Thus, the main problem in WS is defining the source of bleeding in order to postulate the correct therapy.

In our case, it was not possible, in the acute phase, to define the cause of bleeding. Fortunately, the bleeding limited itself spontaneously and the patient was treated conservatively. This did not ensure that the bleeding source was not still present. The literature reports that if a CT scan, followed by angiography, does not reveal the bleeding source, a CT scan should be repeated later, as it is obvious that if the hemorrhage is massive, a possible renal cell carcinoma, angiomyolipoma, or other renal bleeding sites, such as renal cysts, could be seen just after the resorption of the hematoma [13]. That has also been proven, not just in cases of renal angiomyolipoma or clear cell carcinoma, but also in rare cases of renal sarcoma presenting WS [14]. Thus, we performed a CT scan at one, three, and six months after the acute phase. As seen from the presented figures, we were not able to elucidate the real cause of bleeding even six months after the acute event.

It is worth mentioning that hematologic issues can contribute to WS. As reported, some patients with end-stage renal disease are predisposed to bleeding diathesis in the setting of uremic platelet dysfunction, anemia, irregularities in von Willebrand factor, and impaired platelet – vessel wall interaction [15, 16].

All those factors were excluded in our case, given the young age, complete negative anamnesis and normal laboratory findings of the patient.

The patient was treated conservatively, which corresponds to previous findings on WS, stating that if the patient is hemodynamically stable in the acute phase, nephrectomy or partial nephrectomy should be deferred. A recent Korean study of 28 patients with WS stated that the definitive treatment of WS will depend on the clinical condition and the underlying cause, with possible therapeutic options including conservative therapy, angioembolization, nephron-sparing surgery, or radical nephrectomy [3, 17]. More interestingly, they found that five of 28 patients had no obvious cause of perirenal bleeding. This was also the case with our patient, given that nephrectomy or partial nephrectomy were not needed even later, as no malignant pathology could be observed.

In conclusion we can say that, although a vast majority of WS cases are represented by angiomyolipoma or by renal cell carcinoma, the cause sometimes remains unknown. In the present report we described a rare case of idiopathic WS whose cause could not be diagnosed even after six months of follow-up.

Conflict of interest: None declared.

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Редак случај спонтане перирenалне хеморагије – Вундерлихов синдром

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САЖЕТАК

Увод Спонтана перирenална хеморагија или Вундерлихов синдром представља редак ентитет у урологији. У највећем броју случајева узрок овог феномена представљају ангиомиолипоми и карциноми бубрега. Мање заступљени су узроци васкуларне природе, полицистични бубрези, нодозни полиартритис, пијелонефритис или идиопатски фактори. Третман ових болесника зависи од клиничких параметара на пријему, као и од присуства евентуалних малигних бубрежних обољења.

Наш циљ је био представити редак случај релативно младог болесника са Вундерлиховим синдромом који није био узрокован ниједном до данас знаних патологија.

Приказ болесника Приказујемо случај 50-годишњег болесника са спонтаним перирenалним крварењем чији узрок није откривен ни после шест месеци праћења од акутног крварења.

Закључак У случајевима перирenалног крварења, узрок не може увек бити откривен по пријему болесника, упркос данашњим врло развијеним радиолошким методама. У овим случајевима важно је имати на уму да је дуже праћење ових болесника, после акутног крварења, од суштинске важности за успостављање праве дијагнозе, с обзиром на то да перирenални хематом може маскирати присуство евентуалног малигнитета. У врло ретким случајевима узрок перирenалног крварења не може бити откривен ни после дужег праћења.

Кључне речи: Вундерлихов синдром; перирenална хеморагија; ангиомиолипом

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Prognostic value of optical coherence tomography in chronic chiasmal compression

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SUMMARY

Introduction Sellar and parasellar region lesions, such as pituitary adenoma, often lead to the compression of the optic chiasm. Consequentialy, visual field (VF) defects and loss of visual acuity are common complaints in these patients. The aim of this report is to evaluate if optical coherence tomography, measuring retinal nerve fibre layer (RNFL) and ganglion cell complex thickness (GCC), offers a reliable prediction of visual outcome in patients with chronic chiasmal compression from a pituitary macroadenoma.

Case outline We present a case of chronic chiasmal compression from a pituitary macroadenoma with an initial binocular VF defect and low values of optical coherence tomography parameters binocularly. The average value of RNFL on the right eye pre/postoperatively was 48/79 μm, while on the left eye it was 56/63 μm. The average value of GCC pre/postoperatively was 47/46 microns on the right and 45/46 microns on the left eye. Six weeks after surgical optochiasmal decompression, macular GCC on both eyes and RNFL on the left eye remained largely unchanged, while RNFL of the right eye exhibited increases in thickness, as the postoperative consequence of the removal of the conduction block. Neither VF nor visual acuity showed postoperative improvement.

Conclusion Irreversible damage to the GCC and RNFL by longstanding compression results in poor visual outcome after surgery. Ganglion cell layer of the macula is a more accurate and reliable indicator of postoperative visual outcome.

Keywords: optical coherence tomography; macular ganglion cell layer; peripapillary retinal nerve fiber layer; visual outcome; suprasellar mass

INTRODUCTION

Compressive optical neuropathies are among the most important anterior optical pathways diseases that can lead to severe impairment of visual function. Compressive optic neuropathy is a group of diseases caused by mechanical comperssion of retinal ganglion cell (RGC) axons of the optic nerve. Chiasmal lesions may be caused by pituitary adenoma, craniopharyngioma, meningioma, cysts, and aneurysm.

Surgical removal of the lesions is an important aspect of clinical management. One of the primary indications for surgical management of chiasmal compression is the progressive loss of visual function. Surgical treatment enables decompression of the optochiasmatic complex, prevents further visual function deterioration, and enables visual acuity (VA) improvement at the same time. Visual recovery after surgical tretment of the chiasmal compression occurs in stages, with the removal of the conduction block, followed by secondary remyelination and restoration of the axoplasmic flow over months to years [1].

Pituitary adenoma is the most common anterior optical pathways' disease. As a consequence, visual impairment, including visual field (VF) defects and loss of VA, is a common complaint [2, 3].

Several predictors for the improvement of visual function after decompression of the anterior visual pathway have been studied, including duration of symptoms, age, preoperative VA, tumor size, optic disc pallor, funduscopic appearance of the retinal nerve fiber layer (RNFL), with coflicing results [3–6].

