60% of these and tend not to exhibit further growth. In contrast, macroadenomas may slowly expand over years. Pituitary carcinomas are extremely rare, and in these cases the assumption is that they are former benign adenomas

Adresas:
Girėna Slatkevičienė
Department of Ophthalmology
Eivenių 2, Kaunas
Tel. (+370 37) 326 018, e-mail: girenos@gmail.com

that have undergone additional genetic mutations [3]. Approximately half to one third of all pituitary tumors are non-functioning pituitary adenomas (i.e. without hormone secretion detected either by immohistochemistry or by elevated hormonal blood levels). The most common hormone-secreting pituitary tumor is the prolactinoma (lactotroph adenoma – 25–41%), followed by somatotroph adenomas (10–15%), corticotroph adenomas (about 10%), thyrotroph adenomas (<1%), and gonadotroph adenomas (<1%) [1, 4]. Clinically nonfunctioning pituitary adenomas (CNFPAs) are a varied group of tumors with different morphology and biologic characteristics constituting about a third of all pituitary adenomas [4]. They are characterized by the absence of symptoms or signs secondary to hormonal hypersecretion [5]. They are usually macroscopic and generally present with compressive symptoms affecting the visual apparatus and pituitary gland resulting in varying levels of hypopituitarism [5–7]. These tumors can also result in an apoplectic event with varying presentations from headache to visual impairment, often necessitating urgent surgical intervention. Tumor apoplexy poses long-term risk of endocrinological and visual sequelae [8, 9]. Visual disturbances are noted when the tumor grows beyond the sella and compresses the optic nerve. Typical neuro-ophthalmic features include progressive bilateral slow and asymmetric deterioration in visual field defects and optic disc changes [10].

THE AIM OF THE RESEARCH

The aim of our research was to evaluate visual functions (VA, MCCS, visual field) and optic disc changes in patients with functioning and non-functioning PA.

MATERIALS AND METHODS OF THE STUDY

Forty one person (82 eyes) with PA and 100 (200 eyes) age matched controls were tested. The PA was confirmed by MRI scans. The patients' blood samples were taken in order to find hormonal changes in the blood. The patients were divided into two groups. The first group was patients with functioning PA, (N 40 eyes) and the second group – patients with non-functioning PA (N 42 eyes).

The inclusion criteria were as follows: 1) PA identified and confirmed by MRI; 2) patient's good general condition; 3) patient's consent to take part in the study.

The exclusion criteria were as follows: 1) infectious eye diseases (history of keratitis, acute or chronic uveitis), glaucoma, optic nerve diseases, degeneration or dystrophy of the central part of the retina, high-degree refraction defects, lens opacities; 2) systemic diseases (diabetes mellitus, malignant diseases, systemic connective tissue disease, chronic, infectious diseases), tissue or organ transplant surgery; 3) brain tumors of other localization; 4) patient's refusal to participate in the study.

In this study non-corrected and best-corrected VA (measured in decimals from 0.1 to 1.0) was evaluated using Landolt's rings (C optotypes) by Snellen test types at a 5 metre distance from the chart. To reach the best-corrected VA, refraction was performed during each examination. Biomicroscopy was performed in order to assess the corneal and lenticular transparency. The lenses were examined using a slit lamp, positioning the illumination source at a 45-degree angle and the light beam split to a 2-mm width. Pupils of the subjects were dilated with tropicamide 1%. Fundoscopy was performed with an ophthalmoscope of the direct monocular type and the slit-lamp, using a double aspheric lens of +78 diopters. The Goldmann perimetry was performed to all patients. The largest isopter in Goldmann testing extends 90 temporally and 60 in other quadrants.

