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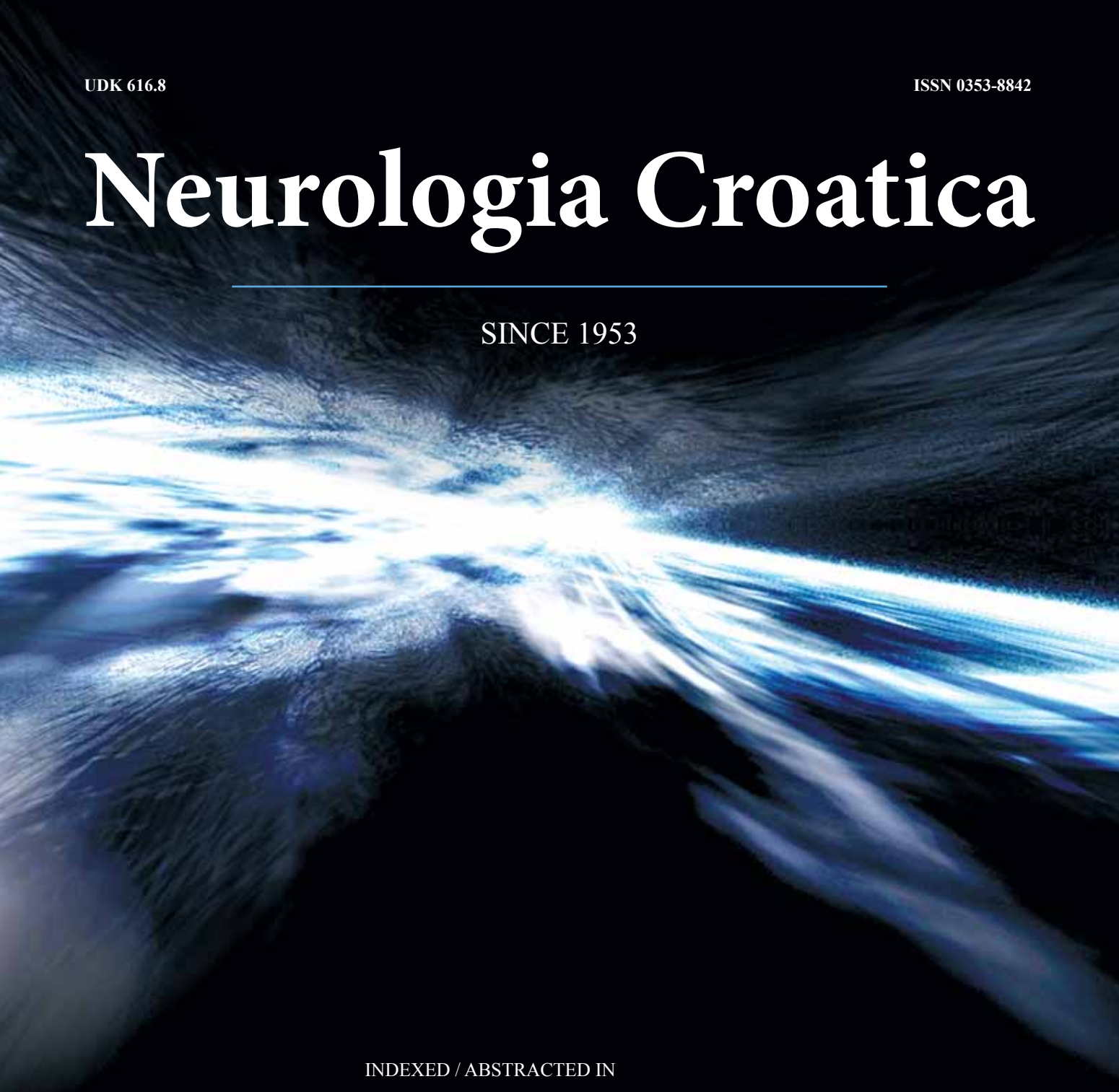

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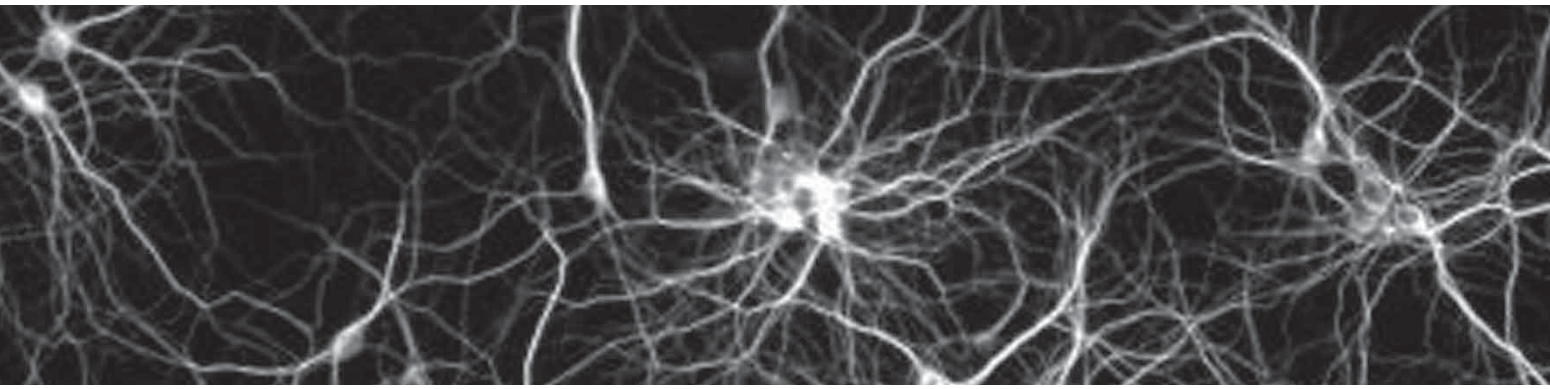


Editorial

Dear readers and colleagues,

Welcome to the second issue of Neurologia Croatica in 2014. We have finished another successful year for Neurologia Croatica in this turbulent era for medical publishing. Due to the constantly increasing costs of publishing a medical journal, many publications have opted for the open access publishing model. This model imposes a great risk for young medical doctors from the low or middle income countries and hardly any investment in science, who are unable to pay for the cost of publication. Therefore, the Editorial Board of Neurologia Croatica together with the publisher has decided to retain the diamond open access model for our journal. In this regard, we invite young medical doctors to submit preliminary results of their research and interesting case reports to our journal.

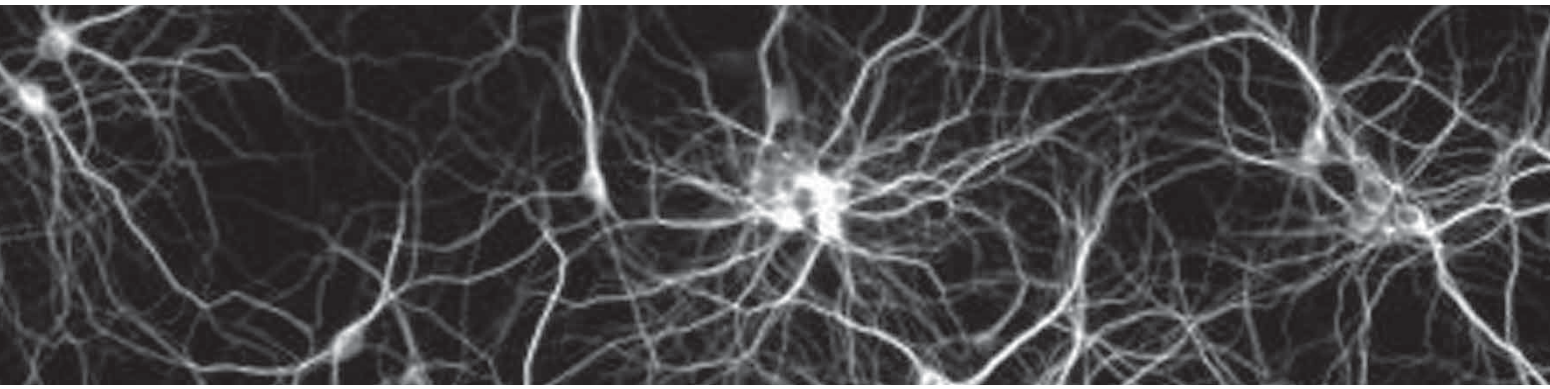
In this issue of the journal, we bring an interesting original article by Dr. Pikija and colleagues. This article shows that a high level of education, healthy diet and moderate consumption of alcohol are associated with lower odds for first-ever ischemic stroke in hospital-based case-control study performed in the Varaždin County, Croatia.

Furthermore, we present several interesting Case Reports and Images in Neurology.

We are grateful to all reviewers who completed their reviews in 2014. The quality of the journal's review process is extremely important for the success of Neurologia Croatica and the contribution of scientific expertise of our reviewers to this process is highly appreciated. A list of all reviewers who completed their review in 2014 is given at the end of this issue.

At the end, I do hope you will enjoy reading this issue and I invite you to submit your next article to Neurologia Croatica.

Mario Habek
Assistant Editor



High level of education, healthy diet and moderate consumption of alcohol are associated with lower odds for first-ever ischemic stroke in hospital based case-control study in Varaždin County, Croatia

Slaven Pikija, Anita Lukić[1], Emina Vrček[2], Branko Malojčić[3], Lucija Juvan[1], Nenad Kudelić[4], Marko Štefinšćak[4], Štefanija Kujundžić[6], Vladimir Trkulja[7]

ABSTRACT – Croatia, a Central European middle-income country, has the highest incidence of first-ever stroke in Europe. This prompted us to search for preventable and/or treatable risk factors for ischemic stroke. We performed a case-control study of first-ever ischemic stroke. Cases were patients with first-ever ischemic stroke. Controls were free from stroke and were matched to patients. All participants or their proxies were asked to fill in a questionnaire. Biometrics and laboratory values were collected. Odds ratios (ORs) were calculated for the association of stroke with selected risk factors. We enrolled 219 stroke cases from Varaždin General Hospital and 144 hospital and community controls. The risk factors significantly associated with higher odds for stroke were atrial fibrillation (OR 10.35, 95% CI 3.96-27.06) and current smoking (OR 4.53, 95% CI 1.45-14.17). Arterial hypertension was not associated with higher odds for stroke. Protective factors

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were education higher than high school (OR 0.36, 95% CI 0.15-0.89), healthy diet (OR 0.40, 95% CI 0.18-0.89), high HDL cholesterol (OR 0.14, 95% CI 0.06-0.33) and in the second model without adjustment for laboratory values alcohol intake of 1-30 drinks *per* month (OR 0.51, 95% CI 0.29-0.89). Anticoagulant therapy for atrial fibrillation, promotion of more healthy diet patterns and smoking cessation seem to be the targets for prevention of ischemic stroke in the population of Varaždin County, Croatia.

Key words: acute ischemic stroke, case-control study, risk factors, atrial fibrillation

INTRODUCTION

Stroke is the leading cause of death and disability worldwide (1,2), and low to middle income countries have the largest burden of stroke (1). There are ten risk factors associated with 90% of stroke risk (3), among them arterial hypertension, current smoking and cardiac causes found to be most relevant (3).

In our previous study, we established an unusually high incidence of stroke in the population of Varaždin County in Croatia (a Central European middle income country) compared to other European countries (4). Results from our population-based study have prompted us to seek for stroke risk factors, so we conducted this hospital based prospective case-control study of first-ever ischemic stroke in Varaždin County in order to elucidate the pattern of risk factors for ischemic stroke in our population. We believe that the results will highlight the problematic issues that we could improve and develop specific preventive strategies for lowering this unusually high burden of stroke in Varaždin County.

METHODS

We recruited consecutive patients with first-ever stroke (FES) admitted to Department of Neurology, Varaždin General Hospital (VGH) in the period from January 2010 to September 2010 (9 months). The VGH Neurology Department was the only source of stroke patients. This approach was reasonable, since in our previous study (4) we showed that virtually all stroke patients came from this source. Inclusion criteria for the case branch of the study were first-ever ischemic stroke in Varaždin County resident (VCR) confirmed by clinical examination and/or computed tomography/magnetic resonance imaging (CT/MRI) scan. In the same time window, we formed a control branch: age- and sex-matched controls (all VCRs, without prior cerebrovascular events) were recruited from departments of Internal Medicine, Urology, Neurosurgery (all in VGH), one urban general practitioner office, one rural general practitioner office, and one retirement home. In control subjects, the same questionnaire was used except for stroke-related data.