With the development of optical coherence tomography (OCT), more objective measurements of optic nerve damage and more objective prediction of visual outcome after treatment of pituitary adenomas have become available [7–19].

The aim of this report is to evaluate if OCT offers a reliable prediction of visual outcome in a case of chronic chiasmal compression from a pituitary macroadenoma. We used objective parameters of the thickness of the RNFL and the thickness of the ganglion cell complex (GCC).

CASE REPORT

A 65-year-old woman presented with an eight-month-long history of malaise, weakness, frontal headaches, and blurred vision in both of her eyes. Complete neuro-ophthalmic examination, including the VA test (Snellen charts), color vision test, VF analysis (Humphrey field analyzer;

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Carl Zeiss Meditec Inc., Dublin, CA, USA), full field 120 point suprathreshold test, ocular motility test, dilated stereoscopic fundus examination, and OCT measurements of the RNFL and the macular ganglion cell-inner plexiform layer (GCIPL) thickness, was done.

OCT imaging was conducted after pupil dilation (administration of 1% tropicamide eye drops), using the Cirrus OCT (OCT-3, OCT software version 6.0; Carl Zeiss Meditec Inc., Dublin, CA, USA). RNFL Optic Disc Cube 200 × 200 and Macular Cube 512 × 128 scan protocols were used. The ganglion cell analysis algorithm was used to determine macular GCIPL thickness within the 14.13 mm^2 elliptical annulus area centred on the fovea. Six sectoral (superior, superonasal, inferonasal, inferior, inferotemporal, and superotemporal) GCIPL thickness values were used for analysis. The Cirrus SD-OCT algorithm calculated the peripapillary RNFL thickness at each point on the circle of 3.14 mm^2 centered on the optic disc. Four-quadrant (superior, nasal, inferior, and temporal) RNFL thicknesses were used for analysis.

The patient had normal ocular position and motility with pupils of equal sizes. Dilated fundus examination revealed atrophic optic nerve head in the right eye and subatrophic optic nerve head in the left eye.

On examination, the patiet's VA (Snellen) was 0.03 in the right eye and 0.6 in the left eye, and there was a mild right relative afferent pupillary defect and red desaturation in the right eye.

VF testing demonstrated preservation of the central 30° in the nasal half of the left VF and total VF loss in the right eye.

Due to the concern of a chiasmal lesion, magnetic resonance imaging of the endocranium was performed and revealed a pituitary macroadenoma measuring 28 × 37 × 36 mm. The tumour extended supra, para, and infrasellary and throughout both cavernous sinuses, with pronounced compressive effect on the prechiasmal part of both optic nerves and the chiasma itself (Figure 1).

Additionally, there were multiple endocrinological disorders observed, including dropout of thyroid, adrenocorticotropic, somatotropic, and gonadotropic function. Patohystologic examination confirmed the case of gonadotropic adenoma, a neuroendocrine hypophyseal tumour.

Neurosurgical treatment involved subtotal tumor resection.

OCT showed pronounced thinning of RNFL (Table 1, Figure 1) and macular GCC binocularly (Table 2, Figure 4).

Nuclear magnetic resonance examination six weeks after surgical treatment revealed a larger residual lesion in the right sellar region and within the right cavernous sinus, with minimal growth of the tumor inside the left cavernous sinus. VA also stayed

Table 1. Thickness of the retinal nerve fiber layer [µm]

Parameter	Preoperative		Postoperative	
	right eye	left eye	right eye	left eye
Average thickness	48	55	79	53
Superior quadrant	50	65	66	64
Inferior quadrant	47	65	73	63
Nasal quadrant	51	48	117	44
Temporal quadrant	44	42	60	42

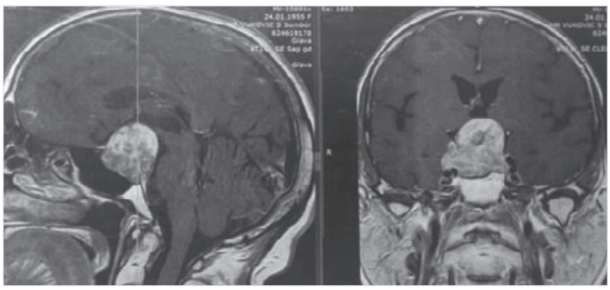

Figure 1. Nuclear magnetic resonance scan of the endocranium with optochyasmal compression

Table 2. Thickness of the macular ganglion cell layer [µm]

Parameter	Preoperative		Postoperative	
	right eye	left eye	right eye	left eye
Average thickness	47	45	46	46
Superior sector	49	44	47	44
Inferior sector	47	44	48	41
Superonasal sector	46	42	45	47
Inferonasal sector	48	40	44	42
Superotemporal sector	42	50	44	49
Inferotemporal sector	45	52	45	52