The MCCST was performed. In the computer test of MCCST, the subject's task is to determine the correct direction of a bar in a circle. The subject has to press a button with a bar matching the direction of the bar in the circle. If the direction is unclear, a blank button is pressed. After each pressing on the button, a blank screen appears and then, after 1 second, the circle with a randomly chosen direction of bars is shown. If the direction of the bar in the circle is chosen incorrectly, its color is automatically highlighted. After the correct choice of the direction of the bar, the intensity of its color is automatically dulled and, in the presence of this intensity of color of the bar, the brightness of background of the circle is changed. The first correct answer after a series of incorrect answers or the first incorrect answer after a series of correct answers is accepted as the subject's maximum sensitivity to the target color of a bar. When the subject's maximum sensitivity to the target color of the bar has been assessed, the color of the bar is changed and everything starts from the beginning again. The bar can be of six colors: red, green, blue, greenish blue, violet, yellow. Once the subject's sensitivity to all these colors has been assessed, all findings are recorded in a database, and the results of the test are presented in a result window.

Statistical analysis was performed using the computer program SPSS/W 13.0 (*Social sciences statistical package program for Windows, Inc., Chicago, Illinois, USA*). The data was presented as real numbers (percent), the average values and standard deviations (SD). The quantitative data without normal distribution was compared using the nonparametric size comparative tests (Buhl, Zofel, 2000). In order to determine the difference between two independent groups, the Mann-Whitney U criterion was used; among several different groups – the Kruskal-Wallis H criteria. Statistically significant difference was concidered $P<0.05$.

RESULTS

VA decline was found in 50 (61%) eyes of patients with PA. VA and visual field were statistically better in the group with functioning PA ($p<0.001$). Mean VA in pa-

Table. **Perimetry test results in patients with pituitary adenoma (PA)**

Parameter	PA producing hormones, number of eyes, (%)	PA non producing hormones, number of eyes, (%)	P-value
Concentric narrowing, n (%)	20 (59)	34 (71)	0.345
Bitemporal hemianopsy, n (%)	6 (17)	10 (21)	0.7838
No visual field defects, n (%)	8 (24)	4 (8)	0.0657

tients with functioning PA was 0.8 (0.78) (distributed from 0.3 to 1.0). In the group of patients with non-functioning PA mean VA was 0.6 (0.62) (distributed from 0.01 to 1.0), $p<0.05$. In the first group of patients, perimetry test results were better than in the second group of non-functioning PA. No visual field loss was found in 12 eyes (16%) and 70 eyes (84%) had visual field defect (table).

In our research, MCCST was affected in 73.17% person with PA. The MCCST was affected in 30.46% patients with functioning PA, and in 94.25% in case of non-functioning PA.

The mean error score of the MCCST in healthy persons was 1.4, in patients with functioning PA 2.5, in patients with non-functioning PA it was 4.2; $p<0.0001$. There was a moderate positive correlation between activity in hormone aspect of PA and MCCST results ($r=0.503$, $P<0.05$).

Optic disc pallor was found in 56 (68%) eyes, compared with normal optic disk appearance, that was found in 26 eyes (32%). OND pallor was found in 52% of patients with functioning PA and in 75% of patients with non-functioning PA. There were no statistical significant differences between these groups.

DISCUSSION

The most common neurological symptoms in patients with PA are headaches and visual changes [11]. Pituitary tumours may compress the anterior visual pathways [12]. This can lead to visual loss in 32–70% of cases [13, 14]. For many patients, visual loss is the initial or the only symptom of the disease; therefore, an ophthalmic examination is of crucial importance since it can provide important data by disclosing the most typical bitemporal hemianopic defect [14]. When tumor enlarges, it compresses the optic chiasm superiorly, primarily causing visual field deficits, most often bitemporal hemianopia [15]. If the adenoma expands laterally into the cavernous sinus, it has the potential to affect the cranial nerves housed there, including cranial nerves III (n. oculomotorius), IV (n. trochlearis), and VI (n. abducens). With more severe compression or direct invasion of the optic nerve, decreased VA may occur. Visual disturbances tend to correlate with tumor size. They also tend to occur insidiously, so that many patients are not aware of them until they are specifically tested [16].

