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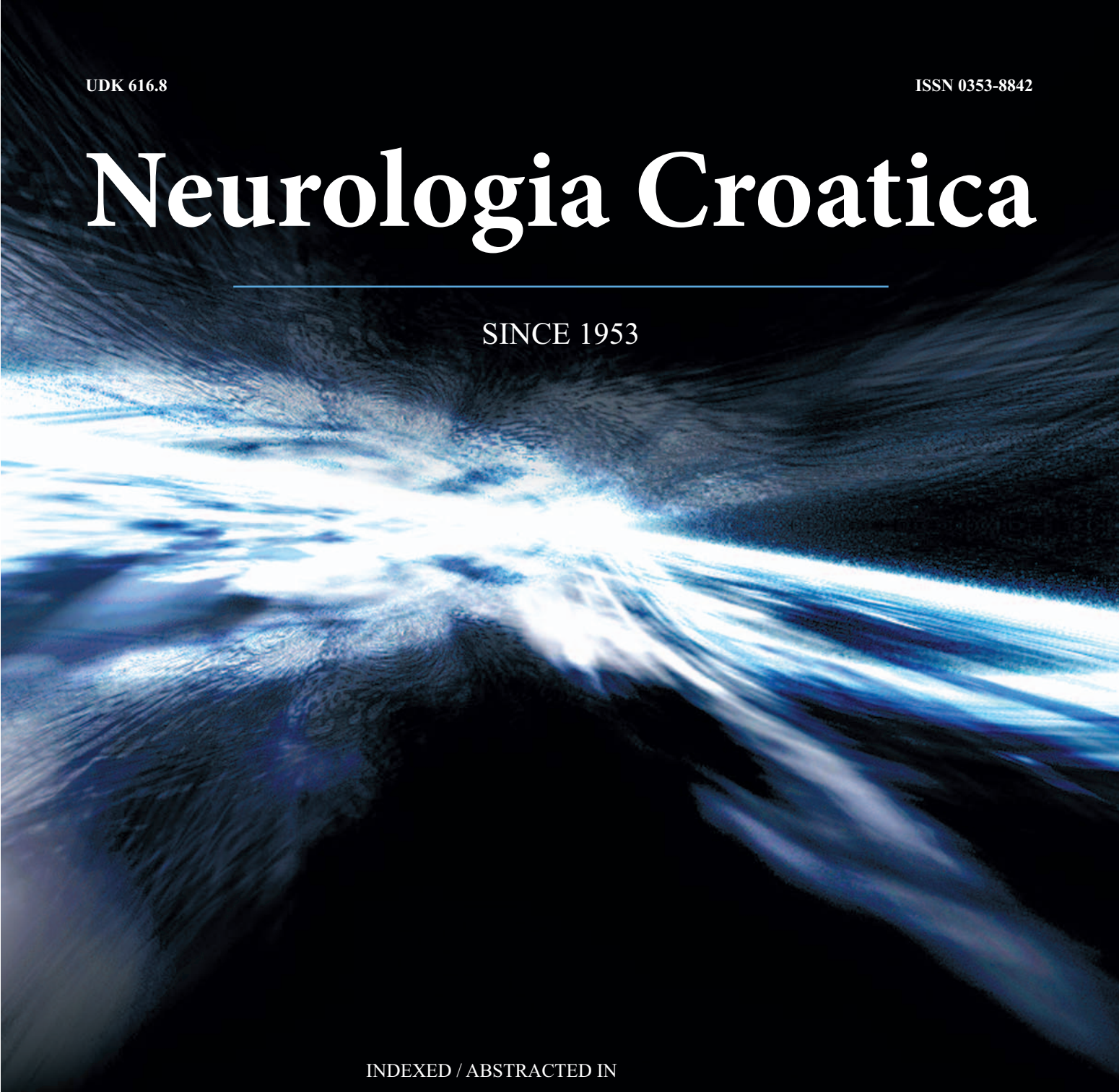

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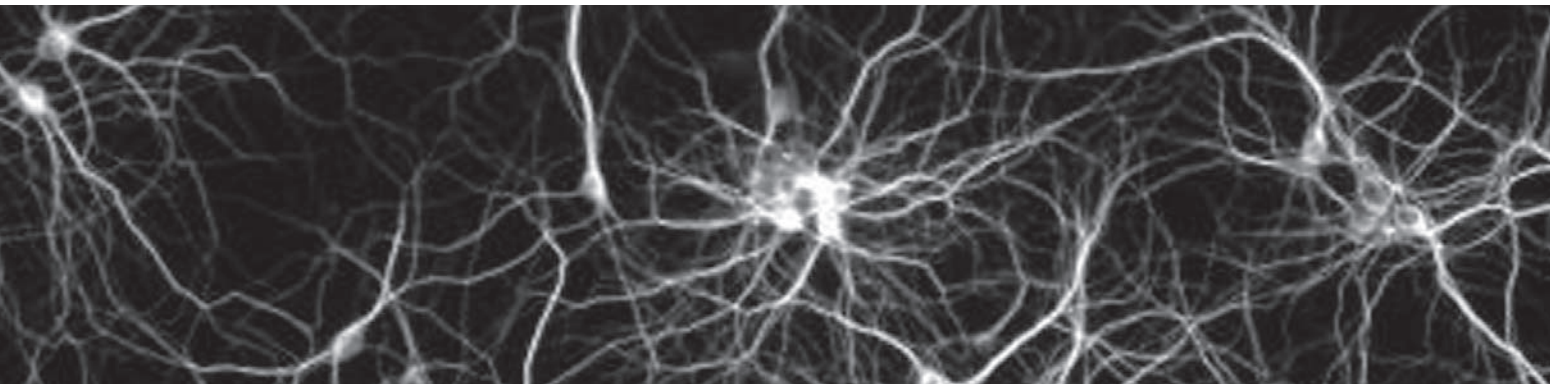

Basic algorithm for management of patients with aneurysmal subarachnoid hemorrhage

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ABSTRACT - Aneurysmal subarachnoid hemorrhage (aSAH) is one of the most urgent clinical conditions among neurologic diseases. If untreated, the disease has high mortality and morbidity, and the outcome depends mostly on optimal diagnostic and treatment procedure. Currently, no national guidelines for the management of aSAH have been published or accepted in Croatia. Therefore, treating procedures depend on individual estimation, knowledge and experience, as well as on technical facilities available at different medical institutions. On the other hand, by accepting a uniform approach in the management of aSAH, according to the specific conditions in Croatian medical institutions, reaching optimal outcome for each patient will be accomplished. The aim of this algorithm is to define the basic characteristics of the disease, its epidemiologic data as well as its clinical picture, and to present appropriate diagnostic algorithm in accordance with specific facilities of different medical institutions. Furthermore, this algorithm will consider optimal management of a patient with verified aSAH in prehospital and hospital conditions, and finally in a Comprehensive Stroke Center. In addition, it will focus on the endovascular management of ruptured aneurysms and on the complications of subarachnoid hemorrhage. This algorithm is based on the already published international guidelines for aSAH management as well as on own experience in treating ruptured aneurysms and subarachnoid hemorrhage at the Referral Center for Intensive Neurology of the Croatian Ministry of Health during a five-year period (2007-2012, altogether 515 patients). The level of evidence of these guidelines is, according to the classification, Level A, grade I to Level C, grade IIb.

Key words: acute subarachnoid hemorrhage, ruptured aneurysm, comprehensive stroke center, endovascular treatment

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INTRODUCTION

Aneurysmal subarachnoid hemorrhage (aSAH) is one of the most urgent clinical conditions among neurologic diseases. It is an acute cerebrovascular event with direct consequences on brain tissue and numerous medical complications (1). Complex multiorgan pathophysiology of aSAH includes injury of the cardiovascular, respiratory and renal systems, which leads to various clinical manifestations and worsens the outcome. Therefore, aSAH medical care does not include only neurointerventional program, but also implies a multidisciplinary approach (2).

Analysis of aneurysm genesis is not the issue of this algorithm; however, considering the risk of hemorrhage and possible prevention of hemorrhage, as well as timely diagnosis and treatment of aSAH, the following should be emphasized:

a) aSAH occurs more often in persons with some genetic predisposition (history of previous SAH or aneurysms, or SAH in family history) or in some special syndromes like Ehlers-Danlos syndrome type IV or autosomal dominant polycystic kidney disease (1);

b) the condition occurs more often in women, persons with low body mass index (BMI), smokers, patients with hypertension, and those with increased consumption of alcohol and cocaine (1);

c) proven aneurysm of more than 5 mm in diameter has a higher risk of rupture, especially if associated with some of the above mentioned risk factors (1); and

d) aneurysms of anterior circulation rupture more often in patients younger than 55 years, and aneurysms of posterior circulation rupture more often in men (1).

The condition complexity demands multidisciplinary approach not only during diagnostic procedure, but especially considering therapeutic approaches when equal engagement of neurocritical care specialists (neurologists, neuroanesthesiologists, vascular neurosurgeons and interventional neuroradiologists) is required.

Fast and precise diagnostic workup and urgent treatment of the aneurysm, followed by timely prevention and management of the complications are critical points of care in patients with aSAH (2).

As it is still impossible to organize the best management at all levels of medical care, optimal approach to aSAH patients, according to the international guidelines, includes the following:

1. high quality network of prehospital and hospital emergency care of patients with aSAH;
2. well organized urgent transportation of patients with aSAH to high-volume centers; and
3. further treatment in high-volume centers which should be reachable within maximum of 6-8 hours from every part of the country.

According to definition, a "high-volume" center for aSAH should be a hospital with more than 60 treated aSAH patients *per* year (2). Recent data on the outcome of treatment in such centers report mortality reduced by about 20% and morbidity by about 30% compared with hospitals that treat less than 20 aSAH patients *per* year (2). Such results justify the costs of primary care in primary medical centers and transportation of the patient to a high-volume center. Transportation of the patient who has been appropriately cared for is considered less risky for outcome than to continue treating such a patient in a center without the possibility of multidisciplinary approach.

EPIDEMIOLOGY

The incidence of aSAH varies among different regions of the world, probably due to different genetic factors (1,2). On the other hand, the influence of the environment and life habits should be less important. According to the World Health Organization, differences in the annual incidence of aSAH vary by more than ten times in different parts of the world (1). In China, for example, the annual incidence is 2/100 000 inhabitants, while in Finland or Japan the incidence is 22.5/100 000. The average incidence in Europe is 10-12 patients *per* 100 000 inhabitants. Women have a 1.24-fold higher incidence recorded for men of the same age (1).

In spite of the modern diagnosis and treatment, aSAH is still an illness with a high mortality. In the first 5 months, it is up to 40% (1,3). Approximately 10%-15% of patients die before reaching the hospital. In hospitalized patients, mortality in the first week is up to 25% and nearly one-third of patients (and according to some statistical data, even up to 50%) have a permanent neurologic deficit of different grade. The mortality and morbidity rates do not depend on population differences in the incidence (1,3).

Epidemiological data for Croatia are not known completely. According to available data, in the last 5 years, the incidence of aSAH in Croatia is about 10 patients *per* 100 000 inhabitants, which means

that in Croatia we have about 450 patients *per* year. According to statistical data on prehospital mortality, 400 patients *per* year reach hospitals in Croatia. In our Referral Center for Intensive Neurology, also including Department of Neurosurgery, we treat 140-150 patients *per* year, which makes more than one-third of all Croatian patients with aSAH.

According to our data, 30-day mortality is 27% and morbidity 41%. In the group of patients with permanent neurologic disability, 68% of patients have minor neurologic deficit, 24% have mild neurologic deficit, and 8% have severe neurologic deficit and are entirely dependent. In the last 5 years, having introduced the multidisciplinary treatment approach, we have reduced mortality of our aSAH patients from 39% to 27% and morbidity from 47% to 41%.

This significant reduction of mortality is the result of the following:

1. lower number of re-ruptured aneurysms, which is due to systemic endovascular approach (having the possibility of treating patients even in poor condition in the acute phase of the illness);
2. shortening the time window from diagnosis of aSAH, diagnosis of aneurysm and treating the aneurysm. We treat most of the aneurysms within 12 hours of patient admission; one-third of the patients are treated within 24 hours, and just 15% of patients are treated after 24 hours of admission; and
3. modern neurocritical intensive care unit managing patients according to recent guidelines.

Decrease in morbidity is the result of neurocritical care treatment using multimodal neuromonitoring approach in the unit.

COMPREHENSIVE STROKE CENTERS

Comprehensive stroke centers (CSC) are highly specialized multidisciplinary hospital units having neurointensive care beds and equipment, as well as all facilities and organization of intensive care units (2,3).

CSC provides care for patients with severe strokes, patients with complications of any type of stroke that require further intervention, patients with intracerebral hemorrhage (of vascular origin), and patients requiring specific methods of treatment (endovascular treatment, neurosurgical care). Experts working in CSC are neurovascular (sub)specialists forming stroke team. Stroke team usually includes intensive neurologists, neuroanesthesiologists, interventional neuroradiologists, and vascular neurosurgeons. All members of the stroke team must be accessible 24 hours/7days, and if needed consultation of other specialists (like neuroinfectologist, cardiologist, ENT specialist, vascular surgeon or neuropathologist) must be ensured.

Furthermore, in CSC all neuroimaging (computerized tomography (CT), magnetic resonance (MR), digital subtraction angiography (DSA)) must be available 24 hours/7days. CSC must also fulfill the high-volume hospital criteria for all types of stroke (1,2,4).

In Referral Center for Intensive Neurology of the Croatian Ministry of Health, a CSC fulfilling the above-mentioned criteria has been formed. It is, for now, the only CSC in Croatia, which also fulfils the high-volume center criteria and has multidisciplinary approach for stroke patients. For now, this is the only center in Croatia with such references. Other university hospitals in Croatia are able to take care of patients with aSAH up to the level of adequate and complete diagnostic procedures (CT, CT angiography, DSA, MR, MR angiography), but cannot provide complete therapeutic approach (lacking endovascular methods, adequate (in technical and organizational terms) neurocritical care units) and do not have characteristics of a high-volume center.

These data are important considering our national diagnostic and therapeutic guidelines, and have to be considered while making decision about transporting patients for further diagnostic and especially therapeutic methods.

RECOMMENDATIONS

Basic facts

1. Aneurysmal subarachnoid hemorrhage is medical emergency that requires multidisciplinary (intensive neurologists, neuroanesthesiologists, interventional neuroradiologists and vascular neurosurgeons) approach during diagnostic procedure and especially during therapeutic procedure (1-3).
2. Special attention during diagnostic procedure should be paid to patients with a clinical picture of aSAH and additional risk factors for this illness (like personal or family medical history of

aSAH, patients with genetic risk factors, women, hypertensive patients, alcohol or cocaine abusers, patients with low BMI, patients with verified intracranial aneurysm) (1).

3. Primary care of a patient with aSAH should be organized, according to guidelines, in every medical center that is, after relevant diagnostic procedure, able to establish the diagnosis of SAH.

4. Final care of a patient with aSAH should be organized in a specialized high-volume (with more than 60 SAH patients *per* year) center, which has the possibility of multidisciplinary approach for 24 hours/7days (2-4).

5. The outcome of patients treated in CSC justifies the risks as well as the cost of transportation to CSC (2,4).

6. In spite of the established approach in the diagnosis and treatment of aSAH, mortality and morbidity are still high (mortality in hospitalized patients is up to 25% during the first 30 days and morbidity is up to 50% during 6-month follow up) (1-3).

7. Such a high mortality rate is due to re-rupture of the aneurysm as the first cause. The highest risk of re-rupture is during the first 24 hours after first rupture; aSAH is therefore an emergency requiring urgent diagnostic evaluation and urgent treatment (closing of the aneurysm) within the first 24 hours of illness, if possible (1,2).