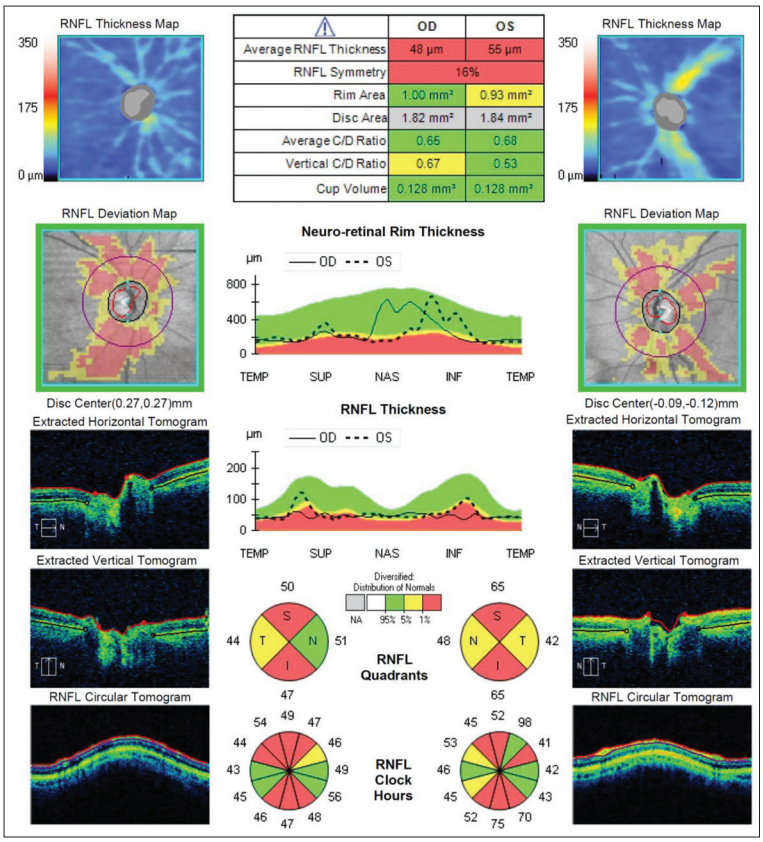

Figure 2. Preoperative retinal nerve fibre layer (RTNL) thickness

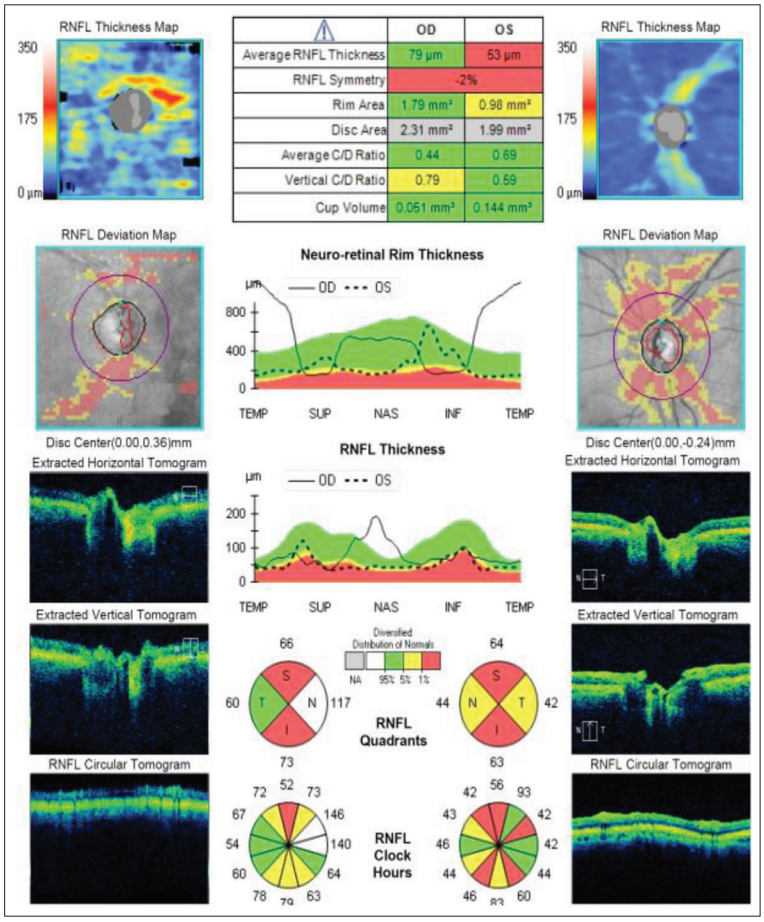

Figure 3. Postoperative retinal nerve fibre layer (RNFL) thickness

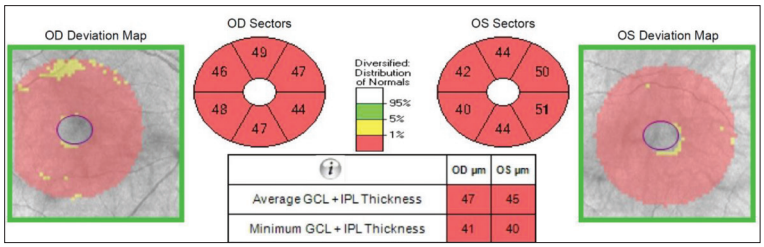

Figure 4. Preoperative ganglion cell complex thickness

GCL – ganglion cell layer; IPL – inner plexiform layer

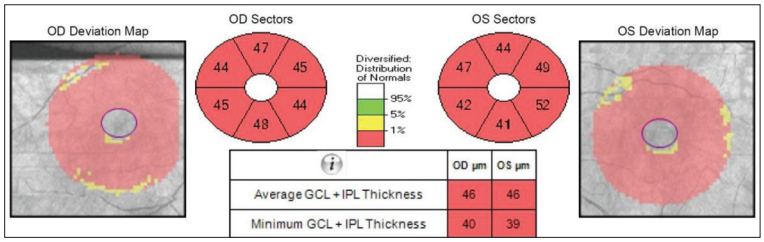

Figure 5. Postoperative ganglion cell complex thickness

GCL – ganglion cell layer; IPL – inner plexiform layer

unchanged. OCT parameters – macular GCC on both eyes and RNFL thickness of the left eye remained largely decreased, as on initial presentation, while RNFL showed signs of improvement as the consequence of postoperative removal of the conduction block (Figures 3 and 5). The VF defect was unchanged binocularly (Figures 6 and 7).

All procedures performed in this report were in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Written consent to analyze and publish all shown material was obtained from the patient and the approval for the study was given by Ethics Committee of the Eye Clinic, Clinical Centre of Vojvodina.

DISCUSSION

Tumors of the sellar, suprasellar, and parasellar region, which compose 30% of all intracranial tumors according to multiple authors, are a complex neurosurgical problem even today. This is mainly the consequence of their close anatomical relations with the vital structures of this region – the internal carotid artery and its branches, the hypothalamus, the infundibulum and the pituitary gland, with the optic nerves and their chiasma.

Individual variations of the chiasmal position and the inclination of its oblique plain determine the duration of the "quiet stage" of the growth of pituitary adenoma needed for the deterioration of the visual function. The gradual, slow decline of the visual function, headaches, a mild endocrine disorder result in the late physician involvement, with already enlarged tumors of uncertain prognosis for visual recovery.

In recent years, it has been established that patients who have an objectively measurable RNFL loss and the loss of retinal GCC at the time of surgery for chiasmal compressive lesions are less likely to have recovery of VA or VF after surgery [9–16]. Thinner preoperative RNFL and macular GCC thickness were found to be associated with poorer VA and VF after surgery. This also supports the notion that preserved OCT RNFL and macular GCC thickness confer a good visual outcome.