All subjects were asked to sign the informed consent form.

In the nine-month period, we recorded a total of 259 FESs: 220 (84.9%) ischemic strokes, 30 (11.6%) intracerebral hemorrhages, 7 (2.7%) subarachnoid hemorrhages, and 2 (0.8%) of unknown type.

All patients underwent standard neurologic investigative workup according to consensus guidelines (5). Neuroimaging was performed in 98.8% of patients (CT or MRI), while electrocardiography (ECG) was performed in every patient. Duplex ultrasonography (US) of neck vessels was done in 58.3% of patients (67.3% of ischemic strokes). The etiology of stroke was determined by the ASCO classification scheme (6), which categorizes strokes into four major etiologies divided by the grade of severity: A – Atherosclerosis, S – Small vessel disease, C – Cardiac source and O – Other cause. Each of these 4 categories is graded 0, 1, 2, 3 or 9, where 1 denotes definitive cause of stroke, 2 causality uncertain, and 3 disease present; 0 denotes no disease present and 9 not sufficient diagnostic workup.

The Scandinavian Stroke Scale (SSS) was performed on admission (7). Along with clinical workup, we measured height, weight, and waist circumference. Patients and/or caregivers were asked to provide comprehensive demographic and sociologic information and risk factor history: we recorded academic degree, years of education, place of residence (rural/urban), and history of standard risk factors along with year and month of the onset of exposure to the risk factor. Extensive smoking history was sought and the following variables were recorded: ever smoking, number of years smoking, current smoker, cigarettes/pipes/cigars *per* day, age when patient stopped smoking, whether patient

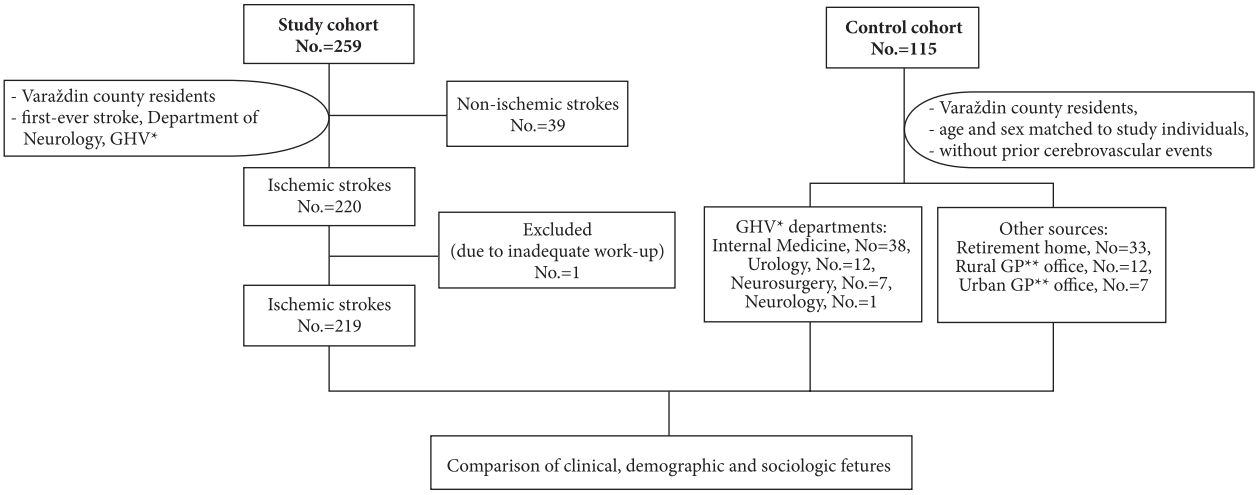

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Fig. 1. *Patient flow chart.*

stopped smoking in the last 6 months, and whether patient is willing to cease smoking (if current smoker). Also, environmental exposure to cigarette smoke (if not smoker themselves) in various settings was noted. Extensive history of diet and drinking was recorded. Specifically, we asked about drinking habits in the last year and how many drinks (white/red wine, beer and short drinks) the patient used *per* day on average. Data were categorized as "Not taking", "Less than one unit *per* day", "One to two units *per* day", "More than two and less than five units *per* day" and "More than 5 units *per* day". Recorded units were glasses in case of wine, bottles of beer, and 0.3 dL of drink for each of the short drinks. When describing dietary habits, patients were expected to report (an average) number of servings of fruit and vegetables *per* day, and usage of lard in eating habits in detail. Regarding individual eating habits, we constructed a variable "Healthy diet" that referred to consumption of more than two servings *per* day of fruit and vegetables, together with eating fried food less than once *per* week, preparing food without lard, and removing most or all of the fat from meat.

For each risk factor we calculated odds ratio (OR) and 95% confidence interval (95% CI). Univariate analysis with the usage of categorical (χ^2) test was performed. Multivariate model for stroke risk odds included age, gender, arterial hypertension, education dichotomized into high school and less and more than high school, currently smoking status, body mass index (BMI), healthy diet pattern, presence of atrial fibrillation (history and detected *de novo*), and alcohol intake (never/former *vs*. 1-30 drinks *per* month and never/former *vs*. more than 30 drinks *per* month). Variables were selected based on previously published studies that showed associations with stroke or $p<0.1$ in univariate analysis. The first model included uric acid, HDL and LDL cholesterol, while the second model was without laboratory values. Two-sided tests were used. Stata SE 11.2 was used for statistical calculations.

RESULTS

During the study period, 259 first-ever stroke patients were admitted to VGH Department of Neurology. Of them, 220 were classified as ischemic stroke, one patient had inadequate workup, and so 219 ischemic FES were left for further analysis. Control subjects were recruited from the following sources: 38 (26.4%) from VGH Internal Medicine Department, 33 (22.9%) from retirement home, 33 (22.9%) from rural general practitioner (GP) office, 20 (13.9%) from urban GP office, 12 (8.3%) from VGH Department of Urology, 7 (4.9%) from VGH Department of Neurosurgery and 1 (0.7%) from VGH Department of Neurology (see Fig. 1). Questionnaires were completed by patients or by proxy responders. At 3-month follow up, 64 (29.2%) stroke patients died.

The ASCO phenotypic classification is given in Table 1.

Lower educational background was strongly associated with the risk of stroke. Specifically, those with education less than high school had a greater risk of stroke (Table 2). The effect was most pronounced when elementary school (less than 9 years

Table 1. *Demographics and clinical characteristics of cases and controls*

	Cases (219)	*Controls (144)*
Age (yrs)	73 (68-80)	73 (65-78)
Women	122 (55.7)	78 (54.2)
ASCO classification		
A1 (large artery atherosclerotic)	23 (10.5)	-
S1 (small vessel disease)	45 (20.6)	-
C1 (cardiac causes)	88 (40.2)	-
O1 (other causes)	1 (4.6)	-
Strokes with some sign of atherosclerosis (A1, A2, A3)	122 (55.7)	-
Academic degree**		
Less than high school	140 (65.7)	74 (51.4)
High school and more	73 (34.3)	70 (48.6)
Arterial hypertension, self- reported	122 (55.7)	92 (63.9)
Currently smoking	36 (16.4)	8 (5.6)
Healthy diet‡	27 (12.3)	34 (23.6)
Atrial fibrillation, self-reported	43 (19.6)	13 (9.0)
Atrial fibrillation, self-reported and detected *de novo*	87 (39.7)	-
History of diabetes mellitus	45 (20.5)	28 (19.4)
Alcohol intake†		
Never/former	98 (44.7)	49 (34.0)
1-30 drinks *per* month	71 (32.4)	70 (48.6)
>30 drinks *per* month	36 (16.4)	15 (10.4)
Waist circumference*	100 (92-110)	100.5 (93-109)
Body mass index	27.3 (24.5-30.9)	28.9 (25.4-31.5)
Uric acid	296.5 (231.5-382.5)	332.5 (266.0-411.0)
Total cholesterol	4.87 (4.17-5.74)	5.30 (4.70-6.22)
HDL cholesterol	1.01 (0.85-1.23)	1.25 (1.1-1.47)
LDL cholesterol	3.08 (2.5-3.82)	3.20 (2.8-4.0)
Total triglycerides	1.39 (1.03-1.89)	1.47 (1.07-1.96)
Blood sugar	5.78 (5.09-7.08)	5.61 (5.1-6.67)

*Waist circumference: unknown 16 patients, 4 controls; †Alcohol intake: unknown 14 patients, 10 controls; ‡Diet pattern: unknown 16 patients, 5 controls; **Academic degree unknown 6 patients; Laboratory values unavailable in 16 patients, 30 controls.

of education) was compared with college or university degree (more than 12 years of education) and was preserved even when adjusted to all variables (Fig. 2). Also, usage of lard was consistently associated with the level of education, as lower educated people used lard more often (p=0.027).

We found no self-reported history of hypertension and/or blood pressure >160/90 mm Hg to be associated with odds for stroke.

In univariate analysis, lower HDL cholesterol was associated with a higher risk of stroke (1.35±0.51 *vs*. 1.07±0.37 mmol/L) and (unexpectedly) lower cholesterol levels (5.51±1.43 *vs*. 4.99±1.26 mmol/L) were associated with a higher risk of stroke (p<0.001 both). Smoking status, i.e. current smokers, had a significantly higher risk of stroke (Table 2). Biometric measurements showed that BMI and waist-circumference ratio were not associated with

Table 2. *Risk of stroke (multivariate analysis)*

	Odds ratio (95% CI)	*p*
Model 1 (N=265)		
Arterial hypertension, self-reported	0.53 (0.26-1.09)	0.087
Education – more than high school	0.36 (0.15-0.89)	0.027
Currently smoking	4.53 (1.45-14.17)	0.009
Body mass index	0.97 (0.91-1.04)	0.336
Healthy diet	0.40 (0.18-0.89)	0.025
Atrial fibrillation	10.35 (3.96-27.06)	0.000
Alcohol intake		
Never/former vs. 1-30 drinks per month	0.58 (0.28-1.12)	0.140
Never/former *vs*. >30 drinks *per* month	0.71 (0.24-2.03)	0.519
Uric acid	0.99 (0.99-1.00)	0.086
HDL cholesterol	0.14 (0.06-0.33)	0.000
LDL cholesterol	1.10 (0.79-1.53)	0.578
Model 2 (N=329)		
Arterial hypertension, self-reported	0.74 (0.43-1.27)	0.278
Education – more than high school	0.38 (0.19-0.72)	0.003
Currently smoking	6.29 (2.41-16.46)	0.000
Body mass index	0.98 (0.93-1.04)	0.573
Healthy diet	0.37 (0.19-0.71)	0.003
Atrial fibrillation	8.00 (3.97-16.1)	0.000
Alcohol intake		
Never/former *vs*. 1-30 drinks *per* month	0.51 (0.29-0.89)	0.019
Never/former *vs*. >30 drinks *per* month	0.82 (0.34-1.96)	0.066

Model 1: accounting for laboratory values; Model 2: without laboratory values.
All models were adjusted for age and sex.

stroke risk. The lack of association was observed across both genders.

Healthy diet was associated with a reduced risk when adjusted to other variables. Cooking with lard in univariate analysis was strongly associated with stroke risk; this association remained also when adjusted for age, sex and educational level (OR, 95% CI: 2.52, 1.59-4.00).

Diabetes mellitus was not associated with the risk of stroke. Elevated fasting blood sugar levels in univariate analysis showed an association with stroke (OR, 95% CI: 1.12, 1.01-1.25) and this association persisted after adjustment to other variables (OR, 95% CI: 1.12, 1.00-1.24).

Alcohol intake in the amount of 1-30 drinks *per* month *vs*. never (white wine most prevalent) was associated with a reduced risk of stroke in univariate analysis (OR, 95% CI: 0.53, 0.33-0.84), and that association persisted after adjustments to age, sex and educational level (OR, 95% CI: 0.51, 0.29-0.89) (Fig. 3). However, this association was no longer evident with adjustment to laboratory values.

Atrial fibrillation, self-reported or detected *de novo* in hospital, was associated with an increased risk of ischemic stroke. There were no gender differences, but individuals with atrial fibrillation were significantly older than those without it (75.5 *vs*. 69.3 years, p<0.001).

Laboratory values were available for 88.9% of controls and 98.2% of patients. Cholesterol and triglycerides were not associated with an increased stroke risk. HDL cholesterol was associated with a decreased risk of stroke.