8. High morbidity rate is the result of various neurologic and/or organic complications. The management of patients in Neurological Intensive Care Units and by multimodal neuromonitoring significantly reduces the mortality and morbidity (1,2).

Diagnostic algorithm in aSAH

1. More than 10% of aSAHs are misdiagnosed on initial exams. Every patient with sudden intensive headache must raise suspicion of SAH, especially if, beside headache, the patient had a sudden loss of consciousness, even without any other symptom, or focal neurologic deficit (1).

2. Every patient who has probable SAH must be referred to a medical facility with the possibility of appropriate diagnostic workup. Urgent diagnostic workup includes brain CT, and if CT is inconclusive, analysis of cerebrospinal fluid obtained by lumbar puncture (1).

3. Proven SAH requires urgent (within 24-hour time window, if possible) examination of intracranial blood vessels with one of the appropriate methods (CT angiography or DSA). If at least one of these methods is not available, the patient has to be transported to a hospital where diagnostic procedure can be completed and where appropriate treatment can be provided. Transportation has to be as urgent as possible, but after stabilization of the patient.

4. In perimesencephalic SAH, CT angiography can be sufficient for definitive diagnosis. However, even then, follow up angiography in delayed (between day 14 and day 28 after SAH) phase of the illness is recommended (at least repeated CT angiography, yet DSA is preferred) (1,2).

5. In diffuse SAH and/or SAH with initial loss of consciousness, even after a negative finding of CTA or DSA, a follow up angiographic (DSA) examination in delayed phase of the illness is recommended (1).

Primary management of the patient diagnosed with aSAH

1. Clinical assessment of a patient with aSAH is crucial for determination of further management. For clinical assessment, implementation of international scales is recommended. Such assessment enables precise presentation of clinical status of the patient, helps making decisions on therapy approach and can even help in final outcome prognosis. Considering the complexity of the illness, the best assessment is achieved by using a combination of three traditional scales: Hunt-Hess (HH) scale, Fisher's scale and Glasgow Coma Scale (GCS). Initial medical documentation of the patient must, beside other data, also include the above mentioned clinical assessment by using all three scales (5).

2. In patients with aSAH, clinical status should be assessed continuously, and obligatorily if changes in neurologic status are noticed, or after medicamentous therapy with influence on neurologic status. It should be presented in Hunt-Hess scale and GCS. The most recent available grade of Fisher's scale should be documented as well. These data are very often crucial for further management decisions for the patient (1,3,5).

3. If further diagnostic procedure (CTA or DSA) can (within 24 hours) be performed in the first-contact hospital, it is reasonable to do it. If it is

not possible, the patient should be transported to the hospital where it can be done. However, it is reasonable to transport the patient to the facility where both diagnostic and therapeutic measures can be done, in order to avoid additional transportation (3,6).

4. Therapeutic measurements of aSAH consist of excluding the aneurysm from the circulation by one of the possible methods (neurosurgical or endovascular treatment) during acute phase (up to 72 hours of the initial bleeding) of the illness. The patient should undergo necessary examinations before therapeutic procedure, and should be managed in the neurointensive care unit after the procedure. Postoperative care should be especially focused on the early detection of complications (1,2,6).

5. Patients who are estimated as first group according to the severity of their clinical state (HH I and II, Fisher 1, 2, 3 and GCS 11-15), are hemodynamically stable, require only analgesics and proper venous access during primary care. These patients are candidates for urgent (within the first 24 hours) treatment (neurosurgical or endovascular approach) in a hospital where it can be organized. If optimal treatment is not possible in the hospital of primary care, such a patient should be transported to the appropriate facility as soon as possible. During this time, continuous clinical assessment according to the guidelines, is obligatory (1-3,5).

6. Patients who are estimated as second group according to the severity of their clinical state (HH III, Fisher 2, 3 and GCS 8-10) are often hemodynamically unstable and require more extensive primary care. They are also candidates for urgent treatment, but in this group endovascular treatment is preferred. Extensive anesthesiologic care implies airway management (including intubation with rapid sedation induction if needed) as well as hemodynamic stabilization and antiedematous therapy (in patients with signs of raised intracranial pressure). In this group, continuous clinical assessment according to the guidelines is crucial. Unnecessary sedation should be avoided, as well as hyperventilation (pCO_2 should be about 30-35 mm Hg). Adequate analgesic measures are obligatory. These patients should be treated within the first 24 hours. If optimal treatment is not possible in the hospital of primary care, such a patient should be transported to the appropriate facility as soon as possible (1-3,5).

7. Patients who are estimated as third group according to the severity of their illness (HH IV and V, Fisher 2, 3, 4 and GCS 3-7) are clinically unstable patients and further therapeutic decisions are made individually. Patients in this group should be hemodynamically stabilized, which includes intubation and analgosedation. In this group, further clinical deterioration is highly probable. Most of them have signs of raised intracranial pressure and need antiedematous treatment. They must be managed in intensive care units, with the possibilities of continuous multimodal neuromonitoring and in hospitals that have continuous neurosurgical service. Also, in these patients continuous clinical assessment is often impossible due to therapeutic measures, and the first clinical assessment is critical for further therapeutic decisions (1-3,5).

8. Hemodynamically stable patients in the third group can also, in some cases, be candidates for urgent treatment if there was no deterioration in their clinical status within the first 8 hours. If so, these patients should only be treated endovascularly, which is important while choosing the hospital, if transportation from the initial facility is necessary.

9. Hemodynamically unstable patients, patients who have deteriorated within the first few hours after bleeding, or patients who are initially in group III without achieving stabilization, are not candidates for immediate treatment. They should be treated in the delayed phase of the illness. Until then, medical care should be provided in the nearest appropriate intensive care unit.

10. In patients who are candidates for urgent treatment, but for some reasons treatment is not possible within the first 24 hours, measures for preventing re-rupture are indicated. Such specific measures include analgesic therapy, mild analgosedation according to clinical indication, control of hemodynamic parameters, especially blood pressure (BP) (systolic BP should not be over 160 mm Hg to diminish the risk of re rupture, but still not too low to maintain cerebral perfusion; values should be about 150/90 +/- 10 mm Hg), and antifibrinolytic therapy (1,2).

Therapeutic approach in the hospital of ultimate management

1. Hospital of ultimate management should be able to:

a. offer at least one of the possible methods of treating aneurysms. Treatment should be available continuously (24h/7d);

b. offer continuous availability of diagnostic methods which are essential for treatment and appropriate follow up procedures;

c. offer appropriate intensive care unit, with optimal equipment and experts in neurovascular field, and with at least minimal level of essential multimodal neuromonitoring; and

d. offer multidisciplinary approach for individual assessment of optimal method for each patient with aSAH (1-3).

2. In hospitals where both methods of treatment are available, endovascular treatment can have some advantages compared with neurosurgical method (1). Endovascular method is also the first choice treatment in patients with worse clinical status, patients with aneurysms that are morphologically not acceptable for neurosurgery, and for aneurysms that are located in posterior circulation (1).

3. Neurosurgical treatment is preferred in patients with large intracerebral hematomas (>50 mL), patients with middle cerebral artery aneurysm, or patients with aneurysms that are morphologically not acceptable for endovascular approach (1).

4. Treatment options should be assessed by multidisciplinary stroke team in high-volume centers. In hospitals without stroke team, assessment should be made by a neurologist and neurosurgeon according to the guidelines. For patients in which, due to some specific clinical conditions, actual guidelines are not applicable, transportation to the hospital with multidisciplinary stroke team, or to the CSC is advisable (4).

5. No matter which therapeutic approach is chosen, after treating the aneurysm, follow up diagnostic procedure should be performed by one of the angiographic methods in order to estimate the efficacy of the treatment. If aneurysmal growth, recanalization or some residual flow is observed, it is necessary to repeat the treatment and to exclude the aneurysm from the circulation entirely (1).

6. In the hospital where patients with aSAH are definitely managed (CSC), patients should be treated in intensive care units (ICU), preferably in neurointensive care units (NICU). In such units, an adequate level of neurointensive care is established with experts in neurocritical care field, which are organized by continuous principle (24 hours/7 days/year) and which have minimal necessary level of multimodal continuous neuromonitoring (2,4,7).

Special features of monitoring of patients before and after endovascular treatment of intracranial ruptured aneurysm

1. Diagnostic algorithm for these groups of patients is not significantly different from the usual diagnostic workup of patients with aSAH. In patients in whom initial treatment refers to the posterior circulation aneurysms or patients who due to the previously mentioned reasons are primary candidates for endovascular treatment, the preferred noninvasive diagnostics is MSCT angiography, since DSA has to be done anyway in the first phase of endovascular procedure.

2. Special workup of the patients before endovascular approach includes the usual laboratory tests (complete hematology, biochemistry, blood type, including PT, APTT, fibrinogen), x-ray of the heart and lungs, 12-lead ECG, and preoperative examination by neuroanesthesiologist. Before the procedure, the patient must be hemodynamically stable, with corrected metabolic and electrolyte parameters, if necessary analgosedated with correctly managed airway (6,8).

3. The most common form of complication of endovascular approach is thrombosis of the treated vessel and consecutive ischemic damage to the brain parenchyma. The prevention and treatment of thrombotic complications are therefore antithrombotics (9).

4. Monitoring of clinical status in patients who, before surgery, were in the first group: waking up after anesthesia should occur no later than within 60 minutes of the operation, after which further sedation/mechanical ventilation is usually not necessary. Measures of adequate analgesia with hemodynamic monitoring, especially blood pressure monitoring should be applied (continuous noninvasive or manual measurement every 15 minutes in the first 2 hours, then every half an hour in the next 4 hours, then every hour for the next 12 hours, then every 2 hours up to 24 hours. Invasive blood pressure measurement is indicated only for patients with highly unstable and variable pressures. Blood pressure should be maintained within the values of 140-160/80-95 mm Hg). Clinical neurological assessment

should be performed every hour for the first 6 hours after surgery, then every 6 hours until 48 hours after the procedure. If clinical follow up reveals neurologic deterioration within the first 24 hours, urgent neuroradiological diagnostic workup should be done.

5. Monitoring of clinical status in patients who, before surgery, were in the second group: waking up after anesthesia should occur no later than within 60 minutes after the procedure, however, the need of prolonged intubation and mechanical ventilation is individually assessed. Excessive sedation should be avoided because of the impossibility of appropriate monitoring of neurologic status, which is the basic parameter to estimate the possible complications or worsening of the patient's condition. Analgesia is allowed and required. Other hemodynamic monitoring and neurological follow up workup is carried out as in the first group.

6. Monitoring of clinical status in patients who, before surgery, were in the third group: analgosedation is continued, as well as continuous hemodynamic monitoring for a minimum of 48 hours, after which cessation of sedation should be assessed individually. No later than 24 hours after the procedure, and in case of noticed oscillations in hemodynamic parameters despite controlled conditions, neuroradiological diagnostic workup should be implemented.

7. Monitoring of complete laboratory tests is carried out after 24 hours of the operation. Monitoring of electrolytes and essential metabolic parameters is performed 4-6 hours after the procedure, or if there is any suspicion of the development of complications (prolonged awakening, changes in neurologic status, changes in heart rate, oxygen saturation, respiration, or vegetative instability) immediately, and then according to clinical indication. APTT should be controlled immediately after the procedure and then for 4-6 hours, and if necessary, repeated according to clinical indication.

8. Neurological assessment is performed normally 24-48 hours after surgery in patients with no signs of complications. It is recommended to do MSCT of the brain, which gives enough information about the intracranial status in these patients. Earlier CT (within the first 24 hours) is generally not indicated, due to the high probability of contrast artifacts occurrence.

9. If procedural complications occur within the first 24 hours after the procedure regardless of whether they are verified by clinical examination, hemodynamic monitoring (extreme fluctuations in blood pressure, respiratory failure or arrest, electrocardiographic disorders, vegetative dysfunction), or specific neurological monitoring (TCD, EEG, ICP), urgent MRI, MRA should be performed. Sometimes it may be necessary to perform control DSA and additional endovascular or neurosurgical intervention as well. In patients with a high risk of thrombotic incidents, or already observed thrombotic complications during the procedure, DSA should be performed after the first 24 hours. If necessary, additional endovascular treatment should follow. In patients with prolonged awakening (more than 2 hours after the procedure despite adequate hydration and perfusion), even if there are no other listed signs of deterioration, and if the cause of this condition cannot be connected with the applied therapy or significant disturbance of laboratory parameters, urgent follow up workup is indicated. Preferably, it should be MRI.

Further follow up of patients with aSAH and workup of aSAH complications

1. Patients with acute subarachnoid hemorrhage regardless of the severity of their illness and their current clinical status must finally be managed in the ICU, where the minimum of multimodal neuromonitoring is enabled (2,7).

2. Hemodynamic monitoring and basic laboratory parameters should be performed even during primary management of the patient. In the hospital where patients are ultimately managed, patients with aSAH must be put on invasive monitoring by clinical indication, not routinely. Central venous catheter inserted solely for the purpose of routine measurement of central venous pressure, routine measurement of intracranial pressure, pulmonary artery catheters or invasive measurement of blood pressure are not justified in this group of patients. Therapeutic measures in primary care settings include adequate rehydration (it is recommended to maintain euvolemia, preferably with isotonic crystalloid solutions, and to measure input/output of fluids), control and correction of laboratory parameters, control and correction of blood pressure, nimodipine (Nimotop) at a dose of 60 mg every 4 hours, or 5-10 mL/h/24h IV (2,7).

a) The extent and frequency of continuous monitoring in the first two weeks of disease depend on the clinical stage of the disease:

A) Patients classified in group I (HH I and II):

a) continuous neurologic monitoring (monitoring of neurologic status)
b) traditional measures of continuous hemodynamic monitoring
c) TCD monitoring of vasospasm (daily from the third to the twelfth day, and by clinical indication)
d) CT of the brain – not later than 24 hours after the procedure, later according to indication or at least once in 7 days
e) laboratory diagnosis – at patient admission, all routine laboratory parameters, further monitoring requires basic laboratory parameters (bedside device) on daily basis during the first 14 days, or follow up of abnormal laboratory values according to indication
f) MRI/DSA according to indication
g) continuous EEG according to indication, or if epileptic seizures are observed at any stage of the disease, for at least 48 hours after the seizure

B) Patients classified in group II (HH III or higher stage of Fisher scale)

a) continuous neurologic monitoring (monitoring of neurologic status)
b) traditional measures of continuous hemodynamic monitoring
c) TCD monitoring of vasospasm (daily until the condition stabilizes)
d) CT of the brain – not later than 24 hours after the procedure, later according to indication, at least once every 72 hours during the first 10 days of illness
e) laboratory diagnosis tic – at patient admission, all routine laboratory parameters, further monitoring requires basic laboratory parameters (bedside device) on daily basis during the first 14 days, or follow up of abnormal laboratory values according to indication
f) invasive methods of continuous monitoring according to indication
g) continuous EEG monitoring during the first ten days of illness
h) MRI/DSA according to indication

C) Patients classified in group III (HH IV, V HH)

a) continuous neurologic monitoring (monitoring of neurologic status) – in this group of patients less reliable
b) traditional measures of continuous hemodynamic monitoring
c) TCD monitoring of vasospasm (daily until the condition stabilizes)
d) CT of the brain – not later than 24 hours after the procedure, later according to indication, at least once every 72 hours during the first 10 days of illness
e) laboratory diagnosis – at patient admission, all routine laboratory parameters, further monitoring requires basic laboratory parameters (bedside device) on daily basis during the first 14 days, or follow up of abnormal laboratory values according to indication
f) continuous EEG monitoring during the first ten days of illness or until patient stabilizes
g) invasive methods of multimodal neuromonitoring
h) measuring brain metabolic parameters according to indication
i) MRI/DSA according to indication

3. The most important complications of aSAH are re-rupture of the aneurysm, vasospasm, hydrocephalus, electrolyte disbalance, epileptic seizures, and cardiopulmonary complications (2).