In this case, chronic chiasmal compression caused not only a conduction block but also a significant atrophy of the RGC, confirmed with OCT parameters that remained mostly decreased.

Although our study's follow up period was only eight weeks, the results proved to be comparable with the findings of Danesh–Meyer et al. [11], which, in a series of 40 cases with chiasmatic compressive lesions, with OCT and VF analysis, showed that pre- and post-decompression treatment in patients with thin RNFL did not demonstrate significant improvement in VA and VF. Min et al. [5], Zhang et al. [15], as well as Lee

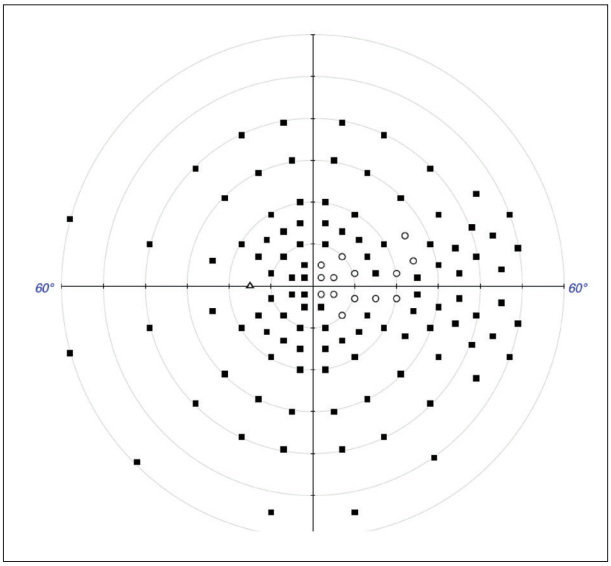

Figure 6. Full-field 120 point perimetry test of the left eye preoperatively

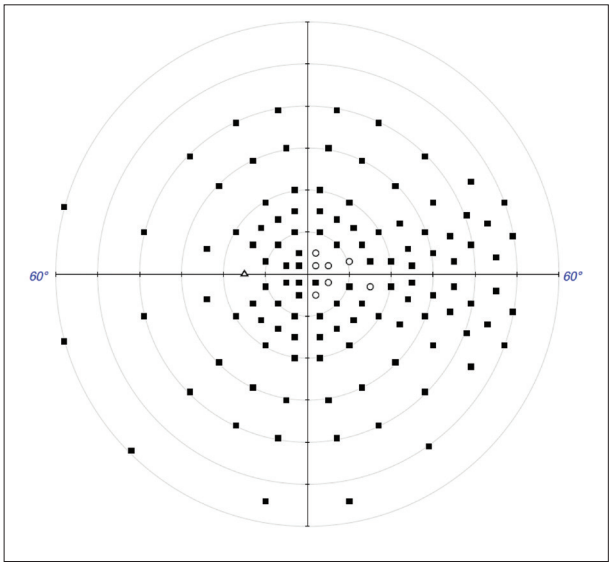

Figure 7. Full-field 120 point perimetry test of the left eye postoperatively

et al. [16] found with preoperative and postoperative RNFL thickness analysis that eyes with visual defects but normal preoperative RNFL thickness showed a significantly greater improvement in postoperative visual function than those with thin preoperative RNFL thickness. Similarly, Jacob et al. [6] demonstrated that circumpapillary RNFL thinning measured by OCT decreased the patient's chances of recovery of initial VF defect three months after treatment.

Some researchers also explored the predictive value of RNFL thicknesses in different quadrants [2, 6, 15, 17, 20]. Chiasmal compression is well-known to cause more thinning of the nasal and temporal sectors of the peripapillary RNFL thickness, and predominantly nasal hemiretina thinning of macular GCC, something we were not able to confirm in our patient due to extreme thinning of RNFL and GCL in all sectors [2, 17, 20].

While the majority of the research has focused on measuring the peripapillary RNFL, recent data suggest the ganglion cell layer – inner plexiform layer of the macula may be a more accurate and reliable biomarker of vision [6, 7, 8, 10, 12, 15, 17, 18]. According to numerous authors, GCC thinning, found in our patient as well, remaines relatively unchanged before and after decompression [17–20]. Consequently, patients with GCC loss before decompression had decreased chances of recovery of postoperative VF, the fact we can agree based on the postoperative VF in our patient [17–20].

RNFL and GCC thickness measured by OCT have been identified as useful prognostic indicators in the preoperative assessment of chiasmal compression and became an important aspect of the pre-treatment evaluation of pituitary tumors. OCT analysis may be an objective method to diagnose and follow patients with chiasmal lesions.

In the patient from our report, chronic chiasmal compression led to pronounced axonal damage, manifested in significant RNFL and GCC thinning and poor postoperative recovery of visual function. Ganglion cell layer of the macula proved to be a more accurate and reliable indicator of postoperative visual outcome.

Conflict of interest: None declared.

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Прогностичка вредност оптичке кохерентне томографије код хроничне хијазмалне компресије

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САЖЕТАК

Увод Супраселарне експанзивне лезије, као што су макроаденоми хипофизе, притиском на оптичку хијазму доводе до пада видне оштрине и испада у видном пољу најчешће на оба ока. Данас се употребом оптичке кохерентне томографије могу утврдити степен оштећења и могућност постоперативног побољшања видне функције.

Циљ рада је да се кроз приказ болесника са макроаденомом хипофизе и хроничном компресијом оптичке хијазме испита да ли мерењем дебљине слоја нервних влакана ретине и макуларног слоја ганглијских ћелија оптичком кохерентном томографијом добијамо објективну и реалну процену постоперативног стања видне функције.

Приказ болесника Приказали смо болесника са макроаденомом хипофизе и хроничном компресијом оптичке хијазме са иницијалним бинокуларним испадом видног поља, падом видне оштрине и веома ниским вредностима дебљине слоја нервних влакана ретине и макуларног слоја ганглијских ћелија на оба ока. Средња вредност дебљине слоја нервних влакана ретине преоперативно/постопертивно на десном оку износила је 48/79 микрона, а на левом 56/6 микрона. Средња вредност дебљине макуларног слоја ганглијских ћелија преоперативно/постоперативно била је на десном оку 47/46, а на левом 45/46 микрона. Видно поље на оба ока не показује постоперативно побољшање, као ни видна оштрина.