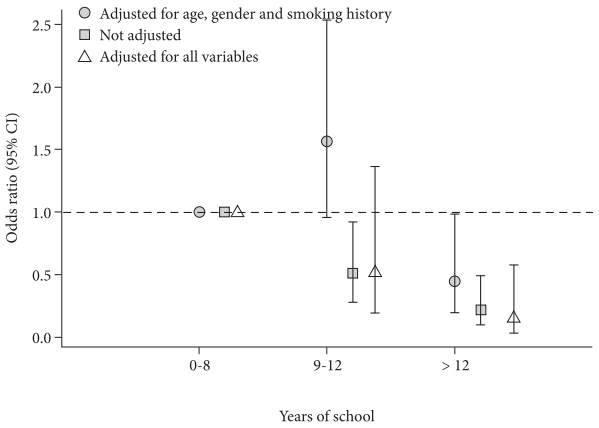

Fig. 2. *Risk of stroke associated with years of school.*

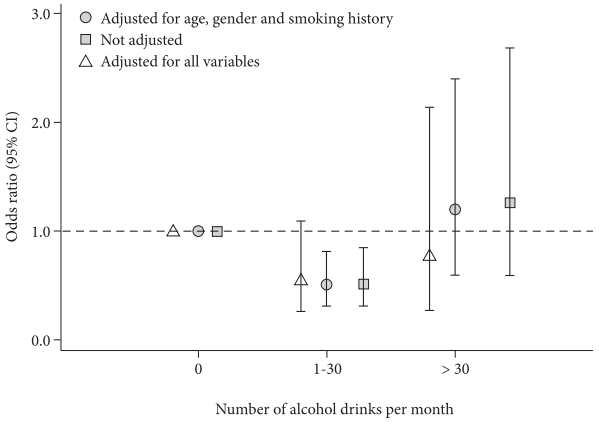

Fig. 3. *Risk of ischemic stroke associated with number of drinks per month.*

DISCUSSION

This was the first hospital-based case-control study of first-ever stroke in Croatia, a European middle-income country. The study recruited patients from a single acute stroke center in the well-defined geographical region and controls from community and hospital-based sources. We have shown that lower educational level along with some better known risk factors (such as atrial fibrillation, current smoking, HDL cholesterol and unhealthy diet) poses significant risk of stroke in our County.

Low educational attainment certainly is correlated with multiple risk factors. Ten years ago, Qureshi *et al*. showed that less than 12 years of education conferred higher odds for fatal stroke independently of other standard variables (8). In their study, this association was more pronounced in persons less than 50 years of age, while socioeconomic disparities as a risk factor for mortality decreased in advanced age (9,10). However, the results of this study showed that this may not be the case: in this study, the age of patients with FES ranged from 68 to 80, and FES was still associated with low level of education. Although we did not consider other socioeconomic factors such as occupational position, income and parental socioeconomic status, we believe that our data corroborate the notion that persons with lower educational status have greater odds for stroke.

Healthy dietary pattern consisting of high consumption of fruit and vegetables, avoidance of lard in cooking, and removing visible fat from meat, along with rare eating fried foods was demonstrated to reduce the risk of stroke. In this part of Croatia, older generations are traditionally accustomed to cooking with lard. So, we feel that stroke prevention campaigns in Varaždin County should be targeted to lowering the usage of lard in cooking, especially in the elderly.

As previously described (11,12), this study also showed moderate alcohol consumption (1-30 drinks *per* month) to be protective for stroke. Our data showed that white wine was the most frequent beverage among the people in Varaždin, while the frequencies of other beverages were too small for separate analysis. Heavy alcohol usage was not significantly associated with stroke risk, although we had a rather small sample of those patients. Since our population is rather old, we can speculate that the competing risk effect is in place in heavy alcohol group.

Compared to never smoking, current smoking and heavy smoking were associated with higher odds for stroke. Ever smoking status or status of former smoker was not associated with stroke, which is in concordance with previously published studies (3), so smoking cessation should be a mandatory agenda for stroke prevention programs.

The association of BMI and stroke is rather controversial; various studies produced different results, from positive (whether raised or lowered risk of stroke), U-shaped or negative association patterns (13-16). Biometrics, such as BMI, did not show greater odds for stroke in our study. BMI influences other risk factors such is arterial hypertension, diabetes mellitus and high cholesterol. Since none of these three risk factors showed association with stroke risk, the lack of BMI association is expected. Increased waist circumference was associated with the risk of stroke in men (13). Such a gender specific risk was not found in our study.

Atrial fibrillation, which was highly prevalent in ischemic stroke population in a previous study (4),

was also a predominant cause of stroke in our patients. Atrial fibrillation, either reported by the patients or newly detected by ECG, was present in nearly 40% of our patients, which makes the highest odds ratio of all risk factors. Such a high prevalence is in direct contradiction to recently published results showing that cardiac cause is responsible for 14% of stroke cases (3). However, a study that used ASCO classification showed that cardiac source was responsible for 36.9% of strokes (17). Since elderly people do have a higher prevalence of atrial fibrillation (18), respectable age of our population could explain such a high prevalence of atrial fibrillation among our study subjects. Furthermore, according to our results, atrial fibrillation in Varaždin County is highly unrecognized: we found 20% of previously undetected atrial fibrillation, which is more than reported in previous studies showing only 0.95% of atrial fibrillation in general population (19), 9.0% in those over 80 years of age (18), or 4.7% in population over 65 years of age. Therefore, the early (prior to stroke) detection of atrial fibrillation by routine ECG (e.g., on annual basis) and appropriate treatment, especially in elderly population, should be one of the key targets for future preventive strategies. As suggested by one study, nearly 61% of those with atrial fibrillation could benefit from some kind of anticoagulation (19). With the advent of new convenient anticoagulants, we could possibly turn the tide of atrial fibrillation associated (cardioembolic) stroke.

Unexpectedly, arterial hypertension was not associated with the risk of ischemic stroke. This is in direct contrast to the study by O'Donnell *et al*.; they found direct relationship of arterial hypertension and stroke in more than 20 countries worldwide (3). The reason for the lack of association is not clear. One of the reasons is age of the investigated population. Our case cohort was more than 10 years older than the INTERSTROKE cases (73.0 *vs*. 61.1). Since the effect of arterial hypertension is more pronounced in younger patients, it could be that we missed this relationship in our study, since patients in our study were rather old, the youngest patient being 68 years old. Moreover, in our study, there were only few (n=18, 8.2%) cases of *de novo* diagnosed arterial hypertension.

There were few limitations of this study. The number of control subjects was much lower than the number of study subjects. Furthermore, the unusual lack of stroke association with traditional risk factors of hypertension and diabetes most probably was due to the selection bias, since controls were also recruited from hospital setting with a presumably high incidence of comorbidity. Also, medical history was taken mostly from proxy respondents, but we believe that credibility of our data is similar as in other studies, since most of stroke studies recruit patients that are unable to communicate, and medical history is actually acquired by proxy. Finally, we could have done a more profound risk factor search, but the lack of funding prevented us from doing so. Therefore, we focused on the search for risk factors that are easily prevented, such as atrial fibrillation.

To conclude, we identified some risk factors, such as unhealthy diet, smoking and undetected atrial fibrillation, with a high preventive potential that could in the future lead to effective preventive strategies to reduce the high incidence of stroke in Varaždin County. Arterial hypertension and diabetes did not contribute to the higher odds for stroke in our population, most probably due to the selection bias. So, smoking, undetected atrial fibrillation and unhealthy diet are "the big three" modifiable factors for stroke.

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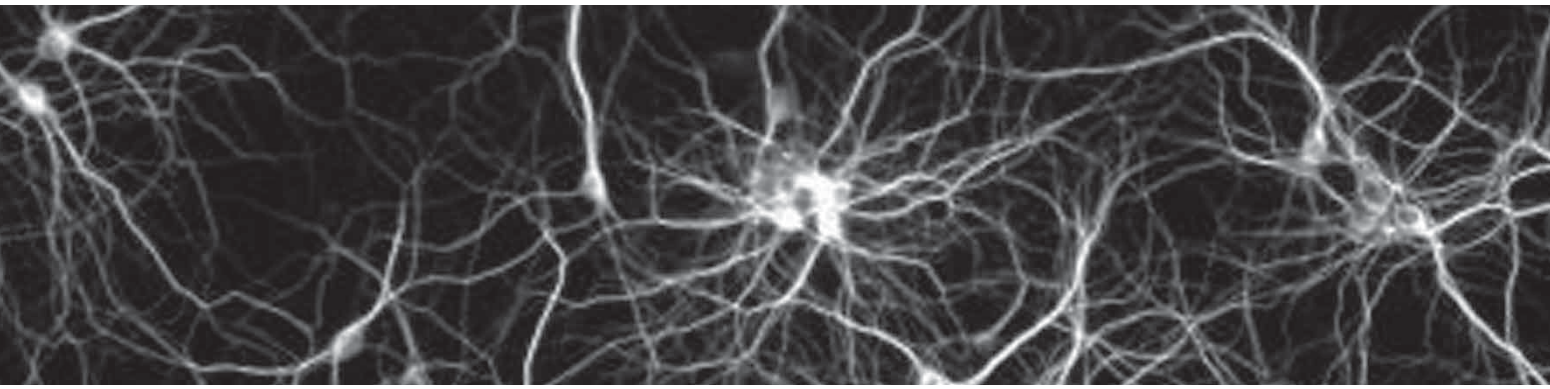
Visoka naobrazba, zdrava prehrana i umjereno pijenje alkohola povezani su s manjim izgledima za prvi ishemijski moždani udar u bolnički provedenoj kontroliranoj studiji u Varaždinskoj županiji

SAŽETAK – Hrvatska, srednjo-europska zemlja sa srednjim prihodom, ima najvišu incidenciju prvog moždanog udara u Europi. To nas je ponukalo da istražimo rizične čimbenike moždanog udara koji se mogu spriječiti i/ili liječiti. Učinili smo kontrolirano istraživanje bolesnika s prvim moždanim udarom. Kontrolni ispitanici nisu imali moždani udar i bili su podudarni s bolesnicima. Svi su ispitanici ili njihovi pomagači zamoljeni da ispune upitnik. Sakupljene su biometrijske i laboratorijske vrijednosti. Izračunate su razlike za povezanost moždanog udara s odabranim čimbenicima rizika. Uključili smo 219 slučajeva moždanog udara iz Opće bolnice Varaždin i 144 kontrolna bolnička i izvanbolnička ispitanika. Čimbenici rizika koji su bili značajno povezani s višom razinom moždanog udara bili su: atrijska fibrilacija (OR: 10,35; 95% CI 3,96-27,06) i postojeća navika pušenja (OR: 4,53; 95% CI 1,45-14,17). Arterijska hipertenzija nije bila povezana s većim izgledom za moždani udar. Zaštitni čimbenici bili su izobrazba viša od gimnazije (OR: 0,36; 95% CI 0,15-0,89), zdrava prehrana (OR: 0,40; 95% CI 0,18-0,89), visok HDL kolesterol (OR: 0,14; 95% CI 0,06-0,33) te u drugom modelu bez usklađivanja s laboratorijskim vrijednostima pijenje alkohola 1-30 pića/mjesec (OR: 0,51; 95% CI 0,29-0,89). U zaključku, čini se da su ciljevi za prevenciju ishemijskog moždanog udara u populaciji Varaždinske županije antikoagulantna terapija atrijske fibrilacije, promicanje zdravijeg načina prehrane i prestanak pušenja.

Ključne riječi: akutni ishemijski moždani udar, *case-control* studija, rizični čimbenici, atrijska fibrilacija



Diagnostic challenge of anti-GQ1b syndrome: differential diagnosis between Miller Fischer syndrome and Bickerstaff's brainstem encephalitis

Ivan Sonnenschein[1], Zoran Tomić[1], Olivio Perković[1,2], Barbara Zadković[1], Mira Bučuk[1,2]

ABSTRACT – Miller Fisher syndrome (MFS) may be considered as a rare variant of Guillain-Barré syndrome (GBS). Together with GBS, Bickerstaff's brainstem encephalitis and acute ophthalmoparesis without ataxia, MFS is in the group of anti-GQ1b syndrome disorders (anti-GQ1b Sy). Among all GBS variants, MFS is distinctive, presenting with acute symptoms of ophthalmoparesis, ataxia and areflexia, but without progressive limb weakness as the most characteristic symptom of GBS. MFS is a clinical entity based on typical clinical presentation and defined symptoms, and the finding of specific anti-GQ1b antibodies is not sufficient for MFS diagnosis. The objective of this case report is to demonstrate the diversity of anti-GQ1b Sy clinical presentation. Here we describe a case of a male patient with acute bilateral ophthalmoparesis, mydriasis and unilateral right infranuclear facial nerve palsy, in whom muscle tendon reflexes were preserved and no ataxia was present. Serum antiganglioside antibody test was positive for anti-GQ1b antibody, confirming the presupposed diagnosis of MFS. Although MFS is rare, it should be considered in patients with acute development of ophthalmoplegia. In rare cases of MFS with uncommon presentation, as it was in our case, positive serum antiganglioside antibody test will lead to the right diagnosis.