4. Re-rupture occurs more frequently in patients with severe neurologic deficits, initial loss of consciousness, "sentinel" headache, larger aneurysms, and higher or unstable blood pressure (systolic blood pressure higher than 160 mm Hg). The most effective prevention of re-rupture is early treatment of the aneurysm. If the treatment is, for some reason, delayed, it is necessary to provide emergency care for patients in ideal hemodynamic conditions and using continuous monitoring. Application of antifibrinolytic therapy (aminocaproic acid) during a maximum of 72 hours is recommended in the group of patients with a high risk of re-rupture. It is very important to maintain hemodynamic stability and stabilization of blood pressure from the recommended upper limit of up to 160/90 mm Hg. Also, during this period prevention of deep venous thrombosis is recommended, but solely by mechanical methods, or using elastic stockings (2-4).

5. Vasospasm usually develops on the third day after initial bleeding and is mostly pronounced between day 7 and day 10 after aSAH. Later it gradually regresses, and usually completely disappears after day 21 of the disease. The most se-

rious consequence of vasospasm is the development of delayed neurologic deficits due to ischemic lesions of the brain. Diagnosis of vasospasm is based on the assessment of the clinical picture, permanent monitoring of cerebral perfusion parameters (measurement of intracranial pressure or monitoring of vasospasm by transcranial ultrasound), and on neuroimaging methods (MSCT perfusion, MSCT angiography, DSA).

Treatment of vasospasm includes:

a) nimodipine

b) triple-H treatment

c) intra-arterial medical vasodilatation

d) balloon-angioplasty

e) statins (1,2).

6. Acute hydrocephalus develops in 15%-85% of patients with aSAH, and approximately half of these patients require continuous drainage. It is significantly more common in patients with intraventricular hemorrhage or rupture of the aneurysm of the posterior circulation. In both groups, more intensive monitoring of intracranial pressure or the volume of ventricles by neuroimaging methods is necessary. If hydrocephalus develops, external ventricular drainage should be a treatment option (1,2).

7. The most common form of electrolyte imbalance in acute aSAH is impairment of serum sodium concentration. When it drops to values lower than 135 mmol/L, correction or substitution therapy should be applied.
Hypomagnesemia is also common in aSAH. Magnesium substitution therapy should be given, however, hypermagnesemia is not justified. In hypothalamic dysfunction, the administration of minerals or corticosteroids is required (1,2,7).

8. Epileptic seizures occur in approximately one-quarter of patients with SAH. Preventive use of antiepileptic therapy is not indicated. Patients who are at a higher risk of developing epilepsy are patients with middle cerebral artery aneurysm, intracerebral hematoma, re-rupture, patients after surgically treated aneurysms, patients with a greater amount of blood in the subarachnoid space, patients who developed ischemia, patients with poor initial neurologic status and with a history of hypertension. In all patients with aSAH and especially in patients who are at an increased risk, continuous EEG monitoring for at least first 72 hours from the onset of aSAH is required (1,2,7).

9. About 35% of patients present with elevated troponin levels and cardiac arrhythmias. Pulmonary edema is the cause of death in about 12% of patients with aSAH, while pulmonary complications in general (usually cardiogenic or neurogenic edema or acute respiratory distress syndrome) are found in nearly 20% of patients. Because of this, continuous monitoring is essential, while treatment of these complications does not differ from common treatment of such illnesses.

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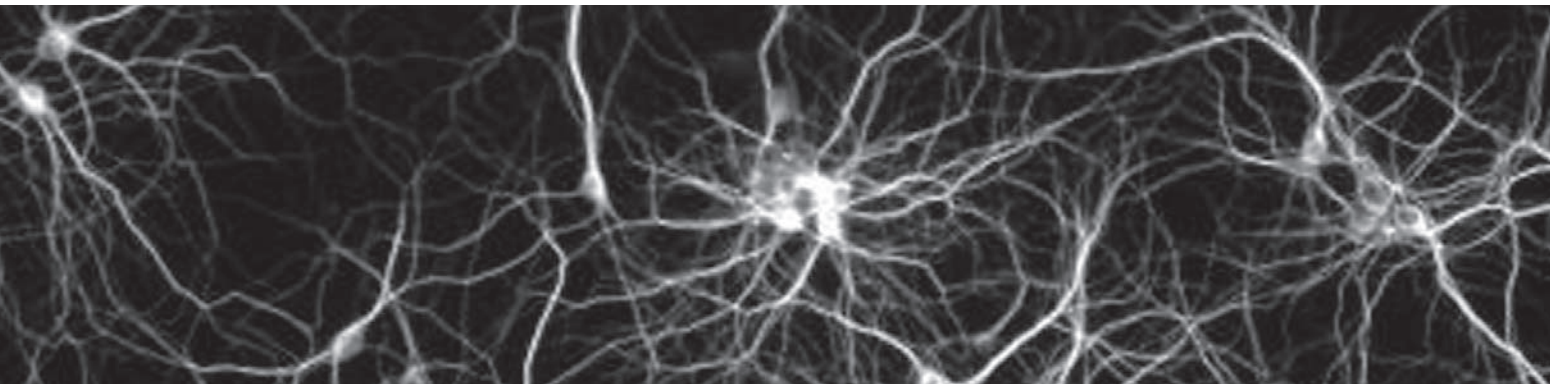
Temeljni algoritam zbrinjavanja bolesnika s akutnim subarahnoidnim krvarenjem

SAŽETAK - Subarahnoidno krvarenje nastalo kao posljedica prsnuća intrakranijske aneurizme (aSAK) jedno je od najhitnijih stanja u neurologiji. Neliječena bolest ima visoku smrtnost i pobol, a konačni ishod najviše ovisi o pravodobnom i primjerenom dijagnostičkom i terapijskom postupku. U Republici Hrvatskoj (RH) nije u dosadašnjoj kliničkoj praksi prihvaćen niti objavljen jedinstven pristup zbrinjavanju bolesnika s aSAK-om te liječenje uvelike ovisi o individualnoj procjeni pojedinog liječnika te tehničkoj opremljenosti pojedine medicinske ustanove. S druge strane, usvajanjem zajedničkog pristupa zbrinjavanju bolesnika s aSAK-om, a poštujući specifičnosti ustanova, moguće je osigurati optimalan način liječenja za svakog bolesnika. Cilj ovih Smjernica jest definirati osnovne značajke bolesti, objaviti osnovne epidemiološke podatke za aSAK, prikazati kliničku sliku i primjeren dijagnostički algoritam ovisno o specifičnim mogućnostima pojedine ustanove u RH, prikazati optimalan medicinski pristup bolesniku s verificiranom dijagnozom aSAK-a u izvanbolničkim i bolničkim uvjetima u RH, prikazati optimalan terapijski postupnik u kliničkim centrima RH, kao i u specijaliziranom centru za liječenje moždanog udara (*Comprehensive Stroke Center*) s posebnim osvrtom na postupnik pripreme i praćenja bolesnika liječenih endovaskularnim pristupom te prikazati najčešće komplikacije subarahnoidnog krvarenja i postupnik njihovog zbrinjavanja. Gore navedene Smjernice izrađene su temeljem objavljenih podataka iz svjetske literature i podataka o liječenim bolesnicima s aSAK-om Referentnog centra za intenzivnu neurologiju Ministarstva zdravlja RH u razdoblju od 2007. do 2012. godine (ukupno 515 bolesnika). Snaga dokaza ovih Smjernica je prema klasifikaciji preporuka od razine A, stupnja I. do razine C, stupnja IIb.

Ključne riječi: akutno subarahnoidno krvarenje, ruptura aneurizme, specijalizirani centar za liječenje moždanog udara, endovaskularno liječenje



Postural orthostatic tachycardia syndrome

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ABSTRACT - Orthostatic intolerance can be defined as inability to tolerate upright posture relieved by recumbence. Postural orthostatic tachycardia syndrome (POTS) is a form of orthostatic intolerance defined as sustained increase in heart rate of ≥30 bpm or increase of heart rate to ≥120 bpm within 10 min of standing or head-up tilt associated with symptoms of orthostatic intolerance and absence of orthostatic hypotension. POTS patients are mostly female with 4-5:1 ratio and age range from 15 to 50. Several pathophysiological mechanisms are thought to underlie POTS. Some of the possible mechanisms are distal peripheral neuropathy, abnormalities of central control of sympathetic nervous system, impaired synaptic norepinephrine reuptake, renin-angiotensin-aldosterone axis disturbance and altered norepinephrine synthetic pathway. The most common symptoms related to POTS are light-headedness, presyncope, weakness and palpitations. Exacerbation of symptoms with standing and symptoms relieved with recumbence is a characteristic feature of POTS. Active stand test and passive head-up tilt table test are used in diagnosing POTS, along with detailed history and examination. Nonpharmacological therapy of POTS includes increase in daily salt and water intake, and exercise training. Pharmacological therapy is directed at expanding fluid volume, increasing peripheral vascular resistance and reducing central sympathetic activity. The majority of patients experience substantial improvement after correct diagnosis and appropriate therapy.

Key words: orthostatic intolerance, postural orthostatic tachycardia syndrome (POTS), pathophysiology, neuropathic POTS, hyperadrenergic POTS, diagnosis, therapy

INTRODUCTION

Orthostatic intolerance (OI) can be defined as inability to tolerate upright posture relieved by recumbence. Patients with OI experience characteristic symptoms and signs during orthostasis. These include loss of consciousness, visual difficulties, lightheadedness-dizziness, headache, fatigue, orthostatic hypotension and sometimes hypertension, weakness, nausea and abdominal pain, sweating, tremulousness (1). Depending on the level of sympathetic activity, patients with OI can be classi-

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fied into two types. One type comprises patients with diminished sympathetic activity who develop hypotension during standing. This is acute in those with vasovagal syncope and chronic in patients with central or peripheral neurodegenerative diseases. The second type patients have increased sympathetic activity, without development of hypotension and with notable tachycardia as a response to orthostasis. The latter is referred to as postural orthostatic tachycardia syndrome (2).

The postural orthostatic tachycardia syndrome (POTS) is a form of orthostatic intolerance defined as a sustained heart rate (HR) increment of ≥30 bpm (3-5), or increase of heart rate to ≥120 bpm within 10 min of standing or head-up tilt associated with symptoms of orthostatic intolerance and absence of orthostatic hypotension. For individuals aged 12-19 years, the required increment is at least 40 bpm (3). Diehl proposes a surrogate criterion for diagnosing POTS in patients with typical symptoms but not fulfilling the HR increment of ≥30 bpm or HR ≥120 criterion as HR increase between minutes 5 and 10 of more than 8 bpm during head-up tilt test (6).

The aim of this review is to investigate and summarize the latest literature on POTS.

EPIDEMIOLOGY

POTS patients are mostly female with 4-5:1 ratio and age range from 15 to 50 (4), but with relatively few patients over the age of 40 (7). This demographics may be due to the effect of female sex hormones on adrenergic receptor sensitivity and norepinephrine (NE) metabolism (8,9). The true prevalence is not known, but is likely to be higher than 170 cases *per* 100,000 (10).

PATHOPHYSIOLOGY

Normal physiology of standing

Within a few seconds of assuming upright from previously supine position, 300-800 mL of blood is gravitated downwards from the thorax into the abdomen and lower limbs, thus decreasing venous return to the right side of the heart causing reduction in stroke volume and cardiac output. These changes are then registered by arterial baroreceptors and cardiopulmonary mechanoreceptors leading to activation of compensatory reflexes – increased sympathetic and reduced parasympathetic nervous system output with final outcomes of peripheral arterial vasoconstriction and reduced vagal tone to the heart with cardio-acceleration (4). Normal subjects react with 5 to 15 bpm increase in heart rate, systolic blood pressure remains stable and diastolic blood pressure rises slightly (about 5-10 mm Hg) (4,6). It is important to note that this reaction is swift and occurs within the first minute of assuming the upright position in normal subjects (6).

Several underlying mechanisms are thought to be involved in the pathophysiology of POTS.

Neuropathic

Some studies link POTS with partial dysautonomia, which predominantly affects lower limbs. Evidence supporting this hypothesis will be mentioned hereafter. Jacob *et al*. examined sympathetic nervous system function by measuring norepinephrine-spillover in response to three stimuli: cold pressor test, nitroprusside and tyramine infusion (11). These stimuli increased norepinephrine-spillover to similar extent in arms of normal subjects and POTS patients, but failed to increase it in the legs of POTS patients. One study showed that arterial vasoconstriction, which is normal response to orthostasis, is impaired in POTS patients (12). This finding is consistent with defective norepinephrine secretion (11,12). In an animal model of neuropathic POTS, partial dysautonomia in rats was achieved by selectively lesioning peripheral postganglionic sympathetic neurons using neurotoxin 6-hydroxydopamine hydrobromide (6-OHDA) resulting in significant heart rate increase (13). Vascular α1-sensitivity examined with selective agonist phenylephrine was also increased after administration of 6-OHDA. The latter finding is consistent with the early work of Streeten in which he describes hypersensitivity of foot veins to NE infusion typical of denervation (14). Distal sudomotor abnormalities can be found in approximately half of patients with POTS (7,15), although this finding does not appear to correlate with symptom measurements (15).

Taking these findings into account, it can be concluded that the neuropathic form of POTS is caused by distal peripheral neuropathy resulting in inadequate vascular response to orthostatic stress. This leads to excessive venous blood pooling and increased capillary filtration in lower extremities causing functional decline in circulatory volume, which results in a compensatory increase in HR and myocardial contractility (6). It has been esti-

mated that neuropathic POTS is the most common form of POTS (16,17).

Hyperadrenergic

The hyperadrenergic form of POTS is less frequent, accounting for about 10% of POTS patients. Patients with this form of POTS often display orthostatic hypertension, significantly elevated serum norepinephrine (>600 pg/mL or >3.5 nmol/L) on standing or exaggerated response to intravenous isoproterenol. This group of patients appear to have abnormalities of central control of sympathetic nervous system or defective norepinephrine uptake resulting in excess systemic NE spillover (4,16-18). Some studies reported abnormally low concentration of plasma dihydroxyphenylglycol (DHPG), intraneural NE metabolite, in relation to NE concentration, providing evidence of impaired NE uptake (19-21). In some patients, hyperadrenergic response may be a compensatory reaction to hypovolemia or peripheral neuropathy with venous pooling (4).

Genetic

Norepinephrine transporter (NET) is a presynaptic transporter responsible for the clearance of approximately 70% of synaptic NE (19). Heart is more sensitive to impairments in NE reuptake because cardiac sympathetic nerves recapture at least 80% of released NE (22). Point mutation of gene encoding NET resulting in 98% loss of function has been recorded in one POTS patient (21). Two studies showed reduced NET protein expression in POTS patients (20,22). In the work by Schroeder *et al*., POTS-like phenotype was achieved in healthy subjects by administering 8 mg of reboxetine, a selective NET blocker (23). Impaired NE clearance in the synaptic cleft may result in excess NE spillover and consequent elevated NE plasma levels. The relation between impairment of NE reuptake and POTS symptoms is unknown (20,22), except for tachycardia, which might be explained by failure of clearance of NE from cardiac sympathetic nerve synaptic spaces (22).