Закључак У овом случају изражено оштећење ганглијских ћелија макуле и нервних влакана оптичког нерва услед хроничне компресије потврђено је параметрима оптичке кохерентне томографије – слојем нервних влакана ретине и макуларним слојем ганглијских ћелија. Дебљина макуларног слоја ганглијских ћелија у односу на дебљину слоја нервних влакана ретине је бољи показатељ могућности постоперативног побољшања видне функције.

Кључне речи: оптичка кохерентна томографија; слој ганглијских ћелија макуле; слој ретиналних нервних влакана; исход видне функције; супраселарни тумор

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Leber's hereditary optic neuropathy with complete visual recovery – the first report

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SUMMARY

Introduction Leber's hereditary optic neuropathy (LHON) typically affects young adults, with a higher prevalence in men, but can ultimately occur at any age, as well as in women. LHON is caused by point mutations in the mitochondrial DNA. Classically, LHON presents as a subacute unilateral loss of visual acuity, dyschromatopsia in the red–green axis and a central or centrocecal scotoma. The contralateral eye usually develops similar symptoms within 3–6 months of the disease onset.

Case outline A 55-year-old male patient presented to a neurologist 20 days after the onset of vision loss. The patient was admitted as an emergency case to the Clinic for Eye Diseases due to a sudden vision loss in both eyes. The best corrected visual acuity in both eyes was 4/60. The intraocular pressure on both eyes was normal. Oedema of the optic nerve head was found on the right eye and a disc with blurred borders was seen on the left eye. During hospitalization, several consultative examinations and diagnostic procedures were performed, together with blood laboratory and visual field perimetry. Genetic testing for LHON as well as antibodies to AQ4, immunoserology, virology, and lumbar puncture were performed, as well as the visual evoked potential and ultrasound examinations.

Conclusion In our patient, the presence of a heteroplasmic mutation m.11778 G>A (*MT-ND4*) in the mitochondrial DNA analyzed from a peripheral blood sample was shown. In the available literature, this is the first documented LHON case demonstrating complete restitution of visual acuity in both eyes.

Keywords: Leber's hereditary optic neuropathy; sudden loss of vision; mitochondrial DNA mutation

INTRODUCTION

Leber's hereditary optic neuropathy (LHON) typically affects young adults with a higher prevalence in men, but it can ultimately occur at any age and in women. LHON is caused by point mutations in the mitochondrial DNA, which lead to a defect in complex I of the mitochondrial respiratory chain. This in turn causes dysfunction and later degeneration of retinal ganglion cells, followed by ascending optic atrophy [1]. Mitochondrial deficiency of respiratory complex 1 compromises adenosine triphosphate production and oxidative stress management in retinal ganglion cells. The most common LHON-causing mutations are 11778G>A, 3460G>A, and 14484T>C point mutations in *MT-ND4*, *MT-ND1*, and *MT-ND6* [2]. Classically, LHON presents as a subacute unilateral loss of visual acuity, dyschromatopsia in the red–green axis, and a central or centrocecal scotoma. The contralateral eye usually develops similar symptoms within 3–6 months of the disease onset. In 25% of the cases, however, the disease begins bilaterally [1]. Most patients deteriorate to acuities poorer than 20/200 (0.1). Pupillary light responses may be relatively preserved when compared with the responses in patients with optic neuropathies from other causes [3]. The classic fundus appearance triad includes the following: 1) hyperemia and elevation of the optic disc, with thickening of the peripapillary retina; although the disc appears swollen, it does not leak on fluorescein angiography; 2) peripapillary telangiectasia, and 3) tortuosity of the medium-sized retinal arterioles. These findings can develop before vision loss begins.

The fundus can also appear entirely normal (in > 40% of cases in one referral series) [4]. No treatment has been demonstrated to be effective. Corticosteroids are still one of possibilities for LHON treatment despite newer drugs such as idebenone or gene therapy. Idebenone may increase mitochondrial energy production and may improve the outcome of LHON. Novel therapies such as estrogen and gene therapy are being explored. Controversy exists whether tobacco or excessive alcohol intake, which might stress mitochondrial function, play an initiating role in LHON [5].

CASE REPORT

A 55-year-old male patient presented to a neurologist 20 days after the onset of vision loss. Simultaneously, he was treated by an otorhinolaryngologist for antibiotic-treated sinusitis. The patient had been treated for arterial hypertension for several years, and had been wearing a hearing aid. On examination, the neurological status was otherwise unremarkable.

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Multi-slice computer tomography of the endocranium revealed no pathology. Blood laboratory analyses were performed. Complete blood count showed mild erythropenia (4.34×10^{12}/l); mean corpuscular volume was 104 fL, and mean corpuscular hemoglobin of 35 pg. Biochemical analyses showed a high value of total bilirubin (43 μmol/L); ferritin was 325 ng/mL, aspartate transaminase was 81 U/L, alanine transaminase 145 U/L, gamma-glutamyl transferase 536 U/L. Electrolyte and inflammatory factor values were within the reference ranges.

The patient was emergently admitted to the Clinic for Eye Diseases due to a sudden vision loss in both eyes. The best corrected visual acuity in both eyes was 4/60. The intraocular pressure was 16 mmHg on both eyes measured by applanation tonometry. Signs of dry eye were found on the anterior segment examination. The optic nerve head manifested oedema on the right eye and blurry borders on the left eye.

Computerized perimetry was performed on the first, fourth, and eighth day. A centrocecal scotoma was observed in both eyes, enlarging on each subsequent image. On the first day, visual field demonstrated a mean deviation (MD) of -9.51 dB on the right eye (RE) and of -13.38 dB on the left eye (LE). On the fourth day, the MD in the RE was -9.58 dB, and in the LE it was -19.42 dB. On day 8, MD was -19.24 dB in the RE and -26.65 dB in the LE.

During hospitalization, several ancillary examinations and diagnostic procedures were performed. X-rays of the lungs and heart as well as paranasal sinuses did not show pathological changes. On the second day of hospitalization, magnetic resonance imaging of the endocranium was performed, which showed supratentorially bilateral chronic microangiopathic changes in the white matter of the brain and initial periventricular ischemic leukoencephalopathy. Chronic mastoiditis was found on both sides. Antinuclear antibodies were not detectable.

The patient was examined by an internal medicine specialist. A gastric volvulus was found and he did not receive consent for the use of pulse corticosteroid therapy at that moment. Multidetector row computed tomography of the thorax was without pathological changes.