The complexity of the examination includes VA, perimetry and eye fundus examination of both eyes. Although these examination methods are very useful, they do not completely reflect the whole condition of the visual system. We are using the new Maximum Colour Contrast Sensitivity (MCCST) test in order to examine the visual functions more accurately in our research. This test is extremely sensitive to the earliest stages of the alterations of visual functions. Colour vision deficiency is one of the commonest disorders of vision and can be divided into congenital and acquired forms. In the estimation of the defects of colour sensitivity it is very important to distinguish whether disorder of colour sensitivity is congenital or acquired. A congenital colour sensitivity defect is stable throughout human life, is found in both eyes and depends on the loss or the decrement of the function of the cones. An acquired colour sensitivity defect is the result of various lesions of the visual system. Due to that it can progress or regress [17]. The type of the defect of colour contrast sensitivity is very important in the diagnostics of PA. Its qualitative estimation can provide much information in the diagnosis of the disease or its progress [18]. These alterations depend on the changes in the whole visual tract from the cones in the retina to the cerebral extrastriatinal regions [19].

In literature we have found studies of visual deficits in cases of PA. In the study of Siddharth Ogra et al. [20] one hundred and three consecutive patients (206 eyes) with PA were recruited. The mean population age was 53.9 years (SD=15). Visual loss was the most common reason (39%). Bitemporal visual field defects were the most prevalent pattern (22.41%) followed by homonymous defects (7.13%). 33% of the patients with visual field loss had unilateral visual field defects [20]. Most patients (63.69%) had non-functioning tumours on presentation. Visual field defects were significantly more prevalent in patients with non-functioning tumours (67%) compared to those with functioning tumours (43%, $p=0.003$) [20].

In our study the average age of the patients was similar 51.7 (SD 10.4). VA decline was found in 50 (61%) of patients eyes. In our study visual field deficit was more prevalent in patients with non-functioning tumours compared to functioning tumours 91% and 76%, respectively ($p=0.4$).

Pituitary tumors are classified as functioning or non-functioning on the basis of their ability to produce and secrete mature hormones [1]. In the study of Monteiro ML et al. [16] thirty patients (60 eyes) with PA participated. A total of 30 patients (13 female, 17 male) were studied [16]. Twenty-one (70.0%) had non-functioning adenoma,

6 (20.0%) had prolactin producing adenoma, 2 (6.7%) had growth hormone producing adenoma, and 1 (3.3%) had thyroid stimulating hormone producing adenoma. The mean age was 44.1 (SD 16.0, range 23–74) years. A complaint of visual decline was present in 47 eyes (78.3%) and absent in 13 (21.7%) [16]. In a similar study of Sangmoon Lee [21] one-hundred and seventy eyes of 85 patients were included for analysis. The mean age for all subjects was 42.8±10.9 (range, 21–60) years and 39 (45.9%) patients were male. Fifty-six (32.9%) eyes had abnormal preoperative VA, 74 (43.5%) eyes had abnormal preoperative visual field. Among 85 patients, 36 (42.4%) had non-functioning adenoma. There were 17 (20.0%) patients with prolactinoma, 10 (11.8%) patients with growth hormone-secreting adenoma, 5 (5.9%) patients with follicle-stimulating hormone-secreting adenoma, 4 (4.7%) patients with adrenocorticotropic hormone-secreting adenoma, and 1 (1.2%) patient with luteinizing hormone secreting-adenoma. Remaining 12 (14.1%) patients had mixed hormones secreting adenoma. There were no significant differences in VA and visual field among each kind of adenomas. Fifty-six eyes (32.9%) of 40 patients had abnormal preoperative VA. Thirty-five eyes among these had preoperative VA of 20/30 or less and better than 20/70, and 21 eye had preoperative VA of 20/70 or less. Seventy-four eyes (43.5%) of 45 patients had preoperative VF defects [21].