Renin-angiotensin-aldosterone system and blood volume perturbation

The renin-angiotensin-aldosterone system (RAAS) plays a vital role in blood volume control. In response to hypovolemia, juxtaglomerular cells secrete renin, which then enzymatically acts on its substrate, angiotensinogen, and produces angiotensin I (Ang I). Ang I is then converted to angiotensin II (Ang II) *via* systemic or locally produced angiotensin-converting enzyme (ACE). Ang II promotes sodium and water retention, both directly by stimulating sodium reabsorption in the proximal tubule and indirectly by stimulating aldosterone secretion. Mineralocorticoid aldosterone regulates sodium transport at several sites in the kidney, thus controlling water retention with the effect on plasma volume (24-26). Ang II is further degraded to Ang-(1-7) by angiotensin converting enzyme (ACE2). ACE2 also converts Ang I to Ang-(1-9), which is thereafter converted to Ang-(1-7). Binding of Ang-(1-7) to Ang-(1-7) receptors induces vasodilatation (27). Ang II has various other effects besides those already mentioned. Ang II is involved in a control loop as negative feedback to renin production (26). Ang II can increase central sympathetic outflow by binding to AT-1 receptors (angiotensin II Type I receptor) in the circumventricular organs of the brain (25). It can also increase the release of NE from ganglionic and postganglionic sympathetic nerves (25,26), and inhibit NE reuptake in the nerve terminals with consequential effect on vasoconstriction (26). It also has direct vasoconstrictive action by binding to AT-1 receptors on smooth muscle cells. Ang II has been shown to decrease bioavailable nitric oxide (NO) (26). Essentially, Ang II is a potent vasoconstrictor and important regulator of plasma volume.

Some POTS patients exhibit low blood volume and inappropriately low plasma renin activity (PRA) and aldosterone concentration (22,24-26), a state sometimes referred to as 'renin-aldosterone paradox' (24). In the work by Raj *et al*., patients with POTS had a mean plasma volume deficit of almost 350 mL (24). At least two studies have reported positive correlation between PRA and blood volume in POTS patients with low blood volume, when negative correlation would be expected (26,29). Several studies have reported POTS patients with increased level of plasma Ang II (25,26,28). Mustafa *et al*. report on blunted systemic vasopressor, but not renal vascular or adrenal secretionary response to Ang II infusion in patients with POTS (28). This study also reports on POTS patients to have blunted baseline spontaneous baroreflex sensitivity (BRS), which showed significant negative correlation to baseline levels of plasma Ang II. Mustafa *et al*. hypothesize that high levels of Ang II could be explained by decreased ACE2 activity (28). This hypothesis is reinforced with findings of another study in which targeted disruption of ACE2 in mice resulted in increased

Ang II levels (30). The work by Stewart *et al*. provides evidence for the latter hypothesis, but they also hypothesize that defective ACE2 resulting in decreased levels of Ang-(1-7) might contribute to excessive vasoconstriction found in some POTS patients (26,27). This subgroup of POTS patients are referred to as low-flow POTS patients (27).

These data suggest that defects in RAAS may play an important role in the pathophysiology of POTS, particularly in a subset of POTS patients with low blood volume and increased level of Ang II.

Altered norepinephrine synthetic pathway

NE is synthesized *via* tyrosine hydroxylation to dihydroxyphenylalanine (DOPA), DOPA decarboxylation to dopamine (DA). DA is then converted to NE through dopamine beta hydroxylase (DBH) action. Garland *et al*. measured DOPA and DA in POTS patients for the first time and found a significantly increased level of DA, along with reduction in supine DOPA (19). The authors hypothesize that a higher NE/DOPA ratio in combination with a higher plasma DA may be consistent with activation of either DOPA decarboxylase or DBH in POTS patients. This could explain high plasma NE in some POTS patients.

The "Grinch syndrome"

In the study by Fu *et al*., 27 POTS patients were submitted to autonomic function test, cardiac magnetic resonance imaging (MRI), and 19 patients completed 3-month exercise training program (31). The following results were obtained: blood and plasma volume were markedly reduced in patients, left ventricular mass in POTS patients was much smaller compared to healthy sedentary controls, patients had smaller cardiac output and stroke volume in both supine and upright postures, as well as greater peripheral resistance than controls. In 19 patients who completed 3-month training program, the peak oxygen uptake, blood volume and plasma volume increased significantly. Ten out of 19 patients no longer met POTS criteria after training. Orthostatic tachycardia observed in these patients appeared to be a physiological compensatory response to the smaller stroke volume, which was attributable to cardiac atrophy and reduced blood volume. These results suggest that POTS may be a consequence of "deconditioning" (i.e. cardiac atrophy and hypovolemia), and that carefully prescribed exercise training can be used as a non-drug treatment for patients with POTS. The authors propose a new term for POTS, the "Grinch syndrome" after the main character in Dr. Seuss's book *How the Grinch Stole Christmas*, who had a heart that was "two sizes too small", emphasizing that a small heart is the primary abnormality and target for therapy.

It is likely that the pathophysiological mechanisms mentioned here are intertwined and that POTS is a result of their combination.

CLINICAL MANIFESTATIONS

About half of patients with the neuropathic form of POTS experience acute or subacute onset of symptoms, often preceded by viral illness. It is presently felt that neuropathic POTS is of autoimmune nature in many cases, which is supported by the presence of acetylcholine receptor ganglionic (G-AchR) antibodies in 15%-25% of POTS patients (7,16,32). Some patients report that their symptoms begin after pregnancy, surgery, sepsis or trauma (10, 16,17). On the other hand, patients with the hyperadrenergic form of POTS often describe a more gradual and progressive appearance of symptoms over time rather than abrupt onset (17,21). One case report attributes the onset of reversible POTS to inadvertent overuse of Red Bull® (33). POTS may be secondary to a variety of conditions that produce a state of peripheral autonomic deinnervation or vascular unresponsiveness with relative sparing of cardiac innervation. A frequent cause of secondary POTS is chronic diabetes mellitus. Other possible causes are amyloidosis, sarcoidosis, alcoholism, lupus, Sjögren syndrome, chemotherapy and heavy metal poisoning. POTS can be a form of paraneoplastic syndrome that can be seen with adenocarcinomas of the lung, breast, ovary and pancreas (17).

Symptoms associated with POTS are numerous. Thieben *et al*. performed a retrospective study involving 152 POTS patients (7). Clinical features documented in this study will be listed hereafter. Symptoms presumably related to cerebral hypoperfusion: light-headedness, 77.6%, presyncope, 60.5%, and weakness, 50.0%. Symptoms presumed to be associated with autonomic overactivity: palpitations, 75.0%; tremulousness, 37.5%; shortness of breath, 27.6%; and chest wall pain, 24.3%. Sudomotor symptoms: loss of sweating, 5.3%; and hyperhidrosis, 9.2%. Several of the chronic symptoms reported may reflect dysautonomia: gastrointestinal complaints, including bloating, 23.7%; nausea, 38.8%; vomiting, 8.6%; abdominal pain, 15.1%;

constipation, 15.1%; diarrhea, 17.8%; bladder dysfunction, 9.2%; and pupillary dysfunction, 3.3%. Generalized complaints: 48.0% experienced fatigue, 31.6% experienced pronounced sleep disturbance, 27.6% had migraine headache, and 15.8% had myofascial pain. Kanjawal *et al*. retrospectively analyzed 27 patients with hyperadrenergic POTS, with the following results: 55%-65% of patients reported symptoms of hyperadrenergic state in the form of anxiety, tremulousness and excessive sweating; orthostatic palpitation was reported by 13 (48.2%) and syncope by 11 (40.7%) patients (16). About 30% of POTS patients have neurally mediated syncope (34).

Symptoms get worse with standing and are relieved with recumbence (34). Aggravating factors include heat or exercise (53.3%), postprandial symptoms (23.7%), and worsening at time of menses (14.5%) (7). The intensity of symptoms is variable. Some patients are severely affected and are unable to work, attend school or participate in recreational activities resulting in substantial morbidity (31).

The principal clinical sign of POTS is abnormal tachycardia on assumption of upright posture. The second frequent sign is acrocyanosis, which can extend from the feet to above the level of knees, with the occurrence of 40%-50% during standing (34). Other signs are rare and include pupillary dysfunction and symptoms consistent with peripheral neuropathy (4).

ASSOCIATED AND OVERLAPPING CONDITIONS

Chronic fatigue syndrome/myalgic encephalomyelitis

Overlapping between clinical manifestations of POTS and chronic fatigue syndrome (CFS), also known as myalgic encephalomyelitis, has been documented in the literature (7,11,35,36). The prevalence of POTS in CFS patients has ranged from 19% to 70%, while studies in cohorts of patients selected for POTS have shown a prevalence of chronic fatigue to range between 48% and 77%, and of CFS between 17% and 23% (11,35,36). In the work by Okamoto *et al*., out of 47 POTS patients enrolled in the study, 30 (64%) fulfilled the criteria for CFS (36). This study also compared groups of POTS patients with and without CFS and found that most common symptoms were unrefreshing sleep, impaired memory or concentration, and muscle pain (36).

Multiple sclerosis

Multiple sclerosis (MS) and POTS share some similar features. Typical age group is between 20 and 50 years, and women are more often affected in both conditions. Common symptoms include orthostatic intolerance, fatigue and anxiety (37). In one prospective study, out of 112 patients diagnosed with relapsing remitting MS, 21 (18.8%) of them met the criteria for POTS; 17 of those patients were in relapse (38). Another study conducted on a large sample of patients, divided into a group of 112 MS patients and a group of 181 patients with symptoms of OI, showed that POTS was more frequent in MS patients in comparison with patients with symptoms of OI with no neurologic illnesses (37). Connection between MS and POTS is explained by the presence of demyelinating brainstem and hemispheral lesions, which disrupt the physiological heart rate variability modulation (39).

Inappropriate sinus tachycardia

Inappropriate sinus tachycardia (IST) is a form of arrhythmia, which is characterized by an exaggerated increase in heart rate that is disproportionate to normal physiologic demands. IST shares some similarities with POTS. Patients with IST are also more often women, presenting symptoms are palpitations, fatigue, exercise intolerance and dizziness (4). IST can be triggered by orthostasis and minimal exertion (40), and exaggerated response to isoproterenol infusion can also be seen in IST (17). Although sometimes it can be challenging to differentiate between POTS and IST, there are some distinguishing features that can help make the correct diagnosis. POTS patients tend to display a more pronounced degree of postural change in HR than those with IST, and supine HR in POTS patients rarely exceeds 100 bpm, which is a common finding in patients with IST (4,17).

Other

Migraine is found in about 42% of POTS patients (7). Joint hypermobility, irritable bowel syndrome, inflammatory bowel disease, mitral valve prolapse, and hypertension are frequently mentioned as comorbidities associated with POTS (4,16,18,34). POTS patients are sometimes diagnosed with anxiety disorders, but that might be due to misinterpretation of their physical symptoms. Patients with POTS often have diminished attention and concentration (34).

DIAGNOSTIC EVALUATION

First, comprehensive history should be obtained and detailed examination should be performed with focus on previously described signs and symptoms. As mentioned before, a cardinal criterion in diagnosing POTS is HR increase of ≥30 bpm or increase of heart rate to ≥120 bpm within 10 min of standing or head-up tilt associated with symptoms of OI and absence of orthostatic hypotension. Two tests can be used to assess patient reaction to postural change. Passive head-up tilt table (HUT) test (Fig. 1) is the standard method, which consists of two phases. In the first phase, the patient is placed on a tilt table for 5-20 min and then supine HR and blood pressure (BP) are monitored. In the second phase, the patient is tilted to 60°-80° and HR and BP are measured periodically or continuously for 10-60 min (4,5,18,39,41). The test should be performed in a quiet, dimly lit, temperature-controlled environment (4). The time spent in supine or tilted

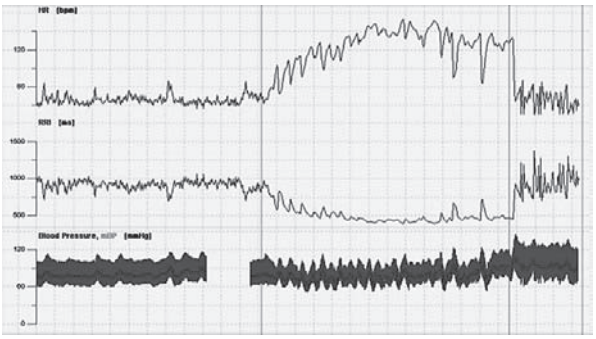

Fig. 1. *An example of head-up tilt test in a patient with POTS: upper line shows continuous heart rate monitoring, lower line shows continuous blood pressure monitoring. Note the increase of heart rate after the tilt (first vertical red line) >30 beats/minute, without fall in blood pressure.*

position depends on the protocol used. Another test is active stand test, which is considered to mimic real life. The patient is asked to assume upright position following the time spent in supine position. Whilst the patient is standing unassisted, HR and BP are measured periodically (4,5,34,41). Plash *et al*. (41) compared HUT to standing test in diagnosing POTS. In this study, 10-min standing was the most accurate test, when using the ≥30 bpm HR increment criterion. Results obtained in this study suggest that 10-min tilt test is highly sensitive (93%), but has poor specificity (40%), when using the ≥30 bpm HR increment criterion. Plash *et al*. suggest that by increasing the HR criterion to 37 bpm the test becomes much more specific (73%), while maintaining good sensitivity (80%). POTS is not diagnosed based solely on hemodynamic criteria. Clinical diagnosis of POTS requires history of orthostatic symptoms lasting for ≥6 months, worsening of symptoms with standing and relief with recumbence, absence of other causes of orthostatic symptoms or tachycardia (e.g., active bleeding, acute dehydration, medications) in addition to hemodynamic criteria. To differentiate the hyperadrenergic from neuropathic type of POTS, supine and standing serum NE levels should be obtained. A high standing NE (>600 pg/mL or or >3.5 nmol/L) identifies patients with hyperadrenergic POTS and predicts their response to β-blockade (7,17).

MANAGEMENT

It is important to educate the patient about the nature of her/his disorder. Aggravating factors, such as heat or dehydration, should be avoided. Consumption of alcohol should be discouraged (18). Patients should be taught three simple measures beneficial in improving OI. The first measure are physical countermaneuvers. Patients contract muscles below the waist for about 30 seconds, which results in reduced venous capacity and increased peripheral resistance. The second measure, which is especially helpful in patients who are hypovolemic, is wearing an abdominal binder. This reduces splanchnic-mesenteric venous capacity. The third measure is water bolus therapy, which consists of drinking two 8-ounce (≈2 dL) glasses of water consecutively inducing sympathetically-mediated pressor response (42,43).

Nonpharmacotherapy

Every POTS patient should be encouraged to begin a gradual program of physical reconditioning, with a goal of performing 20 to 30 min of aerobic activity 3 times a week (4,17). In one study, 10 of 19 POTS patients that completed 3-month exercise training program no longer met the criteria for POTS (31). This and one other study recorded increase in blood and plasma volume in patients who finished 3-month training program (44). Winker *et al*. demonstrated that training can result in shift from sympathetic to vagal predominance, which might be beneficial for patients with OI (44). Many patients with POTS are hypovolemic. These patients should increase salt intake to up to 10-20 g *per* day and take 2-2.5 L of fluids *per* day (4,34,42).

Acute blood volume expansion by applying 1 liter of physiological saline intravenously is highly effective in controlling HR and acutely improving POTS symptoms, but the treatment is not practical on a day to day basis (4,34).