Key words: antiganglioside antibody, anti-GQ1b syndrome, Bickerstaff's encephalitis, Guillain-Barré syndrome, Miller Fisher syndrome

INTRODUCTION

Miller Fisher syndrome (MFS) is a rare acquired autoimmune polyneuropathy, a clinical variant of

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Guillain-Barré syndrome (GBS) that was described in 1956 (1). It accounts for 5%-10% of all GBS cases. Symptoms that make MFS different from other GBS variants are acute ophthalmoplegia, ataxia and areflexia, but without limb weakness. MFS is a clinical entity based on typical clinical presentation and defined symptoms and the finding of specific anti-GQ1b antibodies is not sufficient for MFS diagnosis. MFS is usually preceded by infection of gastrointestinal tract, manifesting in most cases with diarrhea. Even though not specific to MFS, anti-GQ1b antibodies are present in serum of more than 85% of patients with MFS (2,3). In 2001, Odaka coined the term anti-GQ1b syndrome (anti-GQ1b Sy) performing a large study on 194 patients (4) and proving the presence of anti-GQ1b antibody not only in MFS patients, but also in those GBS patients with ophthalmoplegia, Bickerstaff's brainstem encephalitis (BBE), acute ophthalmoparesis (AO) without ataxia, and those in whom the symptoms of MFS/GBS and BBE/GBS overlapped suggesting a common autoimmune mechanism in the pathogenesis of these illnesses. In the clinical presentation they found that every patient in whom the symptoms of MFS and GBS (MFS/GBS) and symptoms of BBE and GBS (BBE/GBS) overlapped had external ophthalmoplegia; every patient with MFS/GBS had hyporeflexia or areflexia; every patient with MFS and BBE had ataxia; 68% of the patients with MFS/GBS and 45% of those with BBE/GBS had ataxia; 91% of the patients with BBE/GBS, 67% with BBE, and 53% with AO had decreased or absent tendon reflexes. This work confirmed, clinically and by immunological findings, the close relation between MFS, GBS, BBE and AO. The course of MFS as well as that of BBE can be favorable, but it can be ameliorated with intravenous immunoglobulin (IVIG) treatment or plasmapheresis (5,6). In one reported case of severe plasmapheresis and immunoglobulin therapy resistant BBE, treatment with rituximab was applied (7).

CASE REPORT

A 19-year-old male student was admitted to our department complaining of double and blurred vision that had occurred three days prior to admission. Moderate headache and unsteadiness while walking were present during the first two days. Seven days before the onset of symptoms, he had diarrhea for one day, but otherwise his medical history was unremarkable. On neurological examination, ocular movements were impaired with prominent limitation of abduction, moderate limitation of supraduction bilaterally, and his pupils were dilated with poor reaction to light. He had no limb weakness, no sensory impairment, and his gait was normal. He was alert, no ataxia was present, his tendon reflexes were normal and the plantar response was flexor at the onset and during the course of the disease. His physical examination and blood pressure were normal. Three days after admission, he developed right infranuclear facial palsy. He could not whistle or wrinkle his forehead on the right side and he could not close his right eye. These findings after admission, normal tendon reflexes and absence of ataxia made the diagnosis of MFS uncertain.

The results of blood tests including erythrocyte sedimentation rate, blood cell count, blood glucose, liver and kidney enzyme analysis, thyroid enzyme analysis, as well as urine analysis revealed no abnormality. Testing for neurotropic viruses (herpes simplex, varicella-zoster, cytomegalovirus, Epstein-Barr virus and human immunodeficiency virus) as well as the results of Western blot analysis to exclude Lyme borreliosis were negative. Cerebrospinal fluid (CSF) analysis performed on day 7 of symptom onset demonstrated albuminocytologic dissociation with protein level up to 0.9 g/L. The analysis of antiganglioside antibody in serum was positive for anti-GQ1b antibody in the first week. Nerve conduction studies of the facial nerves showed slowing of conduction velocities on the right side with normal compound action potential amplitude and absent blink reflex on the right side and normal on the left side. Peripheral motor and sensory nerve conduction studies in the upper and lower limbs (ulnar, median, peroneal, tibial and sural nerve bilaterally) were normal, as well as F-wave studies (ulnar, peroneal and tibial nerve bilaterally). Magnetic resonance imaging of the brain was unremarkable.

According to history data, neurological examination, peripheral nerve conduction studies, results of CSF analysis, and additional result of positive antiganglioside anti-GQ1b antibodies, a variant of anti-GQ1b Sy was presupposed (probably BBE or MFS/BBE overlap) and IVIG therapy was started immediately. The patient gradually improved over the following month and achieved complete recovery within two months.

DISCUSSION

Miller Fisher syndrome is well distinguished from classical GBS by its characteristic triad of symp-

toms: ataxia, areflexia and ophthalmoplegia. Sometimes it can be difficult to differentiate MFS from BBE. BBE is considered to affect central nervous system, but decreased or absent tendon reflexes, ataxia, ophthalmoplegia as well as ptosis, mydriasis and facial palsy may be present in BBE and MFS. Albuminocytological dissociation in CSF may be present in both BBE and MFS (8). Anti-GQ1b antibodies can be seen in both of these entities (8). There are cases of BBE with atypical neurological symptoms (9). Because of the similarities in the clinical presentation of MFS and BBE, there is an opinion that they form a continuous spectrum with variable central and peripheral nervous system involvement (10). Altered sensorium in BBE, if present, can make a distinction between these two entities. Among patients with MFS, some differences in clinical presentation can be seen. Bae *et al*. report on a case of a woman with internal ophthalmoplegia as the first symptom of MFS (11). Fleury *et al*. describe five MFS patients with bilateral acute mydriasis with or without external ophthalmoplegia (12). Sometimes it can be difficult to presuppose the diagnosis of MFS when ophthalmoplegia is the sole symptom, but if ataxia and areflexia are present from the onset, or when they subsequently develop, reaching the diagnosis is much easier. In both circumstances, the nerve conduction studies and the results of CSF analysis can be very helpful, but a positive result of antiganglioside anti-GQ1b antibody test is usually needed to confirm the diagnosis. In a series of 100 patients with isolated bilateral or unilateral abducens nerve palsy, the diagnosis of atypical mild form of MFS was confirmed in 25 patients who were anti-GQ1b antibody positive (13). Our patient developed unilateral infranuclear facial nerve palsy that is not quite common presentation of MFS, and to our knowledge, it is mainly bilateral. Doo-Hyuk *et al*. describe four patients with MFS who developed facial palsy from day 8 to day 16 after initial symptom onset and from day 5 to day 9 after IVIG treatment (14).

In our case, the signs of unilateral infranuclear right facial palsy developed six days after the initial symptoms of external and internal ophthalmoplegia occurred, and before the treatment with IVIG. On neurological examination and during the disease course, neither ataxia nor areflexia were present. Cases of MFS without ataxia have been previously reported, but they are rare (15). Clinical features, the results of blink reflex analysis and the albuminocytologic dissociation in CSF led us to presume the presence of atypical MFS, which was confirmed by the positive findings of serum antiganglioside anti-GQ1b antibodies.

CONCLUSION

Both BBE and MFS are considered to form the same and continuous clinical spectrum of the anti-GQ1b Sy, as there is good evidence that both disorders have similar clinical and laboratory features. We present our case in order to emphasize the diversity of anti-GQ1b Sy clinical presentation and to stress the importance of antiganglioside antibody testing in all, but even more in atypical forms, where this testing is important to confirm the diagnosis.

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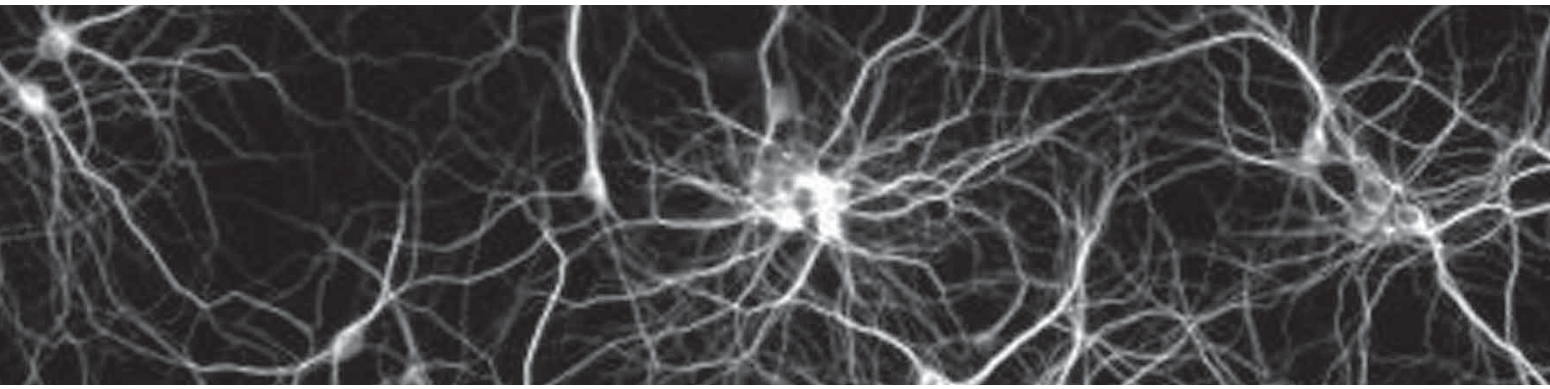
Dijagnostički izazov sindroma anti-GQ1b: diferencijalna dijagnoza između Miller-Fischerova sindroma i Bickerstaffova encefalitisa moždanog debla

SAŽETAK – Miller Fisherov sindrom (MFS) može se smatrati rijetkom varijantom Guillain-Barréova sindroma (GBS). MFS, zajedno s GBS, Bickerstaffovim encefalitisom moždanog debla (BBE) i akutnom oftalmoparezom (AO) bez ataksije, pripada skupini poremećaja unutar anti-GQ1b sindroma (anti-GQ1b Sy). Između svih varijanta GBS, MFS se manifestira na specifičan način akutnim razvojem oftalmoplegije, ataksije i arefleksije, no bez progresivne slabosti mišića ekstremiteta kao karakterističnog znaka GBS. MFS je klinički entitet temeljen na tipičnoj kliničkoj slici i određenim simptomima, no nalaz specifičnih anti-GQ1b protutijela nije dovoljan za dijagnozu MFS. Cilj je ovoga članka prikazati različitosti kliničke prezentacije anti-GQ1b sindroma. Opisujemo slučaj bolesnika s naglim razvojem obostrane oftalmoplegije, midrijaze i unilateralne desnostrane infranuklearne pareze ličnog živca, bez ataksije te urednih miotatskih refleksa. S obzirom na kliničku sliku i razvoj simptoma postavljena je sumnja na MFS, što je potvrđeno i pozitivnim nalazom serumskih anti-GQ1b protutijela. U zaključku, premda se rijetko pojavljuje, na MFS treba pomisliti u diferencijalnoj dijagnozi kod bolesnika s naglim razvojem oftalmoplegije. U rijetkim slučajevima neuobičajene prezentacije MFS-a, kao u našem slučaju, pozitivan nalaz antigangliozidnih protutijela omogućava postavljanje točne dijagnoze.

Ključne riječi: antigangliozidna protutijela, anti-GQ1b sindrom, Bickerstaffov encefalitis, Guillain-Barréov sindrom, Miller Fisherov sindrom



Two cases of polyneuropathy, microcytic anemia and copper deficiency after prolonged allopurinol treatment

Ervina Bilić, Matea Deliu, Ernest Bilić[1], Denis Čerimagić[2], Marija Žagar

ABSTRACT – Copper is a cofactor for numerous coenzymes and metalloproteins essential for normal neurologic function. The most common neurological presentations of copper deficiency are myelopathy, polyneuropathy and optic neuropathy. Here we present two cases of sensorimotor polyneuropathy, copper deficiency and microcytic anemia in conjunction with allopurinol management for gout. These two patients presented with a clinical description similar to that of chronic idiopathic axonal polyneuropathy. It would be advisable to determine the levels of trace elements in patients with polyneuropathy of unknown cause. We believe that further studies are necessary in order to gain better understanding of the role of copper serum levels in the development of sensorimotor polyneuropathy.