In our study we had 8 (19.5%) patients with prolactinoma, 6 (15%) patients with adrenocorticotropic hormone-secreting adenoma, 8 (19.5%) patients with growth hormone-secreting adenoma, and 19 (46%) patients with non-functioning PA. There was no patient with folicule stumulating hormone or thyroid stimulating hormone or mixed hormones producing adenoma in our patients' group. Visual decline was found in 50 (61%) eyes. VA in 14 eyes was 0.3 or less, in 16 eyes VA was between 0.4 and 0.7. VA was 0.8 or better in 20 eyes. Remaining 32 eyes had no decline in VA. Visual field defects were found in 70 (85%) eyes.

Optic disc changes are common in patients with PA. Longstanding compression by pituitary macroadenoma leads to optic atrophy. In the study of Monteiro et al. fundus examination was performed. In their study fundus was normal in 25 eyes (41.7%) and disclosed optic atrophy in the others, graded as mild in 9 (15%), moderate in 14 (23.3%), and severe in 12 (20%) eyes. All 60 eyes had visual field loss, because only eyes with documented visual field loss were included in the study [16]. In our study 70 (85%) eyes had visual field defects. Fundus examination was normal in 26 eyes (32%) and optic atrophy was found in the 56 (68%).

There is not much information about colour contrast sensitivity impairment in early stages in case of PA. This impairment is mostly found when there is VA impairment, i.e. in later PA stages. We have found only a few studies where authors tried to detect early losses of contrast sensitivity (CS) in patients with PA, before the occurrence of VA and visual field defects.

In the study of Porciatti V et al. [22] contrast sensitivity was evaluated in both hemifields of 28 patients with different kinds of PA (mainly intrasellar) and normal VA and visual field, as well as in 15 age-matched controls. Two different stimuli were used: a coarse (0.3 c/deg) dynamic (10 Hz) grating and a finer (2 c/deg) static grating. In their results, an average, CS and/or hemifield asymmetry were reduced in patients, whereas perimetric sensitivity was normal. However selective losses for either stimuli were also found. CS losses did not correlate with anatomical measurements (size, chiasm involvement) of tumors as established by MRI scans. Authors concluded that CS evaluation might provide a simple and effective tool for early detection and monitoring of visual dysfunction in patients with PA. The lack of correlation between CS losses and chiasm involvement suggests causes different from chiasmal compression for visual dysfunction [22].

In the study by Nadezhda Deleva et al. [23] the results of a neuroophthalmological examination in two patients with parasellar pituitary adenoma were presented. The twelve months follow-up of visual dysfunction included standard Snellen visual acuity and Goldmann perimeters as well as low contrast number VA. For the needs of lowcontrast testing they chose standard for Bulgaria number charts, administered monoculary at 3% and 1.5% contrast. Their presented cases indicated that the low contrast acuity tests in patients with parasellar pituitary adenoma were sensitive indicators just like CS yields information for the visual dysfunction when other visual tests were normal [23]. Eleven patients were investigated in the study that was performed by Gutowski NJ et al. They examined tumours of sella turcica with no VA and visual field impairment. In this study colour contrast sensitivity impairment was found [24]. They suspected that the growth of the tumours to the suprasellar region could cause the dysfunction of the foveal vision tract. It can affect both "parvo" and "magno" roads even when VA is normal [24]. The decreasing of the MCCS test results in our study was one of the earliest signs of PA in patients with intact VA. It is interesting to know that even when VA was normal in patients with PA, MCCS test results were worse compared to healthy persons. We are in agreement with study of Kasputytė et al. In this study decreasing of colour contrast sensitivity in patients with PA was found [25]. In our research MCSST was affected in 73.17% of persons with PA, and even when VA was normal in PA patients the group error score was 2.35 times worse compared to healthy persons, $P<0.0001$.

CONCLUSIONS

PA is a common intracranial tumour. Due to the anatomical localization of the PA it can damage optical chiasma and cause specific symptoms. Sometimes these symptoms are not prominent for the patients from the beginning of the disease. Visual function tests for patients with suspicion of

PA are simple, non invasive and could be useful in the detection of PA in its early stages. In that case it could help to treat patients and control the outcomes of the treatment more successfully.