Pharmacological

When nonpharmacological measures alone do not prove efficient, drugs are needed (10). The main goal of medications should be stabilization of the condition enough to enable POTS patients to undergo exercise training program (17). Patients with the neuropathic type of POTS are best treated with a combination of fludrocortisone and α-agonist midodrine (42). Daily dose of fludrocortisone should not exceed 300 μg to avoid adverse effects. Initial dose of midodrine should be 2.5 mg, three times a day before meals and can be increased if needed to a maximum recommended daily dose of 30 mg (10). Some patients have better response when midodrine is combined with the acetycholinesterase inhibitor pyridostigmine, at a dose of 60 mg 3 t.i.d. (42). Pyridostigmine appears to be most effective in patients with postviral onset of POTS (17). In patients who are unresponsive to abovementioned therapy, selective serotonine reuptake inhibitor (SSRI) or norepinephrine reuptake inhibitor can be added. Octreotide administered by subcutaneous injection beginning at 50 μg 2-3 times daily is an additional therapy for refractory patients (17). Octreotide can be beneficial in patients with marked postprandial symptoms (10). Patients with hyperadrenergic form of POTS often respond best to agents that block norepinephrine or its effects (17). Dual-acting β-blocker, such as carvedilol or labetalol, may be more effective than a pure β-blocker (e.g., propranolol). Recommended dosage for carvedilol and labetalol is 3.125-6.25 mg p.o. twice daily and 100-200 mg p.o. twice daily, respectively (18). Central sympatholytic medications, such as clonidine, are often used in patients with hyperadrenergic POTS. Clonidine, an alpha 2 agonist, is administered orally or in the patch form 0.1-0.3 mg twice daily (10,17,34). Ivabradine, a sinus node blocker, is beneficial in some POTS patients. According to one retrospective case series, ivabradine appears to control symptoms associated with POTS with effectiveness similar to that of conventional treatment (45).

According to Thieben *et al*., most commonly prescribed medications are β-blockers (76.7%), followed by SSRI (51.7%), fludrocortisone (39.5%) and midodrine (31.6%) (7).

PROGNOSIS

Younger patients and those with postviral onset of POTS have better prognosis. Over one-half of those with postviral onset make reasonable recovery over 2-5 years and are able to perform activities of everyday life with minimal restriction. Approximately 90% of patients will respond to a combination of physical and pharmacological therapy, but patients with hyperadrenergic POTS will likely require therapy indefinitely. The majority of patients experience substantial improvement after correct diagnosis and appropriate therapy (17,46,47).

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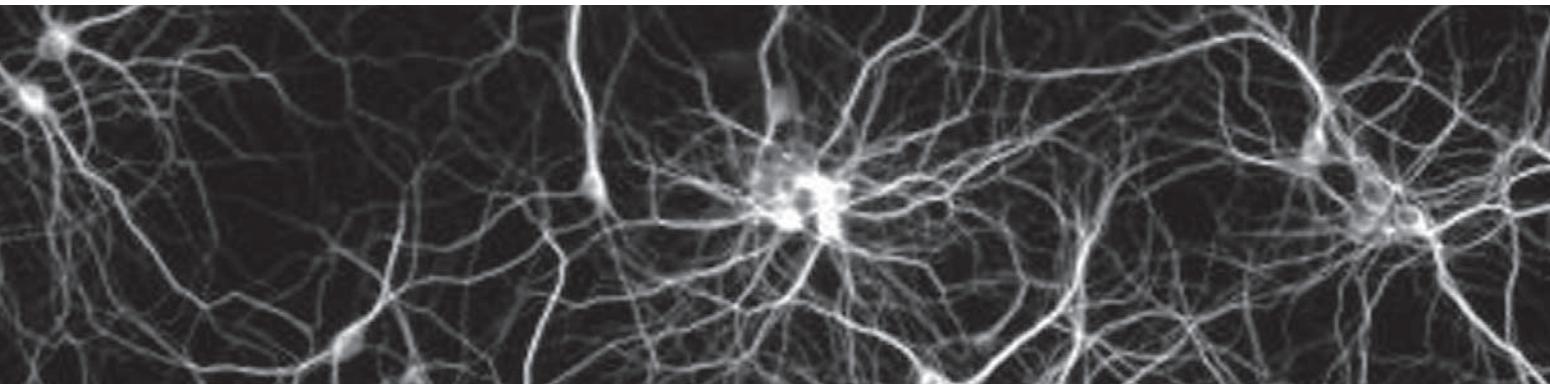
Sindrom posturalne ortostatske tahikardije

SAŽETAK - Ortostatska intolerancija se može opisati kao nemogućnost podnošenja uspravnog stava uz olakšanje simptoma nakon zauzimanja ležećeg položaja. Sindrom posturalne ortostatske tahikardije (POTS) je oblik ortostatske intoleracije definiran kao kontinuirani porast srčane frekvencije za ≥30 otkucaja u minuti ili kao porast frekvencije na vrijednost od ≥120 otkucaja u minuti unutar 10 minuta od početka stajanja ili *head-up tilt* testa uz pojavu simptoma ortostatske intolerancije uz odsutnost ortostatske hipotenzije. Bolesnici s dijagnosticiranim POTS-om su uglavnom žene, s omjerom od 4-5:1, u dobi između 15 i 50 godina. Nekoliko patofizioloških mehanizama bi moglo biti uključeno u razvoj POTS-a. Neki od njih su: distalna periferna neuropatija, poremećaji centralne kontrole simpatičkog živčanog sustava, oštećenje sinaptičkih mehanizama ponovnog unosa noradrenalina, poremećaji osovine renin-angiotenzin-aldosteron, promjene u sintetičkom putu norepinefrina. Najčešći simptomi povezani s POTS-om su omaglice, presinkopa, slabost i palpitacije. Pogoršanje simptoma sa stajanjem i olakšanje nakon zauzimanja ležećeg položaja je karakteristično obilježje POTS-a. Pri postavljanju dijagnoze koriste se aktivni test stajanja i pasivni *head-up tilt* test, zajedno s detaljnom povijesti bolesti i kliničkim pregledom. Nefarmakoterapijski pristup liječenju POTS-a podrazumijeva povećan unos soli i vode i program vježbanja. Farmakoterapija je usmjerena prema povećanju volumena tekućine, povećanju periferne vakularne rezistencije i smanjenju centralne aktivnosti simpatičkog živčanog sustava. Velik broj bolesnika iskusi značajno poboljšanje nakon točno postavljene dijagnoze i pravilnog liječenja.

Ključne riječi: ortostatska intolerancija, sindrom posturalne ortostatske tahikardije (POTS), patofiziologija, neuropatski POTS, hiperadrenergički POTS, dijagnostika, terapija



Concurrence of multiple sclerosis and vascular malformation of the brainstem: case report

L. Radolović Prenc, S. Telarović[1,2], I. Vidović, J. Sepčić[3]

ABSTRACT - Multiple sclerosis (MS) is a demyelinating disease of the central nervous system. In most of cases, the disease follows a relapsing-remitting pattern. Vascular malformations are described in differential diagnosis of MS because of the similarity of clinical presentation, especially when hemodynamic changes resemble the relapsing-remitting course of MS. Advances in diagnostic procedures, particularly magnetic resonance imaging (MRI) of neural axis and cerebral angiography have facilitated differential diagnosis between these two entities. However, simultaneous occurrence of asymptomatic vascular malformations and MS is rare. We present a case report of a patient with these two entities, i.e. MS diagnosed on the basis of clinical findings, supporting evidence from laboratory tests and MRI, and basilar artery aneurysm.

Key words: multiple sclerosis, aneurysm, basilar artery

INTRODUCTION

Multiple sclerosis (MS) is an immune-mediated inflammatory disease that attacks myelinated axons in the central nervous system (CNS), which occurs mostly in young adults. In most cases, the disease follows a relapsing-remitting pattern. As first presentation prominent are sensory loss (40%) and eye symptoms (35%), less motor strength (21%), spinal cord symptoms (16%) and cerebellar symptoms (15%) (1). In some patients, neurologic deficit does not resolve completely and they enter the progressive phase of the disease (secondary progression). A minority of patients experience steadily progressive neurologic deterioration (primary progressive MS). On diagnosing MS, most important are clinical findings, symptomatic episodes "separated in time and space", but other courses of similar clinical findings must be exclud-

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ed (2). Differential diagnosis includes other diseases having relapsing-remitting course in young adults. It could even be expansive processes of the central nervous system (CNS), especially arteriovenous malformations (AVM), angiomas, but also meningeomas, gliomas of the brainstem, etc. (3,4). Sometimes, tumors have a relapsing-remitting course, similar to MS, but accurate diagnosis is made by magnetic resonance imaging (MRI) of neural axis. MS may not be recognized in the initial years, despite obviousness. MRI is the diagnostic procedure of choice for diagnosing MS. There is no laboratory or imaging test pathognomonic for MS (5). Diagnosis of MS or less common diseases includes series of diagnostic procedures (6,7). MS, however, can occur simultaneously with other diseases. Coexistence of MS and intracranial vascular malformation (VM) is very rarely described in the literature.

CASE REPORT

A 29-year-old woman presented with vision disturbance characterized as optic neuritis. Symptoms were preceded by smallpox vaccination one month before. Eighteen months later, in spring, there were signs of pyramidal and brainstem lesion, with vestibular disturbances. In the autumn of the same year, she had a relapse in the form of motor weakness of lower extremities together with bulbar symptomatology, upper limb paresthesias, cerebellar manifestation, and optic nerve atrophy. A year later, she experienced a relapse again, followed by marked spastic paraparesis. Other exacerbations occurred at the age of 35, 45 and 50 years. Clinical presentation was predominated by spastic paraparesis, ataxia, dysarthria and sensory disturbances.

Considering that symptoms were "separated in time and space", we performed additional procedures. Serology for *Toxoplasma gondii* and *Borrelia burgdorferi* was negative, while vitamin B12 and folate findings were normal. HLA phenotype was A2, B5, B40, DR1, DR3, DQ1, DQ2. Anti-tissue antibodies, hepatitis markers, HIV and Wright's reaction were negative. Plasma cells in the cerebrospinal fluid (CSF) were reported. CSF analysis confirmed the presence of oligoclonal bands. Color Doppler and transcranial color Doppler revealed high circulatory resistance at the irrigation of basilar artery and right vertebral artery.

In relapses, the patient was treated with corticosteroid therapy, which led to remission.

Three years after the last exacerbation, at the age of 53, right sided peripheral facial palsy and impairment of bulbar movements were evident. MRI of the CNS indicated demyelinating lesions characteristic for MS (Fig. 1). According to clinical presentation and color Doppler findings, cerebral digital subtraction angiography (DSA) was also performed (Fig. 2). It confirmed basilar artery aneurysm, parasagittal on the right side. Based on clinical findings, "separated in time and space", MRI of the CNS and finding of oligoclonal bands

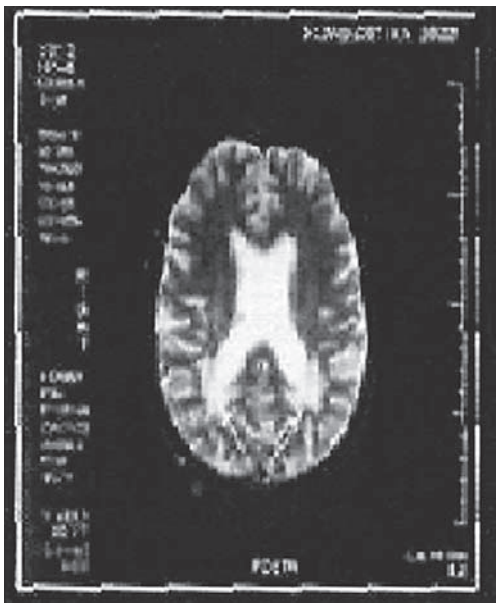

Fig. 1. *(SE TR 2500, TE 25/110, TR 500, TE20) Cerebral MRI: cerebral atrophy, multiple hyperintensive lesions in the white matter, especially periventricularly, typical of MS lesions.*

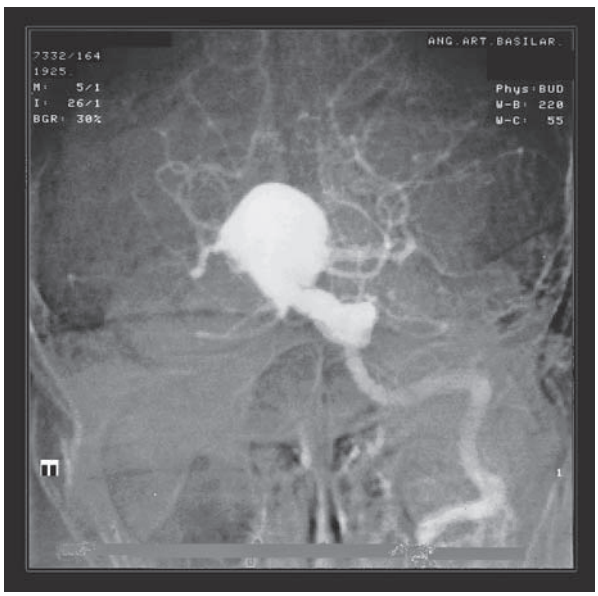

Fig. 2. *Cerebral DSA: aneurysm of the upper part of basilar artery, partially thrombosed, aneurysm diameter 20 mm.*

on CSF examination, definitive diagnosis of MS and intracranial aneurysm of the basilar artery was made. For now, we decided to prescribe conservative treatment with monitoring of the aneurysm.

DISCUSSION

Differential diagnosis of MS, among others, includes cerebrovascular disease, intracranial neoplasms, arteriovenous malformations, especially of the spinal cord (7). De Stefano *et al*. describe the difference between isolated demyelination and astrocytoma (8). Ernst *et al*. (9) report on isolated damage appearing as annular amplification surrounded by edema, which showed good response to corticosteroid treatment and was eventually confirmed as MS on cerebral angiography. Sometimes, arteriovenous malformation can mimic the clinical presentation of MS, particularly primary and secondary progressive MS, but may also have a relapsing-remitting course because of hemodynamic changes (10,11). Thanks to the development of diagnostic procedures, particularly MRI and cerebral angiography, differentiation of these two entities is easier today. Arteriovenous malformations, which mostly occur at spinal cord and brainstem, often have fluctuating symptoms that are not revealed in the initial stage of the disease (12-14). Dhopesh and Weinstein (15) and Ritzenthaler *et al*. (16) point to the importance of early detection of vascular malformation, thus enabling timely operative treatment and prevention of neurologic deterioration.

Simultaneous occurrence of MS and other diseases is possible. Concurrence of MS and vascular malformation of the CNS is rarely reported. Ho and Wolfe report on 20 patients with MS and simultaneous occurrence of glioma and 9 patients with MS and other neoplasms recorded in the literature. In their study, there was only one patient with MS and arteriovenous malformation. It was a 63-year-old patient with a 25-year history of MS. Arteriovenous malformation was revealed on autopsy. This was the first case of simultaneous occurrence of MS and arteriovenous malformation described (17). Only a few similar cases are found in later literature. Our patient is therefore a rare example of simultaneous occurrence of MS and basilar artery aneurysms, verified by MRI and cerebral angiography. The case presented also points to the importance of extra examinations besides the usual diagnostic procedures in the algorithm for a specific disease in case of clinical suspicion and aberration.

CONCLUSION

Cerebrovascular disease, intracranial neoplasms, arteriovenous malformation, particularly of the spinal cord and meninges, may be coexisting with MS. Sometimes, arteriovenous malformation can mimic the clinical presentation of MS, having a relapsing-remitting course because of hemodynamic changes. Thanks to the development of diagnostic procedures, particularly MRI and cerebral angiography, differentiation of these two entities is easier today. Asymptomatic and symptomatic vascular malformation can occur simultaneously with MS, but it is rarely described in the literature. Our case is an example of these two entities coexisting in one patient, who had clinically defined MS and basilar artery aneurysm.