On the third day of hospitalization, a consultant neurologist introduced pulse corticosteroid therapy. Genetic testing for LHON, as well as antibodies to AQ4, immunoserology, virology, and lumbar puncture were performed. It was advised to continue with corticosteroid treatment at the Clinic for Neurology Diseases. Visual evoked potentials testing was performed, and prolonged P100 latency was found on both eyes (right: 136 ms; left: 146 ms).

Immunoelectrophoresis was performed and it identified parallel oligoclonal IgG bands in the cerebrospinal fluid and serum with identical number and intensity. The findings support systemic immune activation. A color Doppler scan of the blood vessels of the neck indicated a moderately thickened intimomedial complex with no plaques. Carotid and vertebral arteries of regular diameter and direction were found. Transcranial color Doppler showed normal findings on the anterior and vertebrobasilar blood flow. Retroorbital ultrasound revealed regular hemodynamic parameters in central retinal and ophthalmic arteries bilaterally. Clinical decision support of the temporal artery neat was with no signs of temporal arteritis.

Detection of these mutations was performed using capillary electrophoresis on an automatic sequencer (3500 Genetic Analyzer; Thermo Fisher Scientific, Waltham, MA, USA). The results were analyzed using Sequencing Analysis Software v. 5.3.1. (Thermo Fisher Scientific). In our patient, the presence of a heteroplasmic mutation m.11778 G>A (*MT-ND4*) in mitochondrial DNA analyzed from a peripheral blood sample was shown. This confirmed the diagnosis of LHON.

Pulse corticosteroid therapy was administered for five days at a dose of 1 g, after which there was a significant improvement in visual acuity. Visual acuity in both eyes was improved to a maximum of 1.0 (200/200) and it was permanently maintained over the next two years of follow-up.

Written consent for publication of the article has been obtained by the patient's family member.

DISCUSSION

In the available literature, this is the first documented LHON case demonstrating complete restitution of visual acuity in both eyes with LHON.

Polymerase chain reaction amplification and sequencing of mitochondrial DNA regions containing mutations m.11778G>A (*MT-ND4*), m.14484T>C (*MT-ND6*), m.3460G>A (*MT-ND1*) have been shown to occur in about 90% of patients with LHON.

In a study by Mashima et al. [6], the effect of idebenone (Raxone; Santhera Pharmaceuticals Holding, Pratteln, Switzerland) was monitored in patients with LHON. Twenty-five (20.5%) of the 122 eyes had a recovery of their visual acuity to ≥ 0.2.

In a study by Newman et al. [7], among 695 patients with LHON, in patients with the m.11778G>A mutation, recovery of meaningful vision likely occurs in less than 20% of patients, irrespective of how recovery is defined, and ultimate visual acuities of better than 20/200 are rare.

The m.11778G>A LHON patients treated with gene therapy rAAV2/2-*ND4* exhibited an improvement of visual acuity over more than four years after vision loss to a degree not demonstrated in natural history studies [8].

Options for the effective treatment of hereditary optic neuropathies have been a long time coming. The successful launch of the antioxidant idebenone for LHON, followed by its introduction into clinical practice, was an important step forward. Nevertheless, other options, especially for a variety of mitochondrial optic neuropathies, such as dominant optic atrophy, are needed, and a number of pharmaceutical agents, acting on different molecular pathways, are currently under development. These include gene therapy, which has reached Phase III development for LHON [9].

Our case advocates that there is no secure treatment for visual outcome in patients with LHON. In our experience, introducing pulse corticosteroid therapy as soon as possible is highly recommended in LHON patients.

Conflict of interest: None declared.

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Леберова хередитарна оптичка неуропатија са потпуним опоравком видне оштрине – први приказ болесника

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САЖЕТАК

Увод Леберова хередитарна оптичка неуропатија (ЛХОН) типично погађа млађе људе са већом преваленцом код мушкараца, али може се десити у било ком животном добу и такође код жена. ЛХОН настаје због мутације у митохондријалној ДНК. Класично се презентује са субакутним унилатералним губитком вида, дисхроматопсијом у црвено-зеленом спектру и централним или центроцекалним скотомом. Друго око обично развија сличне симптоме за три до шест месеци од почетка болести.

Приказ болесника Болесник старости 55 година дошао је на преглед код неуролога 20 дана након изненадног губитка вида. Одмах је упућен као хитан случај на Клинику за очне болести због изненадног губитка вида на оба ока. Најбоље коригована видна оштрина на оба ока је износила 4/60. Интраокуларни притисак је био нормалан на оба ока. Едем главе оптичког нерва је био присутан на десном оку, а на левом се нејасно ограничавала глава оптичког нерва. Током хоспитализације је урађено више различитих консултативних прегледа и дијагностичких процедура, заједно са лабораторијском анализом крви и компјутеризованим видним пољем. Урађена су генетска тестирања на ЛХОН, као и антитела за *AQ4*, имуносерологију, вирологију и лумбалну пункцију. Урађени су такође визуелни евоцирани потенцијали – ВЕП и ултразвучни преглед.

Закључак Код нашег болесника је пронађена хетероплазматска мутација *m.11778 G>A* (*MT-ND4*) у митохондријалној ДНК добијеном анализом узорка периферне крви. Прегледом доступне литературе, ово је први документовани случај ЛХОН који показује комплетан опоравак видне оштрине на оба ока са ЛХОН.