We would like to conclude that the MCCST may be one of the earliest methods to diagnose the damage of chiasm in patients with PA. Our results show that PA can cause the impairments of VA, visual field and color contrast sensitivity. These results depend on the type of PA. In our study patients with non-functioning PA suffered from more severe impairment of visual function than patients with functioning PA.

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G. Slatkevičienė, B. Glebauskienė, R. Liutkevičienė, L. Kriaučiūnienė, G. Bernotas, A. Tamašauskas, D. Žaliūnienė

REGĖJIMO FUNKCIJOS SUTRIKIMAI PACIENTAMS, SERGANTIEMS FUNKCIONUOJANČIA IR NEFUNKCIONUOJANČIA HIPOFIZĖS ADENOMA

Santrauka

Tikslas. Įvertinti regos funkcijas (regos aštrumą, ribinį kontrastinį spalvų jautrumą, akiplotį) ir regos nervo disko pakitimus pacientams, sergantiems funkcionuojančia ir nefunkcionuojančia hipofizės adenoma (HA).

Metodai. Ištirta 41 pacientas, sergantis HA (82 akys), ir šimtas sveikų (200 akių) to paties amžiaus ir lyties tiriamųjų. HA diagnozė patvirtinta atliekant magnetinio rezonanso tyrimą (MRT). Hormoninis aktyvumas tirtas atliekant veninio kraujo tyrimą. Atliekant kompiuterinį spalvų jautrumo tyrimą, paciento užduotis yra paspausti tokios pačios krypties langelį, pagal tai, kokios krypties spalvotą juostelę mato kompiuterio ekrane. Jei pacientas spalvotos juostelės nemato, spaudžiamas tuščias langelis.

Rezultatai. Regos aštrumo sumažėjimas buvo nustatytas 50 (61 %) pacientų, sergančių HA. Normalus akiplotis rastas 12 akių (16 %), 70 akių (84 %) buvo rasti akipločio pokyčiai. Regos aštrumas ir akiplotis buvo statistiškai reikšmingai blogesni pacientų, sergančių nefunkcionuojančia HA nei funkcionuojančia HA ($p < 0,001$). Sergant nefunkcionuojančia HA, vidutinis regos aštrumas buvo 0,6 (0,62) (pasiskirstymas nuo 0,01 iki 1,0), $P < 0,05$. Šioje pacientų grupėje 4 akyse nustatytas normalus akiplotis, koncentriškas akipločio susiaurėjimas – 10 akių, bitempo-

ralinė hemianopsija – 6 akyse. Pacientų su funkcionuojančia HA vidutinis regėjimo aštrumas buvo 0,8 (0,78) (pasiskirstymas – nuo 0,3 iki 1,0), P < 0,05. Šioje pacientų grupėje 9 akyse nustatytas normalus akiplotis, koncentriškas akipločio susiaurėjimas rastas 10 akių, bitemporalinė hemianopsija – 1 akyje. Vidutinis klaidų skaičius, atliekant kompiuterinį spalvų juslės tyrimą, kontrolinėje grupėje buvo 1,4, pacientų su funkcionuojančia HA – 2,5 ir pacientų su nefunkcionuojančia HA – 4,2; p < 0,0001.

Išvados. Mūsų atlikto tyrimo duomenimis, HA gali lemti regos aštrumo, akipločio ir spalvų kontrastinio jautrumo sutrikimą. Sutrikimų pobūdis priklauso nuo HA hormoninės funkcijos. Nustatėme, kad pacientams su nefunkcionuojančia HA randami didesni regos funkcijų pažeidimai nei pacientams su funkcionuojančia HA. Ribinis spalvinio kontrastinio jautrumo tyrimas galėtų būti vienu iš jautrių metodų, diagnozuojant regos kryžmės pažeidimą pacientams, sergantiems HA.

Raktažodžiai: hipofizė, posmegeninė liauka, regos funkcijos sutrikimas, MCCS.

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