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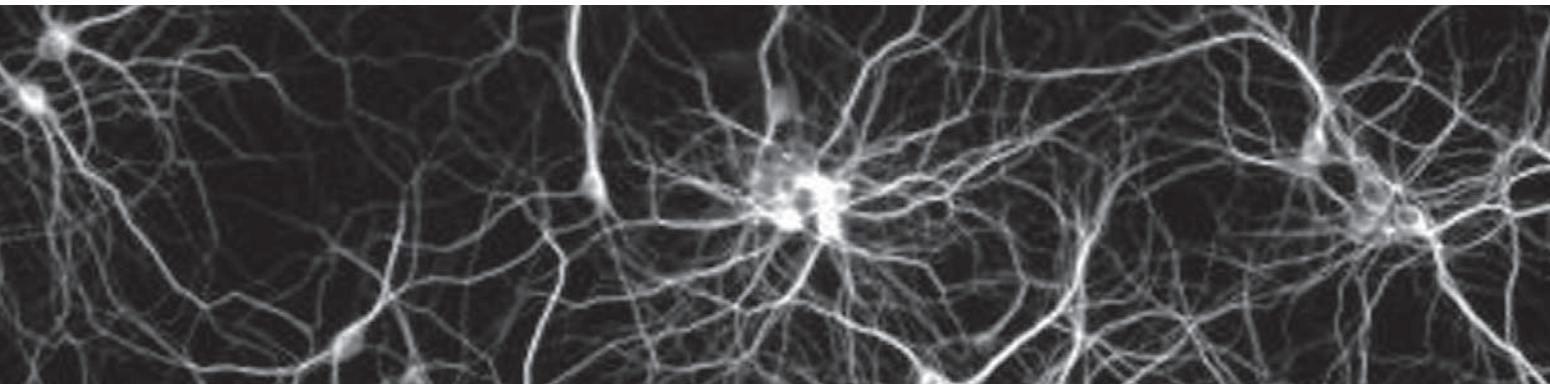
Združenost multiple skleroze i vaskularne malformacije moždanog debla: prikaz bolesnika

SAŽETAK - Multipla skleroza (MS) je demijelinizacijska bolest središnjega živčanog sustava, najčešće relapsno-remitirajućeg tijeka. Vaskularne malformacije opisane su u diferencijalnoj dijagnozi MS zbog sličnosti kliničke slike, osobito u slučaju relapsno-remitirajućeg tijeka, zbog hemodinamskih promjena. Zahvaljujući razvoju dijagnostičkih postupaka, osobito magnetske rezonancije (MR) živčane osi i cerebralne angiografije, razlikovanje ovih dvaju nozoloških entiteta danas je jednostavnije. Rijetka je, međutim, istodobna pojavnost asimptomatske vaskularne malformacije i MS. Prikazujemo bolesnicu s oba klinička entiteta, tj. s klinički sigurnom MS potvrđenom laboratorijskim testovima i pomoću MR, i aneurizmom bazilarne arterije.

Ključne riječi: multipla skleroza, aneurizma, bazilarna arterija



Coexistence of neurosarcoidosis and multiple sclerosis

L. Radolović Prenc[1], S.Telarović[2,3], I.Vidović[1], J. Sepčić[4], L. Labinac Peteh[1]

ABSTRACT - Sarcoidosis is a multisystem inflammatory disease of unknown etiology that predominantly affects the lungs and intrathoracic lymph nodes, but in 6% of cases it also occurs in central or peripheral nervous system. Multiple sclerosis (MS) is an immune-mediated inflammatory disease that attacks myelinated axons in the central nervous system. Coexistence of sarcoidosis and other autoimmune diseases like MS is rarely reported in the literature. We present a case report of a patient with coexisting sarcoidosis and MS, with a positive family history of MS. Symptoms of sarcoidosis appeared three years before the onset of symptoms typical for MS. Similarity of demyelinating lesions in the nervous system, increased IgG in cerebrospinal fluid and good response to corticosteroid treatment point to similar etiology. The onset of diseases like sarcoidosis and MS in the same patient over a period of only a few years opens the question whether the two separate entities come in sequence or the onset of sarcoidosis occurs during development of typical clinical presentation of MS.

Key words: sarcoidosis, encephalomyelitis, multiple sclerosis

INTRODUCTION

Sarcoidosis is an inflammatory disorder of unknown origin, characterized by epithelioid cell granulomas in various organs (1). The disease can occur suddenly or gradually, followed by complete or partial remission. Typically, the diagnosis of sarcoidosis is confirmed by a pathologic radiological finding of the lung, hypercalciuria and hyperglobulinemia, anergy to skin tests, higher value of angiotensin-converting enzyme (ACE), epithelial granulomas in histopathologic analysis of mediastinal lymph nodes (Figs. 1 and 2), or pathologic skin nodes or bone cysts, especially in hands, and positive Kveim test (2). Cerebrospinal fluid (CSF) analysis shows increased IgG, pleocytosis with protein-

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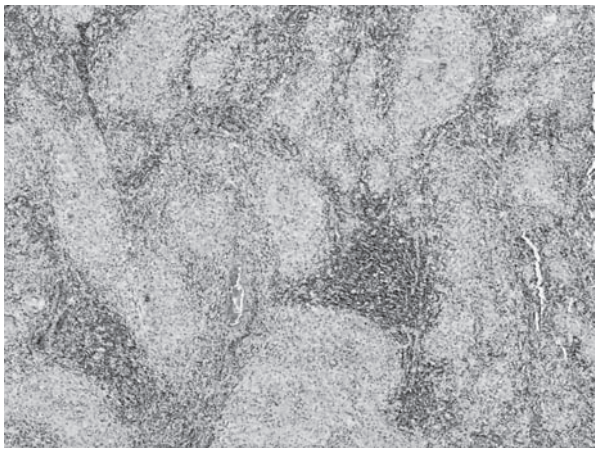

Fig. 1. *Sarcoidosis. Microscopic view of granulomatous reaction in the lymph node (HE, X40).*

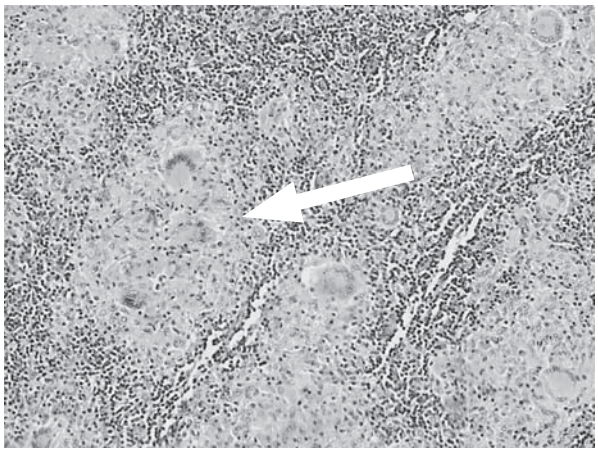

Fig. 2. *Sarcoidosis. Microscopic appearance of noncaseous granulomas in the lymph node, arrow (HE, X200).*

orrhachia, hypoglycorrhachia and impaired blood brain barrier (BBB) (3).

Although sarcoidosis primarily affects the lungs, in 6% of cases neurologic symptoms are the first indicators of the disease. Although the symptoms of sarcoidosis are different from those of multiple sclerosis (MS), patients with sarcoidosis and MS are of similar ages and both have damage to cranial nerves, myelopathy, demyelinating lesions of the central nervous system (CNS) and IgG in CSF, which can result in inaccurate diagnosis (4).

Some forms of sarcoidosis are difficult to distinguish from MS, especially if sarcoidosis affects optic nerve and spinal cord. Myelopathy in sarcoidosis usually manifests as chronic progressive paraparesis as a consequence of compression, ischemia and/or parenchymal damage. Along with positive Lhermitte's sign, the only distinction of this myelopathy from the chronic progressive form of MS is clinical presentation. Damage to the optic nerve can be related to optical neuritis in MS (1).

In 50% of cases of neurosarcoidosis, ACE is elevated in CSF, but it is not a specific feature of the disease (5). Intrathectal synthesis of IgG is not common, but the increased permeability of BBB in sarcoidosis can be useful on differential diagnosis against MS. Some researches showed a specific, locally formed IgG in the CSF of patients with sarcoidosis, with positive reaction to Kveim substances (Kveim specific IgG) (6).

The possible relapsing-remitting course of the disease, demyelinating damage detected on magnetic resonance (MR) analysis of CNS and positive IgG in CSF make the differential diagnostic resolution of MS and sarcoidosis. The diagnosis is finally confirmed by laboratory tests that indicate an increase in the concentration of beta-microglobulin, ACE in serum and CSF, hypercalciuria, positive Kveim test and finding of Kveim specific IgG in CSF (6). Pathognomonic radiological findings of the lung and bone, and histopathologic confirmation of epithelioid granuloma are very important for definitive diagnosis (7).

MR analysis of CNS shows periventricular white matter damages in a quarter of patients with neurosarcoidosis. These changes are difficult to distinguish from damages in MS. Inflammatory leptomeningeal scarring (adhesions), thickening around the chiasm and nerve roots, subependymal granulomas, hydrocephalus and microinfarcts as a result of secondary angiopathy suggest sarcoidosis, but not MS (8). Persistent contrast imbibitions of parenchymal lesions are related to granulomatosis damages in sarcoidosis, which is rare in MS (9).

CASE REPORT

A man born in the mountainous area had a positive family history of MS. At the age of 32, mediastinoscopy biopsy was performed due to enlarged mediastinal lymph nodes, with diagnosis of pulmonary sarcoidosis treated with corticosteroids for 18 months. Three years later, at the age of 35, paresthesias of the right lower extremity followed by gradually increasing weakness were observed. These symptoms were transient. At the age of 38, he felt pain in the left eye, with fogging and occasional double vision, and he was admitted to the hospital.

In somatic status, asthenia and less painless subcutaneous nodules in lower legs were found. In neu-

rologic status, a mild right pyramidal deficit, absence of abdominal skin reflexes bilaterally, right sided dysmetria and horizontal nystagmus on the left eye and hemihypesthesia on the right side of the forehead were recorded. Routine examination showed mild lymphocytosis and lower values of serum Ca and Mg, but without hypercalciuria, and slightly elevated levels of serum ACE. Hepatitis markers and serology for toxoplasmosis, syphilis and borreliosis were normal. Cryoglobulins and antinuclear and antimitochondrial antibodies were negative. Values of the complement components were normal. Analysis of HLA typing showed A1, A2, B5, DR 5, DRW6. The papillae of both optic nerves were pale. Radiographic evaluation of the lungs and respiratory functions showed normal findings. In CSF, protein values were normal with 10 sediment cells, lymphocytes, monocytes and plasma cells.

The patient was discharged as a case of neurosarcoidosis. During hospital stay, he received ACTH (Alexander's scheme), followed by improvement.

Five years later, at the age of 43, he was rehospitalized due to walking trouble. Somatic status was normal. Neurologic examination showed paraparesis, more pronounced in the right leg, and ataxia with heeling on the right side and horizontal nystagmus on the left eye. Analysis of visual evoked potentials (VEP) showed dysfunction of both optic tracts and somatosensory evoked potentials (SSEP) dysfunction of afferent pathways bilaterally, more pronounced on the right side. Laboratory findings showed a slightly elevated component of complement C3. Paraprotein concentrations in serum were normal, as well as the values of ACE and Ca in serum and urine. Brain MRI verified disseminated white matter lesions suggesting MS lesions by their size, shape and arrangement, without spinal cord lesions (Fig. 3). Therapy with oral prednisone resulted in improvement. The patient was discharged as a case of MS.

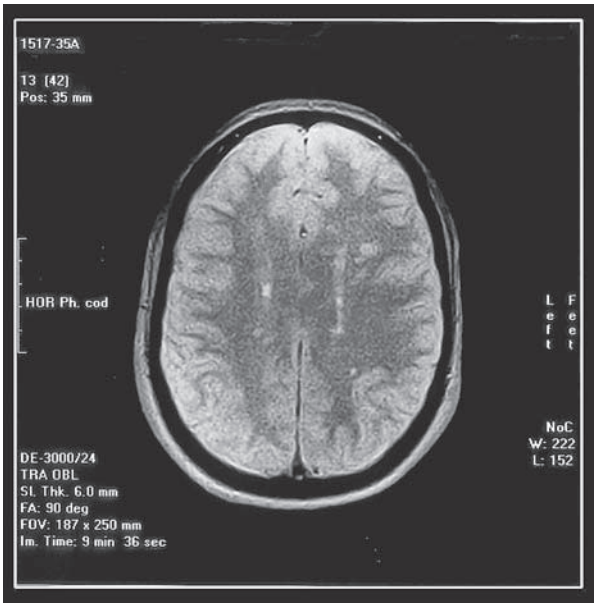

Fig. 3. *SE (TR 2500, TE 25/110, SE TR 500, TE 20) Unequal multiple bilateral disseminated lesions in the white substances. The shape, size and arrangement of white matter damages indicate MS.*

Six years later, at the age of 49, he was rehospitalized due to numbness of the right leg and ataxia. Somatic status was normal. Walking was atactic and paraparetic, the patient used a crutch, with bilateral horizontal nystagmus, right pyramidal and cerebellar deficit and urinary urgency. He received 500 mg methylprednisolone as pulsed therapy over five days in a total dose of 2.5 g and then tetracosactide hexaacetate depot 1 mg intramuscularly, one vial *per* week for one month. Definitive diagnosis was MS.

CONCLUSION

Today, plenty of additional searching facilitates and simplifies the differential diagnosis of neurosarcoidosis and MS, but coincidence of these two diseases is always possible. However, concurrence of both diseases is rarely reported in the literature (10).

Our patient was diagnosed with clinically definitive MS, with positive family history of MS. Three years before the onset of MS symptoms, he developed symptoms of sarcoidosis. The occurrence of both diseases in the same patient within several years opens a question whether it was a sequence of two independent nosologic entity, or the occurrence of sarcoidosis (initial) during development of the typical clinical features of MS. The influence of T cell groups (myelin reactive T cells) and cytokines could be a unique causal mechanism for the occurrence of immune deficiency in both diseases. The similarity of demyelinating damages in the neural axis, IgG in CSF, and efficient response to corticosteroid therapy in MS and sarcoidosis point to at least a partially common etiopathogenetic circuit. The possibility that a disturbed immune system in the presence of one disease (neurosarcoidosis) led to clinical appearance of the other disease (MS) for which there was a genetic predisposition is also a topic for debate (11,12). According to the current knowledge, the pathologic changes in sarcoidosis are caused by cell-me-

diated immune response. The pathogenesis of MS has not yet been fully clarified (13). Today, it is interpreted as an autoimmune disease that is at least partly caused by T cell-mediated disorder triggered by environmental factors in genetically prone individuals (14).

In recent years, the influence of T cell group (myelin reactive T cells) and cytokines in the pathogenesis of MS has been intensively studied. There is an assumption that the duration and intensity of the disease are associated with the type and invasiveness of MPB reactive T cells (15). These disturbances of T cell groups could be a unique etiologic immune moment that leads to the occurrence of both diseases.