Кључне речи: Леберова хередитарна оптичка неуропатија; изненадни губитак вида; митохондријална мутација ДНК

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CURRENT TOPIC / АКТУЕЛНА ТЕМА

Stress and arterial hypertension – from pathophysiology to pharmacology

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SUMMARY
Currently, arterial hypertension is the most massive chronic non-infectious disease of mankind. It may remain undiagnosed for years, provoking later complications, such as acute heart failure, cerebrovascular stroke, myocardial infarction, renal failure, hypertensive retinopathy, or sudden death. Primary arterial hypertension is more common, while secondary occurs in about 5–20% of cases. The recent studies have shown that stress may be a core factor in the development of essential hypertension in some patients. For the patients suffering from post-traumatic stress disorder, stress is the dominant etiological factor that leads to the disease. It has been proven that chronic stress can affect blood pressure regulation and endocrine-metabolic functions through the limbic-hypothalamic centers; therefore, it can affect the arterial hypertension development. The strong association between stress and arterial hypertension has also been confirmed in preclinical and animal studies. For the pharmacotherapy approach, the most important are beta-adrenergic blockers, angiotensin-converting enzyme (ACE) inhibitors and AT1-receptor blockers (sartans). As a second line treatment, calcium channel blockers, diuretics, alpha-adrenergic blockers, and central antihypertensive agents may be required. The anxiolytics, such as benzodiazepines, should be considered if chronic anxiety and psychosomatic disorders are present.
Keywords: stress; arterial hypertension; therapy; anxiolytics

INTRODUCTION

Arterial hypertension (AH) represents the most common illness from the cardiovascular diseases (CVD) group, and, according to the latest data from the World Health Organization, 1.13 billion people worldwide are suffering from it, while every fourth male and every fifth female suffered from AH in 2015. In such context, AH as a contributing factor of CVD is the most massive chronic non-infectious disease of mankind nowadays [1]. AH can be primary and secondary; primary is far more common (approximately 80–95%) and the cause is unknown, while secondary occurs in about 5–20% of cases and occurs as a consequence of other illnesses [2].

AH represents the most common risk factor for CVD. A study from March 2021 concluded that even stage 1 hypertension defined by the American College of Cardiology and American Heart Association guidelines was independently associated with subclinical coronary atherosclerosis [3]. In the United States, considerably higher prevalence of AH has been noted in African Americans compared to other races. Thus, in a recent study conducted on a community-based cohort of African Americans, it was concluded that higher perceived stress over time is associated with an increased risk of developing hypertension [4].

Many organs participate in stress reactivity; however, the essential role is played by the hypothalamic-pituitary-adrenal (HPA) axis with corticosteroid secretion, as well as the neurovegetative system and the adrenal medulla with consequent secretion of catecholamines [2, 5].

ARTERIAL HYPERTENSION AND STRESS

Stress has been noted in SCORE system as one of the contributing factors to CVD risk in the European Society of Cardiology / European Society of Hypertension guidelines for 2018 (Table 1). Blood pressure (BP) represents a circulatory parameter, which is controlled by baroreceptors. When BP rises, it affects the baroreceptors, which are most densely distributed in the bulbus of the carotid artery and the aortic arch, and their main characteristic is that they are sensitive to stretching. Stretching caused by an increase in BP leads to transmission of information by baroreceptors along the vagal and glossopharyngeal pathways toward the solitary nucleus in the brainstem, which makes single and multiple neural connections to pre-autonomic source nuclei in the

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Table 1. Risk modifiers that increase cardiovascular risk estimated by the Systemic Coronary Risk Evaluation

Social deprivation, the source of many causes of cardiovascular diseases
Obesity (according to the body mass index) and central obesity (measured by waist circumference)
Physical inactivity
Psychosocial stress, including vital exhaustion
Family anamnesis of early cardiovascular disease (before the age of 55 in men and before the age of 60 in women)
Autoimmune and other inflammatory disorders
Major psychiatric disorders
HIV infection treatment
Atrial fibrillation
Left ventricular hypertrophy
Chronic kidney disease
Obstructive sleep apnea syndrome

brainstem and also to the forebrain. These structures have crucial role in regulating BP. Psychological stress has been shown to reliably reduce baroreflex sensitivity, specifically cardiovagal sensitivity [6].

Studies conducted on animal and human models have found that the network of cortical areas, limbic system and brainstem plays an important role in generating and regulating stress-provoked cardiovascular reactivity. It should be noted that from the pathophysiological aspect, stress-induced cardiovascular reactions are a consequence of changes in the sympathetic and parasympathetic nervous systems as well as in the HPA axis, which act on the heart and vasculature. Recent research has shown that higher levels of amygdala activity in rest predict the development of CVD over a period of 3.7 years. Increased amygdala activity is associated with changes in immune activity, and also with arterial inflammation and perceived stress, which provides evidence of potential pathways that support the development of CVD [7]. An animal model study published this year also confirms the link between stress and AH, with the very interesting conclusion that V1a and V1b receptors for vasopressin within the paraventricular nucleus contribute to hypertension in male rats exposed to chronic mild unpredictable stress [8].

The function of the HPA axis can be evaluated by measuring cortisol in the blood, saliva or urine. The recent data suggests the measurement of cortisol levels in the hair as a new biomarker of long-term HPA axis activity [9]. Some of the mechanisms that explain the development of cortisol-induced hypertension include its mineralocorticoid action in the form of sodium retention, then the expansion of plasma volume and inhibition of vasodilatory hormones [9]. There are several studies that have studied the ways in which stress can affect the epigenetic regulation of the HPA axis, so one of them states that DNA methylation of genes involved in the regulation of glucocorticoids is associated with AH and subclinical atherosclerosis [10]. Short sleep and discontinuous rest, which are often found in women with depression, disrupt balance of the sympathetic and parasympathetic nervous system and are associated with hypersecretion of cortisol, thus increasing heart rate and BP [11]. Furthermore, it is concluded that the intestinal microbiome disturbance, which can be a consequence of stress, is associated with AH, CVD, and metabolic diseases [12].

A study by Rao et al. [13] demonstrated that adrenergic polymorphism affects the human response to stress, and thus BP levels and catecholamine secretion are influenced by genetic variation of the adrenergic pathway encoding catecholamine synthesis, specifically a step that limits the rate of synthesis, which is the enzyme tyrosine hydroxylase, or a genetic polymorphism for the said enzyme. Arosio et al. [14] proved the existence of influence of mental stress on AH, but also the protective effect of AT1-receptor blockers on noradrenergic and adrenergic stress in hypertensive individuals.

The studies concerning stress and AH have been also conducted in animal models. Earlier publications have already established a cause-and-effect relationship between posttraumatic stress disorder (PTSD), where stress is the dominant etiological factor leading to the disease and AH. This was also confirmed in a recent study by Xue et al. [15].