Key words: allopurinol, copper deficiency, polyneuropathy.

INTRODUCTION

Copper is a trace element essential for proper functioning of all living organisms. Common etiologies of copper deficiency include dietary inadequacy, Menkes disease, previous upper gastrointestinal surgery, zinc overload from denture cream or zinc supplements, malabsorption, and drug-induced deficiency (1). The most common neurological presentations are myelopathy, neuropathy and optic neuropathy (2). Allopurinol, considered to be the prototypical xanthine oxidase inhibitor, continues to be the basis of the clinical management of hyperuricemia. Although there are a few articles describing allopurinol-induced neuropathy (3-5), there have been no studies published on copper deficiency and microcytic anemia in the presence of allopurinol-induced neuropathy.

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CASE REPORTS

Two patients were admitted to the Department of Neurology with almost identical symptoms and laboratory results. Patient 1, a 57-year-old male, was admitted due to chronic paresthesia and numbness in his feet that he described as a 'pins-and-needles' sensation. Patient 2, a 68-year-old female, was admitted due to gait disturbance and paresthesia in her extremities. Upon clinical neurological examination, disturbance in touch, vibration, pain, and temperature sensation was observed in both patients. While patient 2 had absent triceps reflexes and attenuated quadriceps reflexes (1+), patient 1 had bilaterally attenuated triceps reflexes.

Nerve conduction studies (NCS) showed significantly decreased compound muscle action potentials (CMAP) and sensory nerve action potentials (SNAP) amplitudes in all nerves with mild reduction in conduction velocity of sensory and motor fibers of nerves in the legs. Motor unit recruitment in electromyography (EMG) indicated distal symmetrical neurogenic pathology with no spontaneous activity. Quantitative sensory testing (QST) showed moderate and significant elevations of the threshold for pain, cold, heat and vibration as a possible sign of C, A delta and A beta fiber affection. According to EMG, NCS and QST, the diagnosis of sensorimotor polyneuropathy with predominant axonal damage was established in both patients.

Routine laboratory tests showed microcytic anemia with normal iron and serum ferritin levels, but with a decrease in copper levels (2 μmol/L in patient 1 and 4 μmol/L in patient 2; NV: 12-25). The mean corpuscular volume (MCV) was decreased in both patients (72 fL in patient 1 and 75 fL in patient 2; NV: 86-98 fL), hemoglobin value (Hb) was 107 g/L in patient 1 and 110 g/L in patient 2 (NV: women 120-155 g/L, NV: men 135-165 g/L). All laboratory results important for polyneuropathy evaluation were normal in both patients: HbA1c, homocysteine, vitamin B12, folic acid, vitamin E, iron, lead, zinc, anti Hu, Yo, Ri antibodies, paraneoplastic markers, antiganglioside antibodies, erythrocyte sedimentation rate, lipids, immunological parameters, urine and serum proteins analyses. Molecular genetic analysis of PMP 22 (peripheral myelin protein) deletion and mutation was negative. Serologic analyses for cytomegalovirus, herpes viruses, Epstein-Barr virus, varicella zoster virus, hepatitis B and C viruses showed no signs of recent infection. Serologic analyses for *Borrelia burgdorferi* were negative. Our patients did not have any phenotypic markers of Menkes disease, while ceruloplasmin plasma levels and electrophoresis of hemoglobin were normal. The findings of cerebrospinal fluid (CSF) analyses were normal. CSF analysis was performed in order to exclude sensorimotor type of chronic inflammatory demyelinating polyneuropathy (CIDP). Magnetic resonance imaging of the brain and cervical and thoracic medulla showed no alterations.

Both patients were continuously monitored for gout. Patient 1 had a 10-year history of the disease and was maintained on a regimen of allopurinol (600 mg daily). Patient 2 was monitored for 6 years on a 400 mg daily dose of allopurinol. Patient 1 had a five-year history of neuropathy signs and patient 2 had a two-year history of neuropathy. Signs of neuropathy were present in both patients after the introduction of allopurinol.

Following the diagnosis of copper deficiency, both patients were further treated over a period of two and four years, respectively, and mild gradual improvement of neurological symptoms (paresthesia, numbness, and gait disturbance) was noted after continuous copper administration (2 mg *per* day). Copper levels were checked in both patients every three months. In patient 1, the level of copper normalized after 3 months and in patient 2 after 6 months of supplementation therapy. Follow up EMG and NCS were performed but no significant improvement was detected. It is not expected to find impressive improvement in electroneurographic parameters in axonal polyneuropathies because the reduction of CMAP and SNAP amplitude is usually the consequence of irreversible axonal damage. In both patients, we found moderate improvement in QST, especially in vibration sense, as a possible indicator of A beta fiber functional improvement. The dose of allopurinol was not changed during the period of copper supplementation and uric acid levels were normal. MCV and Hb values normalized in both patients during copper supplementation.

A written informed consent was obtained from the patients for publication of this case report.

DISCUSSION

Here we present for the first time two cases of sensorimotor polyneuropathy, copper deficiency and microcytic anemia in conjunction with allopurinol management for gout. These two patients presented with a clinical description similar to that of chronic idiopathic axonal polyneuropathy (CIAP)

(6). CIAP typically manifests in the sixth decade of life and is characterized by a normally symmetrical and insidious onset of mainly sensorimotor (or purely sensory) dysfunction in the legs (7). CIAP tends to progress slowly and will never lead to severe disability.

Several studies have attempted to demonstrate an association between dyslipidemia and impaired glucose tolerance with the signs and symptoms of CIAP. Other factors (alcohol, autoantibodies to axonal antigens, and family history) have also been found to potentially contribute to the development of neuropathy (6). However, all of these potential contributors were absent in our patients. A decreased concentration of serum copper was documented. Furthermore, both patients were on allopurinol treatment for their gout.

Copper is a cofactor for numerous coenzymes and metalloproteins essential for normal neurologic function. Copper levels normalize with replacement therapy but neurologic recovery may be incomplete or absent if treatment is delayed (8). Copper deficiency is an under-recognized cause of reversible leukopenia and refractory anemia that is unresponsive to iron therapy, sometimes found with hypoferremia, and often misdiagnosed as myelodysplastic syndrome (9). Copper acts as a ligand to ferroxidase II, which oxidizes iron, allowing it to be mobilized and transported from hepatic stores to the bone marrow for use in erythropoiesis.

Experimental studies have demonstrated that oxidative stress induces damage to the peripheral nervous system (10). Singer *et al*. have proposed a connection between elevated levels of reactive oxygen species (ROS) and the underwhelming response of cellular antioxidant systems, suggesting that increased ROS damages peripheral nerves while interfering with injury repair (11). Indeed, we can conclude that low levels of Cu and Zn-SOD contribute to the lack of proper antioxidant response in copper deficiency states.

Allopurinol directly decreases the production of uric acid by inhibiting the enzyme xanthine oxidase, and is thus very effective in the prophylactic treatment of gout. Further benefits are the reduction of superoxide anions and other ROS (12).

Only one study attempting to explain the possible connection between the administration of allopurinol and copper deficiency or CIAP has been published. Fields *et al*. fed rats a high-fructose diet inducing hyperuricemia and hyperuricosuria. An overload of uric acid causes an increase in the activity of xanthine oxidase, which catalyzes the oxidation of hypoxanthine and xanthine to uric acid and, in the process, generates ROS (13). Hyperuricemia causes a reduction in the activity of GSH-Px (glutathione peroxidase) and, combined with copper deficiency, causes greater reduction in GSH-Px (14). However, these effects are meant to be ameliorated with the administration of allopurinol, thus allowing us to conclude either that allopurinol has no contributive effect on the symptoms displayed by our patients, or that the gout was not fully controlled. Our patients' polyneuropathic symptoms improved upon the administration of copper. Additional studies are needed to understand the pathophysiology of CIAP in relation to copper deficiency and increased oxidative stress. We could not say with any degree of certainty whether the neuropathy cases presented are the result of long-term allopurinol treatment or consequent copper deficiency.

CONCLUSION

This case report illustrates the importance of comorbidity of other chronic diseases in patients with diagnosed CIAP. Before making the diagnosis of CIAP, it is important to analyze the possible pathophysiological mechanisms shared with other chronic diseases but also the possible influence of various drugs and therapeutic procedures which may have negative influence on peripheral nerves. The pathophysiology of copper deficiency (or a deficiency of other trace elements) has an important role in the processes of neurodegeneration. It would be advisable to determine the levels of trace elements in patients with polyneuropathy of unknown cause. We believe that further studies are necessary in order to gain better understanding of the role of copper serum levels in the development of sensorimotor polyneuropathy.

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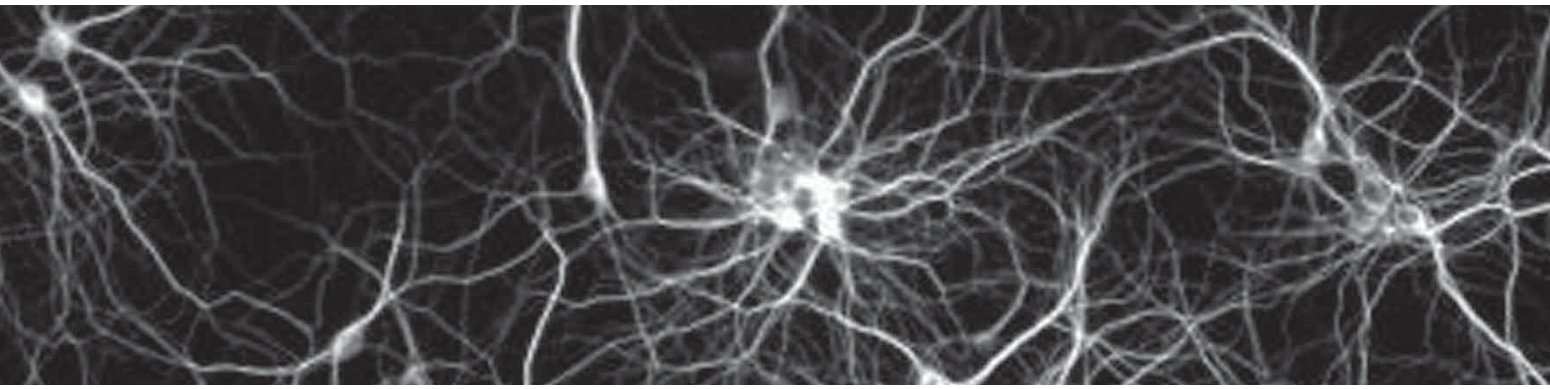
Dva slučaja polineuropatije, mikrocitne anemije i nedostatka bakra nakon produljene terapije alopurinolom

SAŽETAK - Bakar je dodatni faktor za brojne koenzime i metaloproteine koji su bitni za neurološku funkciju. Najčešće neurološke slike pomanjkanja bakra su mijelopatija, polineuropatija, manjak bakra i mikrocitna anemija povezano s liječenjem alopurinolom zbog gušavosti. Ova dva bolesnika su se očitovala kliničkom slikom sličnom onoj kronične idiopatske aksonalne polineuropatije. Bolesnicima s polineuropatijom nepoznatog uzroka trebalo bi savjetovati određivanje razina elemenata u tragovima. Smatramo da su potrebna daljnja istraživanja u cilju boljeg razumijevanja uloge razina serumskog bakra u razvoju senzomotorne polineuropatije.

Ključne riječi: alopurinol, nedostatak bakra, polineuropatija



Upbeat nystagmus due to medullary lesion: case report and literature review

Luka Crnošija[1], Ivan Adamec[2], Nataša Klepac[1,2], Fran Borovečki[1,2], David Ozretić[3], Mario Habek[1,2]

ABSTRACT – Upbeat nystagmus (UBN) occurs as a consequence of disturbance in the cerebello-brainstem network responsible for the control of vertical gaze stability. Lesions responsible for UBN can be found from thalamus to caudal medulla, but are predominantly located in pons or medulla. Over the last 40 years, there have been a relatively small number of reports on patients with UBN resulting from magnetic resonance imaging, computed tomography or pathologically confirmed lesion in medulla oblongata. We report on a patient with UBN as a consequence of demyelinating lesion in medulla oblongata and review all reported cases of this clinico-anatomical association. A more detailed clinical and paraclinical approach to every patient with UBN could possibly provide us with enough information to complete this functional anatomy puzzle.