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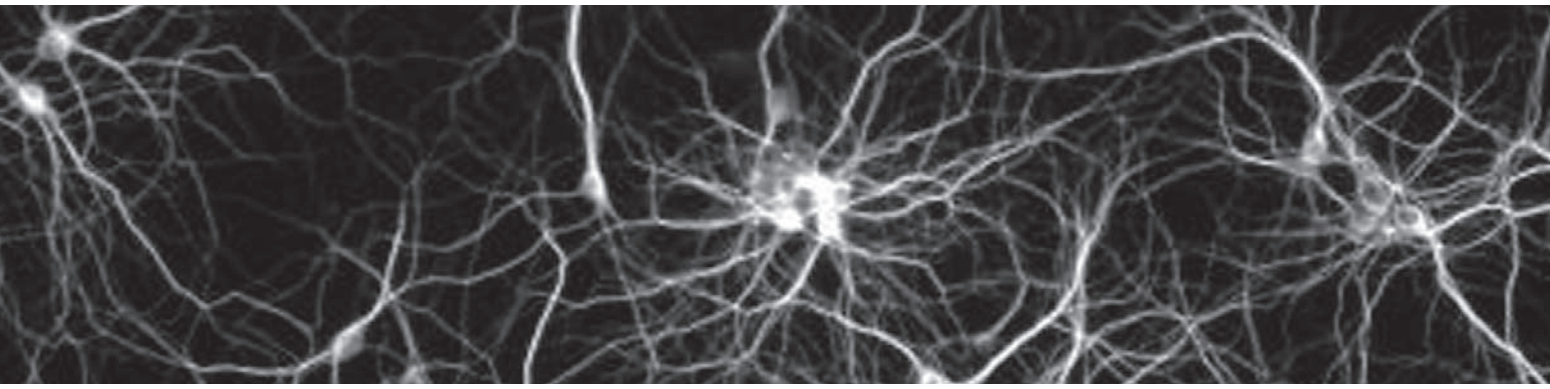
Združena pojava neurosarkoidoze i multiple skleroze

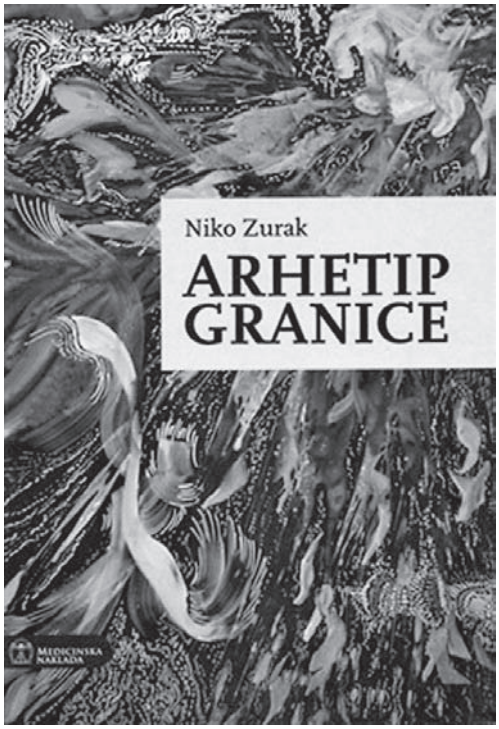
SAŽETAK - Sarkoidoza je upalna sistemska bolest koja primarno zahvaća pluća i limfne čvorove, ali u 6% slučajeva zahvaća središnji ili periferni živčani sustav. Multipla skleroza (MS) je upalna demijelinizacijska bolest središnjega živčanog sustava. Rijetko je u literaturi opisano združeno javljanje sarkoidoze s drugim autoimunim bolestima kao što je MS. Prikazujemo slučaj bolesnika kojemu su dijagnosticirane sarkoidoza i diseminirana primarna demijelinizacija tipa MS, s pozitivnom obiteljskom anamnezom. Tri godine prije pojave simptoma MS u bolesnika se pojavila sarkoidoza. Sličnost demijelinizacijskih oštećenja u živčanoj osi, IgG u cerebrospinalnom likvoru, učinkovit odgovor na terapiju kortikoisterodima i u MS i u sarkoidozi upućuju na barem djelomice zajednički etiopatogenski sklop. Pojavljivanje obiju bolesti u istog bolesnika u razmaku od nekoliko godina nameće pitanje radi li se o slijedu dvaju samostalnih nozoloških entiteta ili o pojavi sarkoidoze (početnoj) u razvoju tipične kliničke slike MS.

Ključne riječi: sarkoidoza, encefalomijelitis, multipla skleroza



Niko Zurak

ARHETIP GRANICE (BORDER ARCHETYPE)



Medicinska naklada, Zagreb, 2013
Hardcover, 136 pages, 29 figures
ISBN: 978-953-176-553-4

The book *Arhetip granice* (*Border Archetype*) is an innovative scientific work divided into two parts. The first part, *Border archetype,* entitled as the whole book, consists of two chapters and is composed of several ideologically connected thematic units – the author explains the archetypic concept of Carl Gustav Jung, subsequently thematic unit of mathematical archetypes of numbers and geometry, mathematical platonism is discussed, and a significant part of the text is dedicated to gestalt psychology, in the spirit of which the author discusses illusory contours. Thematic unit *Hypothesis of border archetype* with *Discussion* is the central part of the first part of the book and of the whole book, in which the author explains the authentic idea that the border archetype is a basic archetype, proto-archetype from which all other archetypes are differentiated. The second part of the book entitled *Neurophysiology of holism* consists of four chapters. The majority of this part is dedicated to the neurophysiology of visual perception. The author also uses holistic approach in analyzing language and speech functions, and one shorter, very interesting part is dedicated to music as a universal language.

This book represents an authentic scientific work with great contribution to the development of science, which cannot be compared with other works dedicated to the same or related subject because such works, with holistic approach to the mentioned issues, according to our knowledge, have not been published so far. In this book, references from a number of scientific disciplines are cited and critically analyzed. The approach to the importance of the subject discussed in this work is very appropriate. This interdisciplinary scientific work is intended for the broad academic society, i.e. physicians, especially neurologists, neurophysiologists, psychiatrists and neuro-ophthalmologists.

The leading thought of this original scientific work is that it is possible to find explanation for the collectiveness of the perception, language, speech functions and cognition in the holistic approach to the understand-

ing of the complexity of the human brain, by extension of the archetypic concept of Carl Gustav Jung using the idea of the border proto-archetype. From the border archetype all other archetypes are differentiated, whether they are mathematical, biological, psychological or sociological. In the potential of differentiating capacity of the border archetype there are hidden possibilities of the evolution of all areas of natural and humanistic sciences, social relations, and art (painting, music, theater, film).

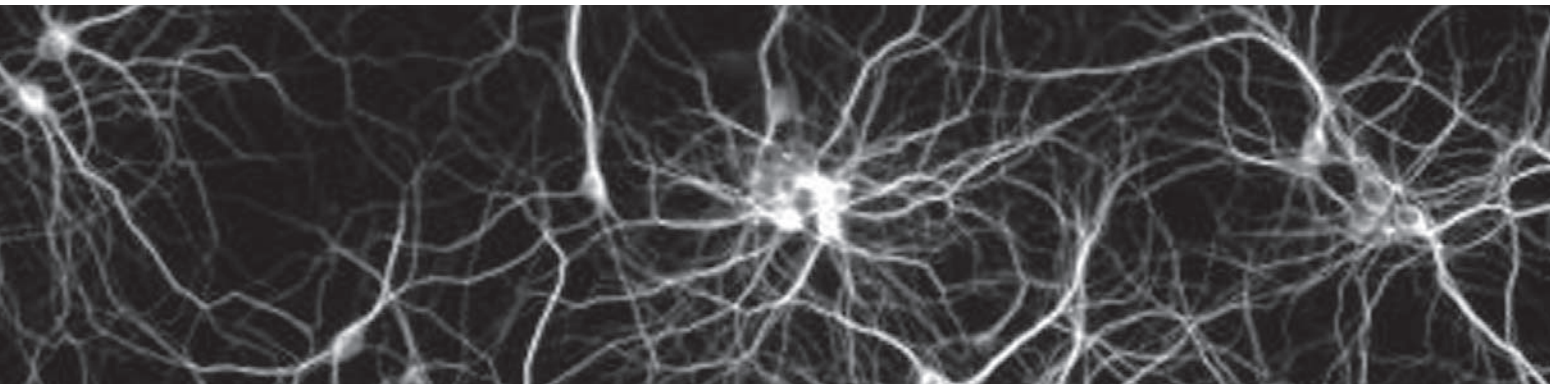
Simple, elegant proof of the genesis of the border archetypic picture in the unconscious part of visual perceptualization is the original scientific discovery, which has escaped the attention of neuroscientists from the field of vision neurophysiology.

Connecting his idea of border archetype with unusual attractors and fractal geometry of the chaos theory, the author affirms nonlinear dynamics as *modus operandi* of the functioning of the human brain. The hypothesis of the border archetype is very encouraging for the explanation of the genesis of some psychopathological entities and psychopathological phenomena, especially hallucinations.

Numerous color illustrations that facilitate understanding of some more complicated parts of the text, as well as a rich glossary of medical and philosophical terms contribute to the quality of this scientific work.

Except for the specialized societies of neurologists, neurophysiologists, neuro-ophthalmologists, psychiatrists and psychologists, we are sure that this book will find readers in a wider academic society, especially among intellectuals who follow one of the most intriguing areas of the general intellectual interest nowadays, the "mind-body problem".

S. Hajnšek
Ž. Petelin Gadže



Neurological Congresses in 2013

May 2013

May 04, 2013

14th Annual UC San Diego Stroke Conference
La Jolla, California, USA

May 04 – May 12, 2013

Advanced Neuroscience Course: Neural Stem Cells in Development and for Brain Repair
Cortona, Italy

May 08 – May 10, 2013

Transcranial Doppler
Los Angeles, California, USA

May 09 – May 11, 2013

Second International Congress on Treatment of Dystonia
Hannover, Germany

May 09 – May 12, 2013

EFNS Spring School for Young Neurologists
Staré Splavy, Czech Republic

May 12 – May 14, 2013

10th Annual World Congress of SBMT on Brain, Spinal Cord Mapping and Image Guided Therapy
Baltimore, USA

May 16, 2013

Recent Clinical and Research Advances in Childhood Epilepsy
London, UK

May 16 – May 18, 2013

EFNS Regional Teaching Course in Skopje
Skopje, Macedonia

May 17 – May 19, 2013

Second International Expert Meeting on Hyperkinetic Movement Disorders
Malta

May 17 – May 18, 2013

Clinical Challenges in Neurology – Multidisciplinary Case Reports
Tuheljske Toplice, Croatia

May 18 – May 23, 2013

ASNR (American Society of Neuroradiology) 51st Annual Meeting & The Foundation of the ASNR Symposium 2013
San Diego, California, USA

May 20 – May 23, 2013

XXVI International Symposium on Cerebral Blood Flow, Metabolism and Function and the XI International Conference on Quantification of Brain Function with PET
Shanghai, China

May 20 – May 24, 2013

6th International Epilepsy Colloquium on Tumoral Epilepsy and Epilepsy Surgery
Cleveland, USA

May 21 – May 23, 2013

Translational CNS Summit
Boston, USA

May 23 – May 24, 2013

Hands-On Carotid & Vertebral Duplex Ultrasound Imaging & Introduction to Transcranial Doppler
Dallas (Irving), Texas, USA

May 23 – May 25, 2013

BIT's 4th Annual Congress of NeuroTalk 2013
Xi'an, China

May 23 – May 26, 2013

4th International Conrgress on Neuropathic Pain
Toronto, Canada

May 24 – May 27, 2013

18th Meeting of European Society of Neurosonology and Cerebral Hemodynamics (ESNCH)
Porto, Portugal

May 25 – May 27, 2013

European Forum on Epilepsy Research
Dublin, Ireland

May 27 – May 30, 2013

16th Quadrennial Meeting of the World Society for Stereotactic and Functional Neurosurgery
Tokyo, Japan

May 28 – May 31, 2013

XXII European Stroke Conference
London, UK

May 29 – May 31, 2013

World Live Neurovascular Conference
Istanbul, Turkey

May 31 – June 01, 2013

8th Annual UCSF Spine Symposium
San Francisco, California, USA

June 2013

June 01 – 05, 2013

SLEEP Annual Meeting
Baltimore, Maryland, USA

June 02 – June 05, 2013

The Jerusalem International Conference on Neuroplasticity and Cognitive Modifiability
Jerusalem, Israel

June 03 – June 07, 2013

XXIV Summer Stroke School
Dubrovnik, Croatia

June 07 – June 09, 2013

Dys-Spas-Bot 2013 – Combined Symposium on Dystonia, Spasticity and Botulinum Toxin Therapy
Middelfart, Denmark

June 07 – June 11, 2013

2013 Meeting of Society of Neurological Surgeons
Boston, Massachusetts, USA

June 08 – June 11, 2013

23rd Meeting of the European Neurological Society
Barcelona, Spain

June 08 – June 13, 2013

International Neuromodulation Society (INS) 11th World Congress
Berlin, Germany

June 10 – June 11, 2013

New Avenues for Brain Repair: Programming & Reprogramming the Central Nervous System
Cambridge, Massachusetts, USA

June 11 – June 13, 2013

Live Interventional Neuradiology & Neurosurgery Course Paris 2013
Paris, France

June 14 – June 16, 2013

3rd International Conference on Interventional Pain Medicine & Neuromodulation
Warsaw, Poland

July 15 – July 17, 2013

Human Brain Anatomy Course
London, United Kingdom

June 16 – June 20, 2013

The 17th International Congress of Parkinson's Disease and Movement Disorders,
Sydney, Australia

June 16 – June 20, 2013

19th Annual Meeting of the Organization for Human Brain Mapping
Seattle, Washington, USA

June 16 – June 20, 2013

11th International Stereotactic Radiosurgery Society Congress
Toronto, Ontario, Canada

June 17 – June 19, 2013

2nd International Conference and Exhibition on Neurology & Therapeutics
Chicago, Illinois, USA

June 17 – June 20, 2013

19th Intensive Care Medicine Symposium with International Participation
Rovinj, Croatia

June 19 – June 20, 2013

Progressive Multifocal Leukoencephalopathy
New York, USA

June 19 – June 22, 2013

53rd International Neuropsychiatric Pula Congress (INPC)
Pula, Croatia

June 20 – June 22, 2013

11th Annual American Academy of Clinical Neuropsychology Conference Chicago
Chicago, Illinois, USA

July 20 – July 28, 2013

Advanced Neuroscience Course: Cellular and System Mechanisms of Learning and Memory
Cortona, Italy

July 21 – July 26, 2013

IUPS 2013 – International Union of Physiological Sciences
Birmingham, UK

June 22 – June 24, 2013

5th Summer School of Neurosonology and Stroke Management
Zadar, Croatia

June 23 – June 27, 2013

30th International Epilepsy Congress
Montreal, Canada

June 25 – June 26, 2013

Clinical Skills in Spinal Assessment and Management
London, UK

June 25 – June 27, 2013

5th International CMT Consortium Meeting
Antwerp, Belgium

June 25 – June 28, 2013

VASCOG 2013: 6th Congress of the International Society for Vascular Behavioral and Cognitive Disorders
Toronto, Canada

June 26 – June 29, 2013

CARS 2013 Computer Assisted Radiology and Surgery: 27th International Congress and Exhibition
Heidelberg, Germany

June 27 – June 30, 2013

2013 International Headache Congress (IHC)
Boston, USA

June 29 – July 3, 2013

2013 Biennial Meeting of the Peripheral Nerve Society
Saint-Malo, Brittany, France

July 2013

July 05 – July 07, 2013

Spine Radiology – 3rd Joint Meeting of ASSR (The American Society of Spine Radiology) and ESNR (The European Society of Neuroradiology)
Milan, Italy

July 10 – July 13, 2013

20th International Meeting on Advanced Spine Techniques: IMAST
Vancouver, British Columbia, Canada

July 13 – July 18, 2013

AAIC 2013 – Alzheimer's Association International Conference
Boston, USA

July 14 – July 26, 2013

Pain Management, Neurology, and Coding and Compliance (12-Night Mediterranean Cruise Conference)
From Venice, Italy to Barcelona, Spain

July 14 – July 27, 2013

111th San Servolo Course on Brain Exploration and Epilepsy Surgery
Venice, Italy

July 24 – July 26, 2013

Transcranial Doppler Course
Los Angeles, California, USA

July 29 – August 01, 2013

Society of NeuroInterventional Surgery 10th Annual Meeting
Miami, Florida, USA

July 29 – August 02, 2013

Joint Meeting of The International Society for Autonomic Neuroscience &
The European Federation of Autonomic Societies
Giessen, Germany