PHARMACOLOGICAL ASPECTS

The specificity of stress-induced AH is that in addition to antihypertensive therapy, drugs that affect the patient's mental status, such as anxiolytics, may be recommended. There are non-pharmacological forms of treatment in the form of psychological support and psychotherapeutic techniques (relaxation techniques, stress management techniques, suggestion techniques, positive thinking and visualization techniques) [16]. For the pharmacological measures, there are several groups of antihypertensive drugs available. The most important ones, when treating stress-induced AH, are beta-adrenergic blockers, angiotensin-converting enzyme (ACE) inhibitors and AT1-receptor blockers (sartans). In case of resistant AH, calcium channel blockers, diuretics, alpha-adrenergic blockers, and central antihypertensive drugs may be required. Moreover, some studies recommend that patients with impaired autonomic activity and stress-induced AH be genetically profiled in relation to adrenergic pathways, and if a genetic risk is identified, it is considered that these patients would benefit from sympatholytic therapy [13]. The type of sympatholytic therapy most frequently mentioned in the literature recently is renal denervation. It is a minimally invasive therapeutic method based on catheter radiofrequency (although ultrasound or alcohol injection may be used) ablation of afferent and efferent renal sympathetic fibers, which is usually reserved for severe AH resistant to pharmacological treatment and AH with concomitant chronic renal failure, although it has recently been suggested to expand the indications to uncomplicated AH [17, 18, 19]. The first study that proves the reduced efferent renal sympathetic innervation after chemical renal denervation in humans, as well as the positive effects of this procedure on AH, was published in March 2021 [20].

Beta-adrenergic receptor blockers are not the first in line for antihypertensive therapy, due to the lower antihypertensive effect compared to some other antihypertensives,

because of the negative chronotropic effect on the myocardium, which is not desirable in all hypertensive patients, as well as due to the effect on beta2-adrenergic receptors in non-selective blockers, thereby reducing insulin secretion. However, for stress-induced AH, in addition to the antihypertensive effect, beta-blockers also have an effect on reducing tachycardia, which is almost always present in these patients. These drugs antagonize the action of catecholamines and partially lead to the patient's relaxation and stress reduction.

The effect of ACE inhibitors is reflected in arterial and venous dilatation, reduction of peripheral vascular resistance, increase in minute volume, effort tolerance, the excretion of sodium and water by the kidneys, preventing the proliferation of the smooth muscle cells, reduction of the left ventricular hypertrophy. They have an important role in AH therapy, but also in cases of stress-induced AH [15]. The indications spectrum of AT1-receptor blockers (sartans) is identical to ACE inhibitors. They are introduced into therapy in case of intolerance to ACE inhibitors; dry cough as a consequence of bradykinin action caused by the action of ACE inhibitors, or reduced ACE inhibitors efficiency in situations of elevated plasma renin. The justification of their use in stress-induced hypertension can be found in the conclusion of the study by Arosio et al. [14], where it has been shown that AT1-receptor blockers act protectively in noradrenergic and adrenergic stress in hypertensive patients.

Calcium channel blockers lead to smooth muscle arteries cells relaxation, vasodilation, reduction of peripheral vascular resistance, and lowering BP. However, these drugs are not the first in line when treating stress-induced hypertension. It is similar in regard to diuretics and alpha-blockers, which have no significant application in this case, except when dealing with resistant stress-induced AH.

The use of anxiolytics should be considered only in the case of chronic anxiety and psychosomatic disorders. There are studies that indicate a favorable impact of GABAergic systems' modulation in the treatment of anxiety with related CVD [21]. Benzodiazepines, as positive GABAergic modulators, are often prescribed with the internal medicine therapy and added to the treatment of chronic hypertension. Both quantitative and qualitative consumption data have confirmed this in practice [22]. The advantages of benzodiazepines are a relatively safe pharmacological profile and a low risk of serious side effects; however, they can produce tolerance and dependence after long-term treatment. The hypertension pharmacotherapy guidelines do not recommend routine use of benzodiazepines except when associated with psychiatric comorbidities. Especially in the older population, simultaneous use of benzodiazepines has been shown to increase the risk of limb fractures and injuries, as well as reduced cognitive abilities [23]. Some recent experimental studies have indicated that certain benzodiazepines, like midazolam and diazepam, can be considered. It has been shown that midazolam induces arterial blood vessels vasodilation, most likely by voltage-gated calcium channel modulation, while diazepam exerts its effect by alpha-1 receptor modulation [24, 25]. However, their efficacy has neither been confirmed by meta-analyses nor by long-term follow-up studies.

CONCLUSION

Nowadays, AH represents the most widespread, non-infectious disease of mankind. Chronic stress represents an increasingly common etiological cofactor, while in some situations it is the main cause of AH. Thus, it is necessary to consider and evaluate the presence of stress in the modern treatment. The decision which pharmacological agents shall be introduced into therapy depends on comorbidity, other CVD risk factors, and the patient's age. There is a need to primarily introduce beta-adrenergic blockers, ACE inhibitors, or sartans for the stress-induced AH, while the use of anxiolytics should only be considered if chronic anxiety and psychosomatic disorders are present.

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Стрес и артеријска хипертензија – од патофизиологије до фармакологије

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САЖЕТАК

Артеријска хипертензија је данас најмасовнија хронична незаразна болест човечанства. Може остати недијагностикована годинама, што изазива касније компликације, попут акутне срчане инсуфицијенције, можданог удара, инфаркта миокарда, бубрежне инсуфицијенције, хипертензивне ретинопатије или изненадне смрти. Примарна артеријска хипертензија је чешћа, док се секундарна јавља у око 5–20% случајева. Недавна истраживања су показала да стрес код неких пацијената може бити кључни фактор у развоју есенцијалне хипертензије. Код пацијената који пате од посттрауматског стресног поремећаја, стрес је доминантни етиолошки фактор који доводи до болести. Доказано је да хронични стрес може да утиче на регулацију крвног притиска, ендокрине и метаболичке функције путем лимбичко-хипоталамичких центара и самим тим да утиче на развој артеријске хипертензије. Снажна повезаност стреса и артеријске хипертензије потврђена је у претклиничким студијама и испитивањима на животињама. За фармакотерапијски приступ најважнији су бета-адренергички блокатори, инхибитори ензима који конвертује ангиотензин и блокатори рецептора *AT*1 (сартани). Као друга линија терапије могу се користити блокатори калцијумових канала, диуретици, алфа-адренергички блокатори и централни антихипертензиви. Увођење анксиолитика, попут бензодиазепина, треба размотрити у случају хроничне анксиозности и психосоматског поремећаја.

Кључне речи: стрес; артеријска хипертензија; терапија; анксиолитици