Key words: upbeat nystagmus, medulla oblongata

INTRODUCTION

Although there have been a number of reports on upbeat nystagmus (UBN), its pathophysiological mechanism still needs to be elucidated. We report on a patient with UBN as a consequence of demyelinating lesion in medulla oblongata and review all reported cases of this clinico-anatomical association.

CASE REPORT

A 53-year-old woman was admitted to our neurology department because of vertigo and unsteady gait. The symptoms started a day before admission, and were constant. The patient vomited three times that day. During neurological examination, primary position upbeat nystagmus (supplementary video) and mild left-sided dysmetria were noted. The

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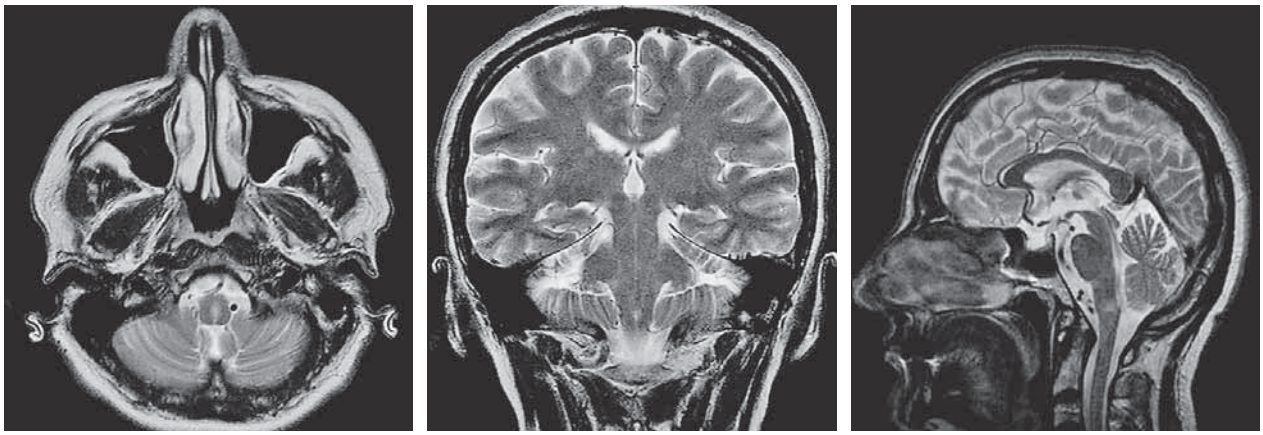

Fig. 1. *Brain MRI: (a) transverse, (b) coronal, and (c) sagittal sections showing demyelinating lesion in medulla oblongata.*

gait was atactic and tandem walk could be performed only with assistance. She reported a sense of tingling in both arms and legs, spreading from distal to proximal portions of extremities. The remaining neurological examination was normal. The patient had elevated blood pressure and heart arrhythmia controlled by a cardiologist. For the past 15 years, she had also suffered from chronic bilateral lumbosacral radiculopathy. Magnetic resonance imaging (MRI) revealed multiple supratentorial periventricular and subcortical demyelinating lesions and one lesion in the central part of medulla oblongata without postcontrast enhancement (Fig. 1).

Cerebrospinal fluid analysis (CSF) showed normal cell count, protein and glucose levels with positive oligoclonal bands only in the CSF. Vestibular-evoked myogenic potentials (VEMP) showed decreased amplitude of myogenic response in both sternocleidomastoid muscles (SCM) and abnormal morphology of the response only in right SCM. Prolonged P13 latency was recorded in right extraocular muscles. Considering clinical presentation and diagnostic tests, the patient was diagnosed with multiple sclerosis. She received intravenous methylprednisolone and Lioresal therapy, on which the neurological symptoms subsided. She was discharged from the hospital nine days after admission.

DISCUSSION

The main concept is that disturbances in the cerebello-brainstem network responsible for the control of vertical gaze stability produce instability resulting in UBN. Structures that could be affected are vertical gaze neural integrator, vertical vestibulo-ocular reflex pathways, or vertical smooth pursuit system (1). Lesions responsible for UBN can be found from thalamus to caudal medulla (2), but are predominantly located in pons or medulla (1,2). Kim *et al*. (2) divided medullary lesions into lateral, medial and lower (or caudal) groups. Lateral lesions may affect vestibular nuclei producing various types of spontaneous nystagmus and medial lesions could encompass decussating fibers of medial longitudinal fasciculus (MLF) in rostral medulla leading to UBN. Caudal medulla comprises perihypoglossal nuclei, nucleus of Roller (NR) and nucleus intercalatus of Staderini (NI), one of which is thought to act as vertical position-to-velocity neural integrator, and nucleus prepositus hypoglossi (1-3). Work by some authors (1,4) provides arguments suggesting that NR is a better candidate for the role of neural integrator. Pierrot-Deseilligny *et al*. (1) have described a possible feedback loop in detail. The following description is a simplified one. In essence, NR (or NI) receives excitatory projections from superior vestibular nuclei (SVN) and projects to the flocculus *via* a probably inhibitory pathway. SVN receives inhibitory projections from flocculus and the loop is completed. SVN transmits excitatory signals to 3rd nerve motor nucleus leading to upward eye deviation. Thus, any lesion affecting NR or its afferent or efferent projections would produce slow downward deviation of the eye, due to relative hypoactivity of the upward gaze system in respect to downward system, followed by corrective fast upward motion producing UBN. In our patient, the lesion located in central medulla may have affected afferent and/or efferent projections of neural integrator (or the neural integrator itself) resulting in UBN. Over the last 40 years, there have been a relatively small number of reports on patients with UBN resulting

Table 1. *List of reports on patients with upbeat nystagmus and MRI, CT or neuropathologic confirmation of medullary lesion*

Authors (ref. no.)	*Lesion location*	*Possibly affected structures*
Tilikete *et al*. 2002 (5)	Caudal medulla - right paramedian part	-
Pierrot-Deseilligny *et al*. 2007 (25)	Caudal medulla - dorsal paramedian part	NI, NR, nucleus paraphales
Saito *et al*. 2010 (6)	Dorsal medulla	NI
Hojin Choi *et al*. 2011 (7)	Dorsal medulla	NI, perihypoglossal nuclei
Hirose *et al*. 1998 (3)	Unilateral medial medullary lesion	NI
Munro *et al*. 1993 (12)	Left central part of medulla	NI
Roh and Lee 1996 (8)	Bilateral medial lesion in rostral medullary tegmentum	-
Adamec *et al*. 2011 (9)	Caudal medulla	NI
Janssen *et al*. 1998 (10)	Caudal medulla - dorsal paramedian part	NI
Rousseaux *et al*. 1991 (11)	Postero-medial part of medulla	NI, nuclei prepositi hypoglossi
Kim *et al*. 2006 (2)	Two patients with lateral medulla lesion, four with medial medulla lesions, and two with lower medulla lesions	-
Kim *et al*. 2012 (13)	Caudal dorsomedial medulla	NI, NR
Choi *et al*. 2004 (14)	Rostral paramedian medulla	Crossing pathways from the bilateral anterior semicircular canal
Larner *et al*. 1998 (4)	Caudal medulla - dorsal paramedian part	NI
Hendrix *et al*. 1992 (15)	Chiari-I malformation	-
Chait and Barber 1979 (16)	Chiari-I malformation	-
Kumar *et al*. 2002 (17)	Chiari-I malformation (4 patients)	-
Kanaya *et al*. 1994 (18)	Postero-medial part of medulla	Nuclei prepositi hypoglossi
Lee *et al*. 1992 (19)	Paramedian medulla	-
Kim *et al*. 1995 (20)	Two patients with medial medullary infarction	-
Ohkoshi *et al*. 1998* (21)	Caudal medulla	Demyelinating lesions in white matter surrounding the hypoglossal nuclei, NI, and MLF
Gilman *et al*. 1977* (22)	-	Low grade cellular astrocytoma infiltrating MLF bilaterally, nuclei prepositi hypoglossi and all vestibular nuclei
Keane *et al*. 1987* (23)	Patient 1 - symmetric destruction of midline medullary structures Patient 2 - medial medulla	Patient 1 - NR, NI, MLF bilaterally Patient 2 - NR, MLF bilaterally
Elliott *et al*. 1989 (24)	Four medulloblastoma survivors	-

NI, nucleus intercalatus of Staderini; NR, nucleus of Roller; MLF, medial longitudinal fasciculus;
*denotes neuropathological studies

from MRI, computed tomography, or pathologically confirmed lesion in medulla oblongata. Table 1 summarizes data from these reports.

A more detailed clinical and paraclinical approach to every patient with UBN may provide us with enough information to complete this functional anatomy puzzle.

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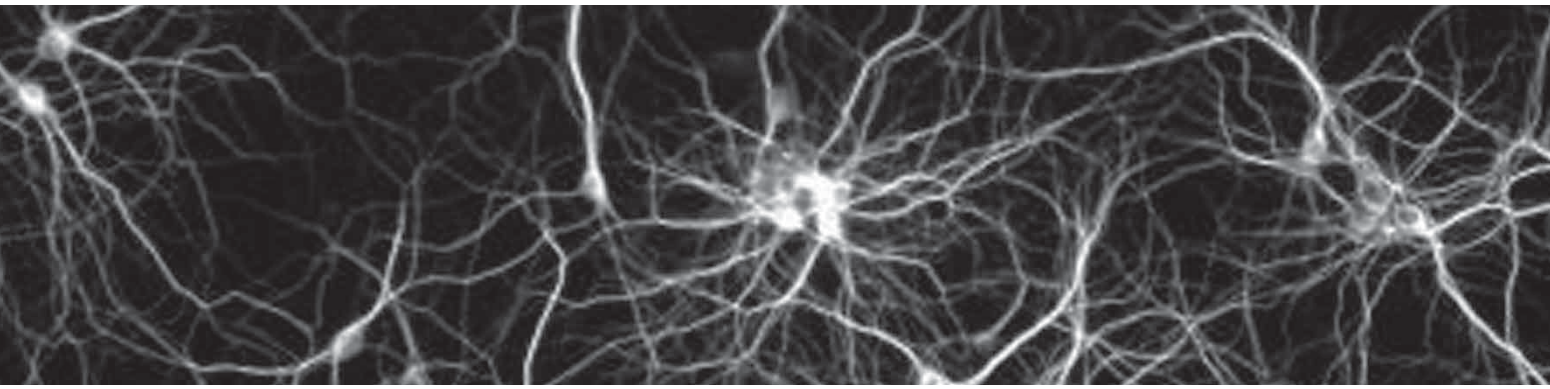
Upbeat nistagmus uzrokovan medularnom lezijom: prikaz bolesnika i pregled literature

SAŽETAK – *Upbeat* nistagmus (UBN) se javlja kao posljedica ustroja malog mozga i moždanog stabla odgovornog za kontrolu stabiliteta vertikalnog pogleda. Lezije koje dovode do UBN mogu se naći od talamusa do kaudalne medule, ali su pretežito smještene u ponsu ili meduli. Unazad zadnjih 40 godina relativno se malo izvještavalo o bolesnicima s UBN otkrivenog pomoću MRI, CT ili patološki potvrđenom lezijom u produženoj moždini. Prikazuje se bolesnik s UBN kao posljedicom demijelinizacijske lezije u produženoj moždini uz pregled svih objavljenih slučajeva ove kliničko-anatomske povezanosti. Pomniji klinički i paraklinički pristup svakom bolesniku s UBN mogao bi dati dovoljno podataka da se odgonetne ova funkcionalna anatomska zagonetka.