August 2013

August 03 – August 11, 2013

Advanced Neuroscience Course: Molecular Signaling in the Aging Synapse
Cortona, Italy

August 16 – August 18, 2013

Colloquium on Drug-Resistant Epilepsy: Current Concepts and Future Directions
Bangalore, India

August 18 – August 23, 2013

7th Baltic Sea Summer School for Epilepsy (BSSSE7)
Tallin, Estonia

August 19 – August 20, 2013

Summer School of Neurosonology for Baltic and Scandinavian Countries (BSSSN)
Druskininkai, Lithuania

August 21 – August 24, 2013

17th Nordic Congress on Cerebrovascular Diseases
Vilnius, Lithuania

August 23 – August 26, 2013

ACCP Sleep Medicine Board Review 2013
San Antonio, Texas, USA

August 26 – August 30, 2013

2nd Alpine Sleep Summer School
Ljubljana, Slovenia

August 27 – August 28, 2013

8th International Postgraduate Practical School of Epileptology: Neurosurgical Aspects of Epilepsy in the Southeastern Europe
Ljubljana, Slovenia

August 28 – August 30, 2013

13th European Conference on Epilepsy & Society
Ljubljana, Slovenia

August 31 – September 08, 2013

Advanced Neuroscience Course: Stress and Mental Illness: From Genomics to Imaging
Cortona, Italy

September 2013

September 05 – September 07, 2013

5th ESMINT (European Society of Minimally Invasive Neurological Therapy) Congress
Nice, France

September 08 – September 13, 2013

15th WFNS World Congress of Neurosurgery
Seoul, South Korea

September 11 – September 14, 2013

FENS (Federation of European Neuroscience Societies) Featured Regional Meeting
Prague, Czech Republic

September 14 – September 18, 2013

12th Asian Oceanian Congress on Child Neurology
Riyadh, Saudi Arabia

September 15 – September 19, 2013

2013 World Congress on Huntington's Disease
Rio, Brazil

September 16 – September 20, 2013

1st International Summer School for Neuropathology and Epilepsy Surgery
Erlangen, Germany

September 19 – September 21, 2013

International Congress on Neurotechnology, Electronics and Informatics (NEUROTECHNIX 2013)
Algarve, Portugal

September 19 – September 21, 2013

TBI (Traumatic Brain Injury) – Challenge 2013 Conference
Vienna, Austria

September 21 – September 26, 2013

21st World Congress of Neurology (WCN 2013)
Vienna, Austria

September 25 – September 28, 2013

10th European Paediatric Neurological Society (EPNS) Congress
Brussels, Belgium

September 25 – September 29, 2013

American Society of Head and Neck Radiology 47th Annual Meeting
Milwaukee, Wisconsin, USA

September 27 – September 29, 2013

SiNAPSA Neuroscience Conference '13
Ljubljana, Slovenia

September 27 – September 29, 2013

Practical Approach to Electromyography and Neuromuscular Disorders
Boston, Massachusetts, USA

September 28 – October 06, 2013

Advanced Neuroscience Course: Novel Perspectives for Basal Ganglia Disorders
Cortona, Italy

September 30 – October 6, 2013

5th Eilat International Educational Course: Pharmacological Treatment of Epilepsy
Jerusalem, Israel

October 2013

October 01, 2013

Parkinson Study Group 27th Annual Symposium on Etiology, Pathogenesis
and Treatment of Parkinson's Disease
Montreal, Canada

October 01 – October 04, 2013

3rd World Parkinson Congress
Montreal, Quebec, Canada

October 01 – October 04, 2013

Neurocritical Care Society 11th Annual Meeting
Philadelphia, Pennsylvania, USA

October 01 – October 06, 2013

18th International World Muscle Society Congress 2013
Monterey, California, USA

October 02 – October 05, 2013

29th Congress of the European Committee for Research and Treatment in Multiple Sclerosis (ECTRIMS)
and the 18th Annual Conference of Rehabilitation in MS (RIMS)
Copenhagen, Denmark

October 03 – October 06, 2013

The 2nd International Multidisciplinary Forum on Palliative Care (IMFPC 2013)
Sofia, Bulgaria

October 05 – October 13, 2013

26th ECNP (European College of Neuropsychopharmacology) Congress
Barcelona, Spain

October 09 – October 12, 2013

8th EFIC Pain in Europe Congress
Florence, Italy

October 10 – October 12, 2013

23rd Annual Conference of Alzheimer Europe
St. Julian's, Malta

October 13 – October 15, 2013

138th Annual Meeting of the American Neurological Association
New Orleans, USA

October 17 – October 19, 2013

Sleep DownUnder 2013 – River of Dreams
Brisbane, Australia

October 17 – October 20, 2013

16th World Neurosonology Meeting
Sofia, Bulgaria

October 17 – October 20, 2013

8th International Congress on Vascular Dementia & The First Cognitive Impairment European Meeting
Athens, Greece

October 19 – October 23, 2013

63rd Annual Meeting of the Congress of Neurological Surgeons
San Francisco, California, USA

October 19 – October 26, 2013

Advanced Neuroscience Course: Autophagy and Neuroprotection
Cortona, Italy

October 23 – October 26, 2013

24th International Symposium on the Autonomic Nervous System Sponsored by the American Autonomic Society
Hawaii, USA

October 23 – October 26, 2013

III International Congress on Dual Disorders – CIPD 2013
Barcelona, Spain

October 24 – October 26, 2013

2013 Alberta Sleep Forum
Edmonton, Alberta, Canada

November 2013

November 01 – November 03, 2013

8th TACT Meeting (TREAT-NMD Advisory Committee for Therapeutics)
Newcastle, UK

November 03 – November 09, 2013

7th Migrating Course on Epilepsy
Nicosia, Cyprus

November 05 – November 06, 2013

Meningitis and Septicaemia in Children and Adults 2013
London, UK

November 6 – November 10, 2013

6th Croatian Congress of Neurology
Split, Croatia

November 9 – November 13, 2013

43rd Annual Meeting of the Society for Neuroscience
San Diego, USA

November 11 – November 14, 2013

EANS (The European Association of Neurosurgical Societies) Annual Meeting 2013
Tel Aviv, Israel

November 11 – November 16, 2013

2013 Educational Course and Biennial Congress of the ISIN (International Society for Intraoperative Neurophysiology)
Cape Town, South Africa

November 14 – November 16, 2013

IX/XV Congress of Serbian Neurologists with International Participation
Belgrade, Serbia

November 21 – November 23, 2013

3rd International Congress on Neurology and Epidemiology (ICNE) – The Use of Academic Research and Neuroepidemiology in Improving Neurological Health
Abu Dhabi, UAR

November 21 – November 24, 2013

4th Quadrennial World Federation of Neuro-Oncology (WFNO) Meeting
San Francisco, USA

November 21 – November 24, 2013

Scottsdale Headache Symposium 2013
Scottsdale, USA

December 2013

December 06 – December 07, 2013

Miami Neuro Symposium
Coral Gables, Florida, USA

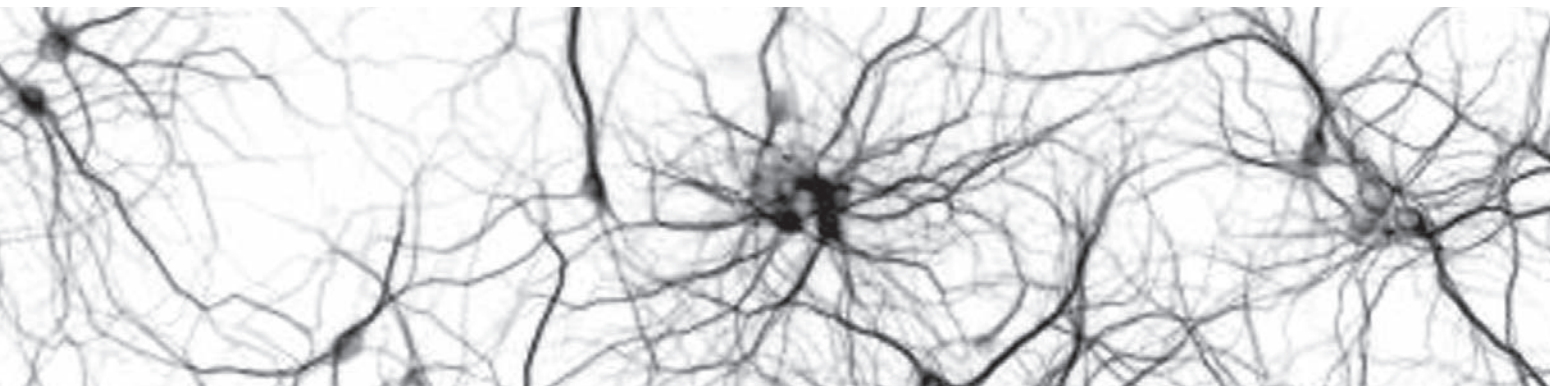
December 06 – December 12, 2013

67th Annual Meeting of the American Epilepsy Society (AES 2013)
Washington, USA

December 08 – December 11, 2013

XX World Congress on Parkinson's Disease and Related Disorders
Geneva, Switzerland

A. Bujan Kovač



Kazalo stvari i imena za volumen 61/2012. /

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Kazalo stvari – vol. 60/2011.

Kazalo imena – vol. 61/2012.

Invited lecture,
3rd Croatian Congress on Dilemmas in Neurology,
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Transcranial Doppler (TCD) or Transcranial Color Coded Doppler (TCCD) Sonography

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In the last 20 years, transcranial Doppler sonography (TCD) has emerged from its initial use as a daily monitoring tool of intracranial hemodynamics for assessment of vasospasm in subarachnoid hemorrhage. Nowadays, TCD is used in emergency room with a fast track insonation protocol for assessment of vessel occlusion or collateral flow in acute stroke. It also enables monitoring of stroke patients and enhances TPA induced recanalization. It is used in intensive care unit for monitoring of daily changes of intracranial hemodynamics in subarachnoid hemorrhage and in assessment of raised intracranial pressure and development of cerebral circulatory arrest. TCD has proved to be a perfect tool for stroke prevention in patients with sickle cell anemia. Vasomotor reactivity testing can identify high-risk patients for first-ever or recurrent stroke in patients with carotid stenosis, and on emboli detection it can detect, localize and quantify cerebral embolization in real time. The addition of „bubbles" can detect right to left shunt in patients with suspected paradoxical embolism or those considered for shunt closure. It enables monitoring of endovascular stenting, carotid endarterectomy and cardiac surgery to detect perioperative embolism, thrombosis, hypo- and hyperperfusion. Hyperechogenicity of nigral substance or basal ganglia can serve as a biomarker and therefore transcranial sonography enables assessment of patients with extrapyramidal disease. In stroke patients, it may show hyperechogenic brain hematoma, and midline shift has a prognostic value in raised intracranial pressure. The addition of color coded flow enables visualization of normal anatomy and variants of the circle of Willis. It is possible to localize the origin of the vessel and its course, to localize the caliber and length of different segments. Transcranial color coded Doppler (TCCD) has similar sensitivity in vessel detection compared to TCD but is less operator dependent, more reliable in detection of vessel segments, collaterals and assessment of occlusion, while also allowing the use of angle correction in certain segments. It enables assessment of certain parts of venous anatomy in 50%-80%. TCD and TCCD are complementary ultrasound methods for assessment of intracranial hemodynamics, each having certain advantages for different applications.

NAPOMENA:

Sažetak je greškom izostavljen iz suplementa br. 5/2012. NEUROLOGIA CROATICA, 3. hrvatski kongres "Dileme u neurologiji", Šibenik, 2012., pa ga uz ispriku autorima i čitateljima objavljujemo u redovitom broju.

Upute autorima

NEUROLOGIA CROATICA, službeno glasilo Hrvatskoga neurološkog društva i Hrvatskoga neurokirurškog društva, izdaje Klinika za neurologiju, Klinički bolnički centar Zagreb, dva puta na godinu. Neurologia Croatica objavljuje radove iz područja kliničke neurologije, temeljnih neuroznanosti i drugih pridruženih područja.

Neurologia Croatica objavljuje slijedeće tipove članaka:

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4. **Izvještaji o slučajevima Klinike za neurologiju Kliničkog bolničkog centra Zagreb** će biti zatraženi od strane urednika.
5. **Slike u neurologiji**: Namjena ove kategorije je da prikaže vizualnu sliku zanimljivog i jedinstvenog neurološkog opažanja. Slike pacijenata zajedno sa slikama provođenja dijagnostičke procedure su dobrodošle. Maksimalna duljina: 200 riječi za opis slučaja, 50 riječi za svaku sliku, maksimalno dvije reference.
6. **Pisma uredniku**: Pisma koja raspravljaju o nedavnom članku objavljenom u časopisu *Neurologia Croatica* su dobrodošla. Pisma trebaju biti primljena unutar 3 mjeseca od objave članka. Kratki komentari o aktualnim pitanjima koja su od javnog interesa su također mogući. Maksimalna duljina: 500 riječi (uključujući sav tekst, opise slike i literaturu).

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Sažetak ne treba imati više od 250 riječi. Izvorni znanstveni radovi trebaju imati strukturirani sažetak sa slijedećim naslovima: ciljevi, metode, rezultati i zaključci. Sažeci za neurološke preglede trebaju biti nestrukturirani. Izvještaji o slučajevima trebaju imati strukturirane sažetke sa slijedećim naslovima: ciljevi, opis slučaj, rezultati, zaključak. Slike u neurologiji i pisma uredniku ne zahtijevaju sažetak. U njemu valja navesti samo glavne rezultate, a izbjegavati općenite opise i poznate činjenice. Iza sažetka treba abecednim redom navesti tri do deset ključnih riječi. Molimo da ključne riječi potražite preko linka MeSH Database na web stranici http://www.ncbi.nlm.nih.gov/pubmed/.

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Časopisi

Treba navesti sve autore ukoliko ih je šest ili manje: Mubrin Z., Kos M. Assessment of dementia. Flow chart approach to clinical diagnosis. Neurol Croat 1992; 41: 141-156.

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Baršić B, Lisić M, Himbele J *et al*. Pneumococcal meningitis in the elderly. Neurol Croat 1992;41:131-140.

Knjige

Critchley M. The ventricle of memory. New York: Raven Press, 1990.

Poglavlje u knjizi

Geschwind N. The borderland of neurology and psychiatry: some common misconceptions. In: Bensom DF, Blumer D, eds. Psychiatric aspects of neurologic disease. New York: Grune and Stratton, 1975:1-9.

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Prof. dr. sc. Sanja Hajnšek, Glavna urednica, NEUROLOGIA CROATICA, Klinički bolnički centar Zagreb, Klinika za neurologiju Medicinskog fakulteta Sveučilišta u Zagrebu, Kišpatićeva 12, 10 000 Zagreb; e-mail: predstojnik.nrl@kbc-zagreb.hr

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3. **Case reports**: Case reports need to have important and novel learning points and report on unusual syndromes or diseases; a simple narrative or challenging patient(s) is insufficient. Maximum length 1500 words, excluding tables, figure legends, and references.
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All authors to be listed in case there are six or less:

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If the article is written by seven or more authors, only names of the first three authors should be listed, followed by *"et al"*.:

Baršić B, Lisić M, Himbele J *et al*. Pneumoccocal meningitis in the elderly. Neurol Croat 1992; 41: 131 - 140.

Books

Critchley M. The ventricle of memory. New York: Raven Press, 1990.

Chapter in a book

Geschwind N. The borderland of neurology and psychiatry: some common misconceptions. In: Bensom DF, Blumer D, eds. Psychiatric aspects of neurologic disease. New York: Grune and Stratton, 1975; 1 - 9.

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