Ključne riječi: *upbeat* nistagmus, produžena moždina



Spontaneous intracranial hypotension

Denis Čerimagić, Ervina Bilić[1]

A 55-old-female was admitted to the Department of Neurology because of diffuse headache, tinnitus in the right ear, stiff neck and vomiting, persisting for one month with various intensity. Magnetic resonance imaging (MRI) of the brain showed a smooth uniform pachymeningeal uptake of contrast (Fig. 1) and subdural collection of fluid (Fig. 2). Cerebrospinal fluid (CSF) analysis showed mild lymphocytic pleocytosis (34/3) and elevated protein level (1.44 g/L). Based on the results of these findings, the diagnosis of spontaneous intracranial hypotension (SIH) was established. The incidence of SIH is about 5 *per* 100 000 population. This syndrome is a result of CSF leakage due to a tear in the dura, most frequently where spinal roots leave the subarachnoid space. Even trivial trauma of the cer-

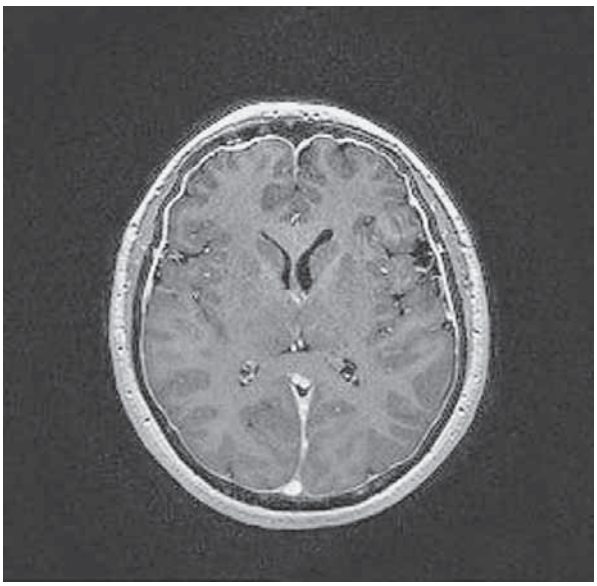


Fig. 1. *Axial contrast enhanced T1-weighted MRI shows diffuse bilateral meningeal enhancement.*

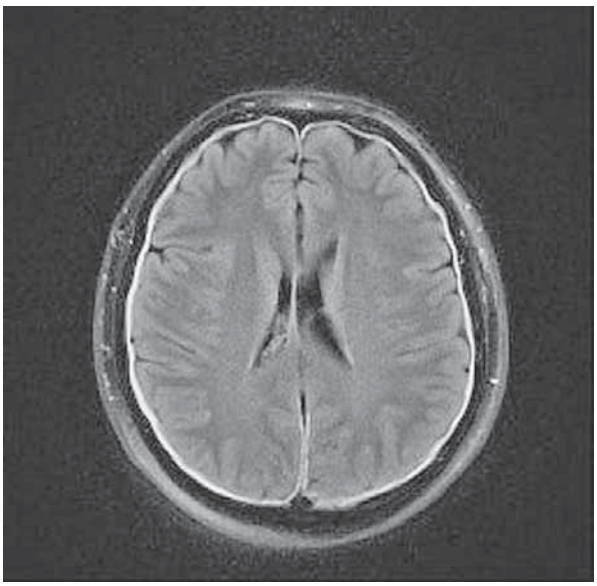


Fig. 2. *Axial FLAIR MRI shows mild diffuse bilateral thin layer of subdural effusion.*

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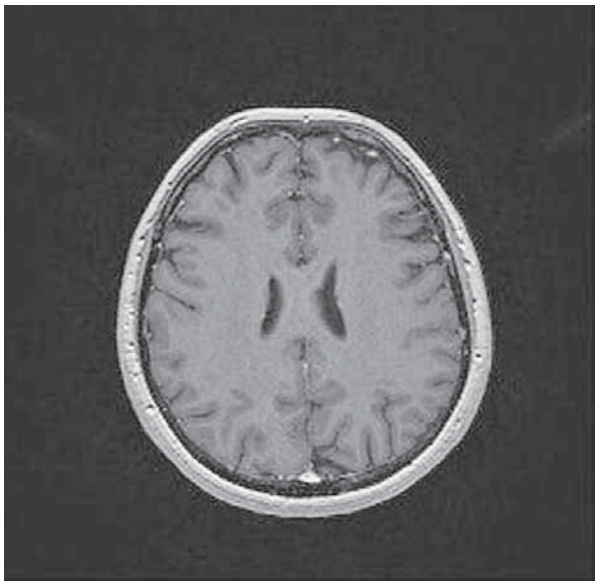

Fig. 3. *Control axial contrast enhanced T1-weighted MRI shows normal findings.*

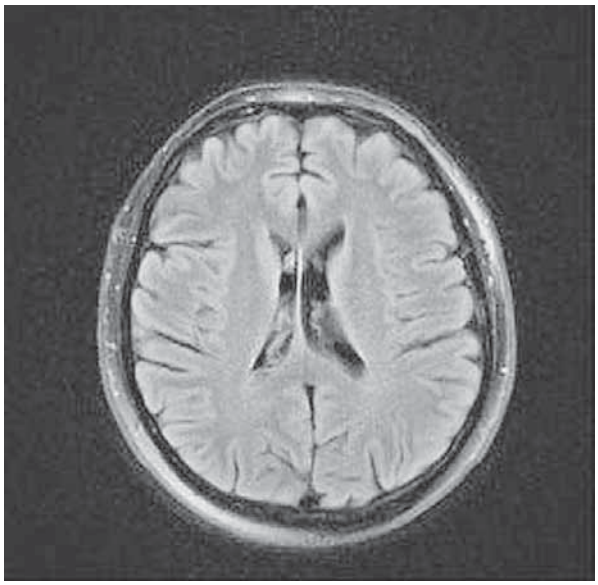

Fig. 4. *Control axial FLAIR MRI shows normal findings.*

vical spine may precipitate intracranial hypotension. If this does not heal with bed rest, an epidural blood patch or percutaneous injection of fibrin glue may be applied. Our patient was treated conservatively and there was complete regression of clinical symptoms and improvement of MRI findings after 4 months (Figs. 3 and 4). Since the introduction of MRI in the diagnostics of headache, SIH has been increasingly diagnosed as an uncommon cause of headache.

R E F E R E N C E

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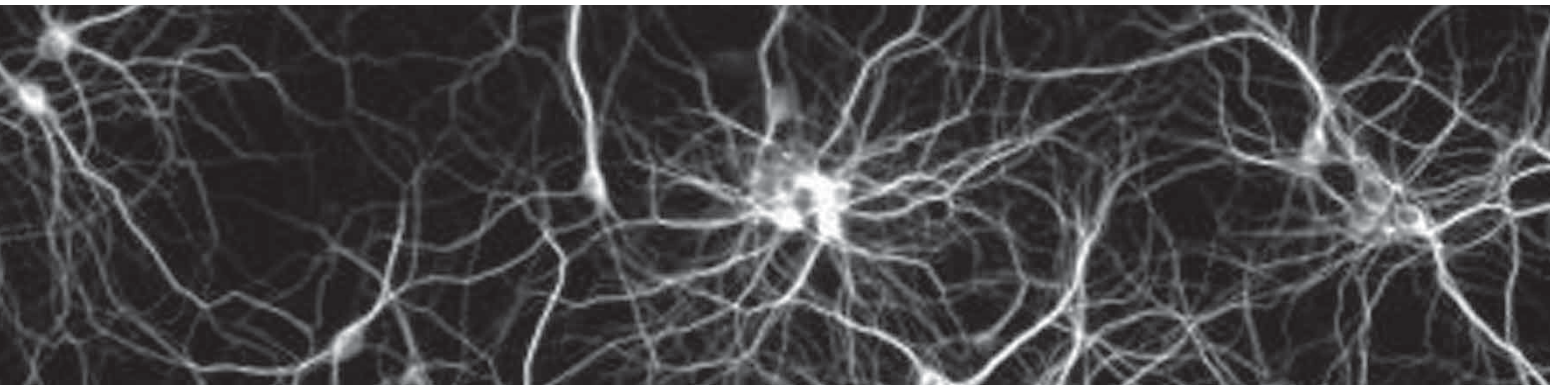
Key words: intracranial hypotension – diagnosis, magnetic resonance imaging, headache –etiology



Old calcified bilateral subdural hematoma in a patient after head trauma

Radek Kaiser, Pavel Haninec[1]

A 50-year-old man was admitted to the neurosurgical department with head trauma resulting from a fall onto pavement. Initial Glasgow Coma Scale (GCS) was 12; he was confused with retrograde amnesia. Except for ataxia, the neurological status of cranial nerves and limbs was normal. A lacera-

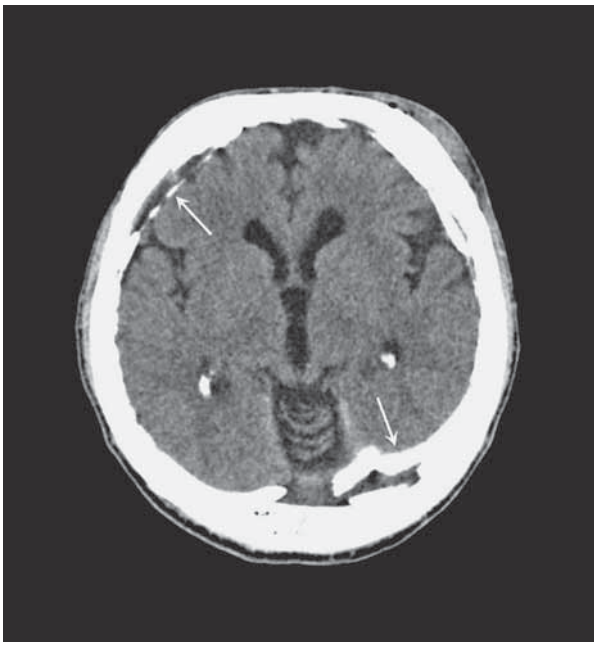


Fig. 1. *Transverse CT scan: the initial interpretation was bilateral acute subdural hematoma (arrows).*

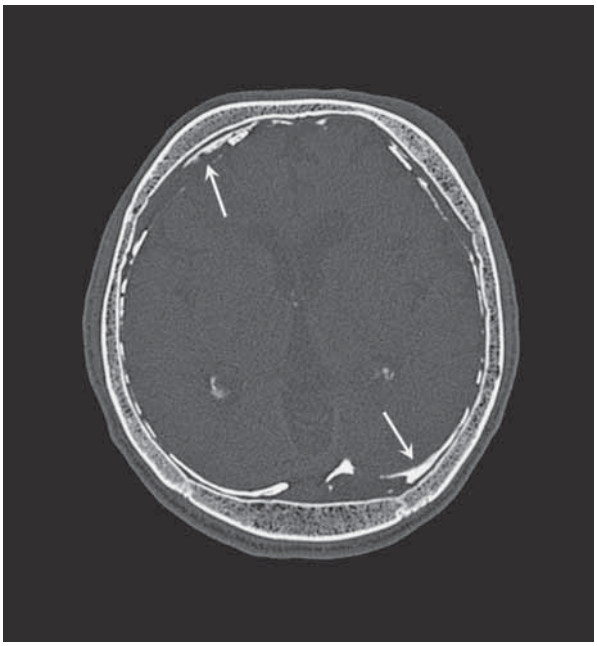


Fig. 2. *CT scan – bone window: calcifications were confirmed on bone window, where the density of hyperdense areas corresponded to bone (≈1900 Hounsfield units) (arrows).*

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tion on the left eyebrow was sutured. Blood alcohol was 0.283 g/dL. Due to his confusion and intoxicated status, a computed tomography (CT) scan was performed. The initial interpretation was bilateral acute subdural hematoma (Fig. 1). Further examination revealed an atypical appearance and unusual distribution of hyperdense areas in subdural space. Calcifications were confirmed on the bone window, where the density of hyperdense areas corresponded to bone (≈1900 Hounsfield units) (Fig. 2). CT scan revealed an old calcified bilateral subdural hematoma, which has generally good prognosis (1,2). Surgery was not indicated. Once sober, the patient denied a cranial trauma history. He was discharged home after 24-hour observation.

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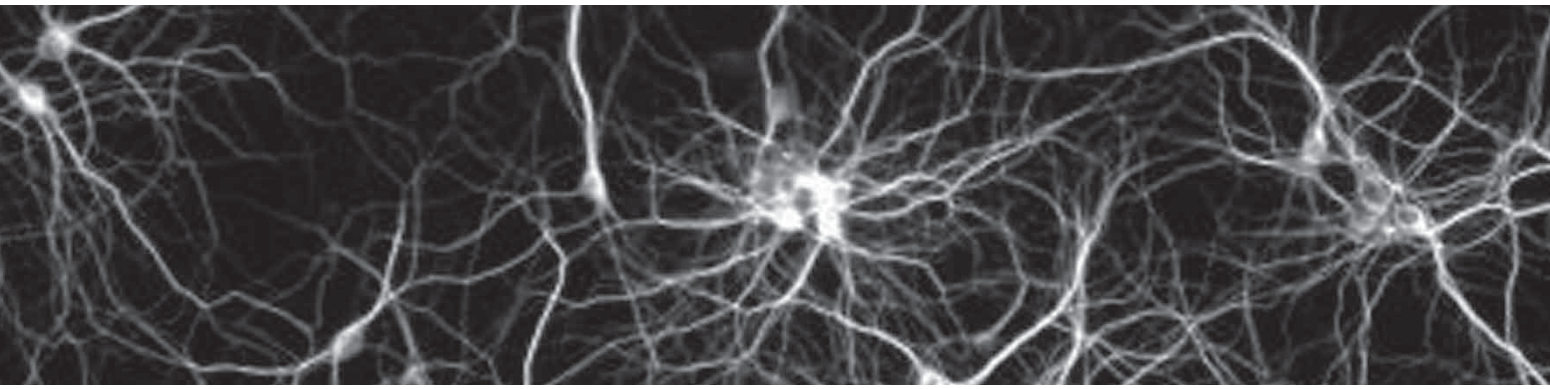

'Wine-glass' sign

Danira Bažadona, Katarina Blažina, Vladimir Miletić

A 56-year-old woman presented with a nine-month history of rapidly progressive limb weakness. Initial examination revealed spastic tetraparesis, dysarthria and dysphagia. Clinical and electrophysiological signs of lower motor neuron (LMN) affection were absent. Brain magnetic resonance imaging (MRI) demonstrated 'wine-glass' sign with symmetrical hyperintensities on T2 and FLAIR sequences, extending along the corticospinal tracts reaching the pontine level (Fig. 1). Immunological panel, onconeural antibodies (Hu, Yo, Ri), very long chain fatty acids, and ganglioside antibodies were all normal. Four months after discharge, the patient underwent control electromyography showing denervation and LMN affection. Six months later, the patient died. According to

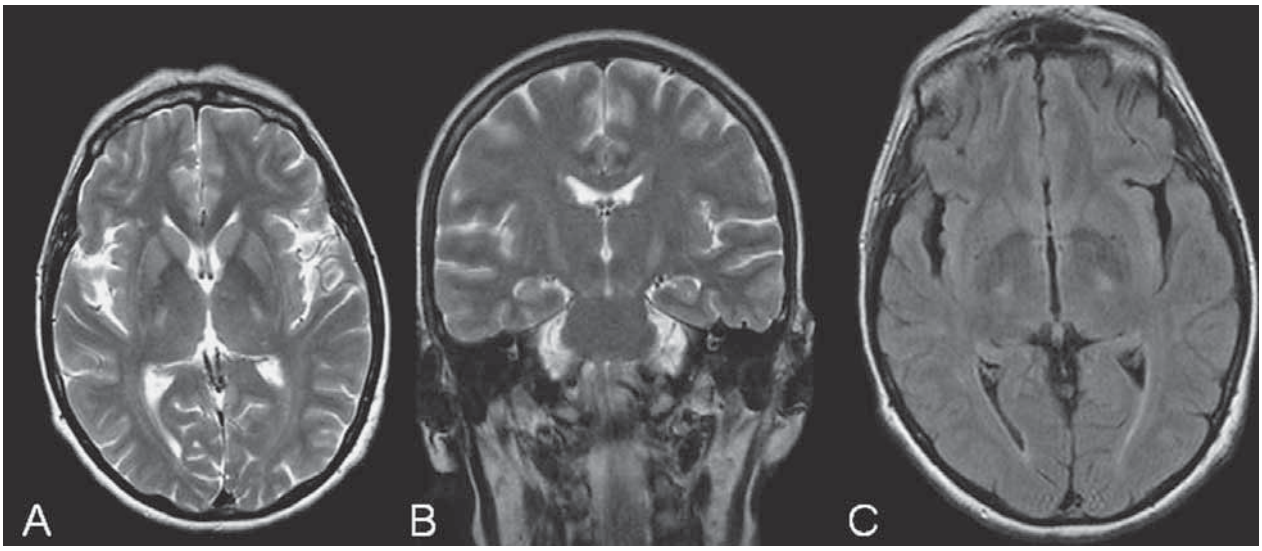

Fig. 1 (A, C). *Axial T2 and FLAIR weighted MR images showing bilateral hyperintensities in posterior limb of the internal capsule; (B) coronal T2-weighted MR image showing 'wine-glass' sign with symmetrical corticospinal tract hyperintensities reaching the pontine level.*

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clinical picture and disease progression, the diagnosis of amyotrophic lateral sclerosis (ALS) was made.

According to current guidelines, use of conventional MRI in patients suspected of having a motor neuron disease is restricted to exclude other possible causes (1). Even more advanced neuroimaging techniques, such as diffusion tensor imaging and proton magnetic resonance spectroscopic imaging, have only modest discriminatory capability in making the diagnosis of ALS (2). Corticospinal tract hyperintensities are not disease-specific, however, lacking a specific image-biomarker for ALS, a unique neuroradiological finding such as 'wine-glass' sign should not be ignored and should complement clinical finding in supporting appropriate diagnosis.

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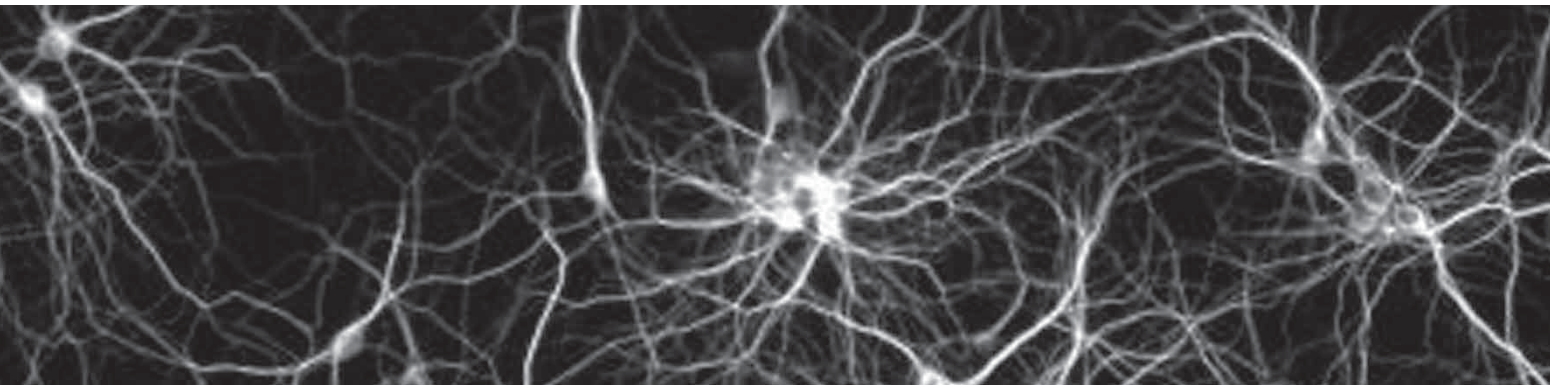
Key words: amyotrophic lateral sclerosis, corticospinal tract hyperintensities, wine-glass sign



Trigeminal neuralgia: the first sign of arteriovenous malformation

Bahar Kaymakamzade, Suha Akpinar[1]

A 45-year-old female was admitted to the hospital with acute onset right sided hemiparesis and left sided abducens palsy. She had a two-year history of paroxysmal shock like pain in the distribution of the second and third divisions of her left trigeminal nerve. The pain was triggered by eating and brushing teeth. She was pain-free with carbamazepine (CBZ) treatment. Computed tomography of the brain demonstrated left pontocerebellar hemorrhage (Fig. 1). Digital subtraction angiography showed an arteriovenous malformation (AVM) located in the cerebellopontine angle fed by the left superior cerebellar and anterior inferior cerebellar arteries and draining into the transverse sinus (Fig. 2). Magnetic resonance imaging of the brain also demonstrated vascular loops of the AVM at the root of trigeminal nerve (Fig. 3). The patient was referred to endovascular treatment. Endovascular embolization was performed with Onyx and the patient underwent gamma knife radiosurgery for the residual AVM nidus. CBZ treatment was discontinued and the patient remained free from pain.

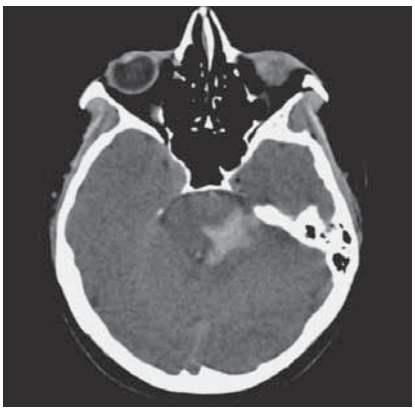


Figure 1.

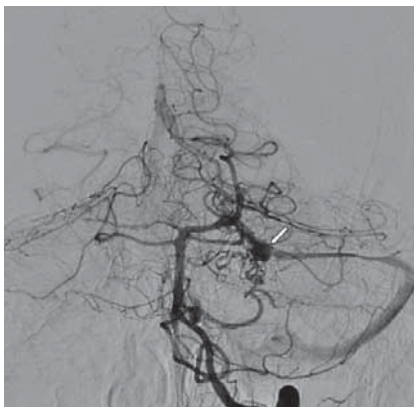


Figure 2.

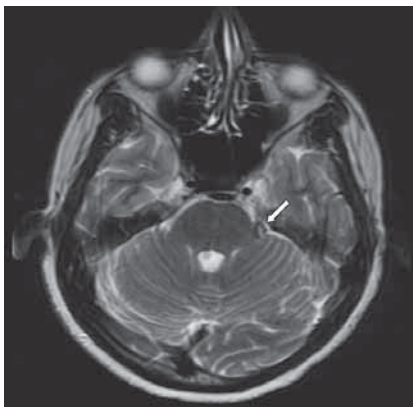


Figure 3.

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[1]Department of Radiology, Near East University, Nicosia, Cyprus

Trigeminal neuralgia caused by compression of an AVM is rare (1). Treatment of AVM is important both for preventing hemorrhage and amelioration of trigeminal neuralgia.

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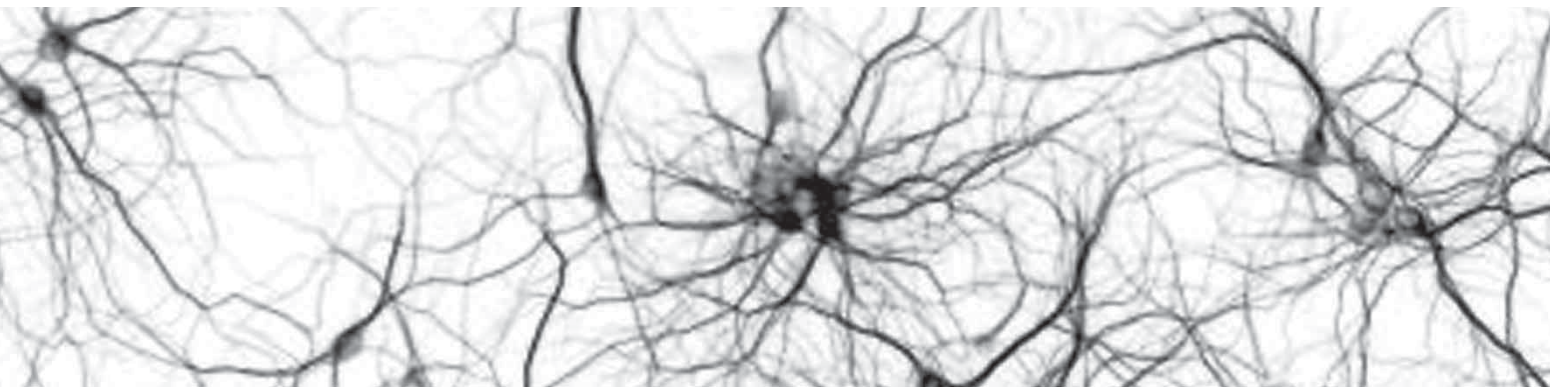
Address for correspondence: Bahar Kaymakamzade, MD, Department of Neurology, Near East University, 99138, Nicosia, North Cyprus, Cyprus; e-mail: bkaymakamzade@yahoo.com

Key words: arteriovenous malformation, magnetic resonance imaging, trigeminal neuralgia, arteriovenous malformation



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Neurologia Croatica publishes the following types of articles:

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2. **Neurological reviews**: Reviews are usually solicited by the editors, however, spontaneous submissions are also welcome. All articles and data sources reviewed should include information about the specific type of study or analysis, population, intervention, exposure, and test or outcomes. All articles or data sources should be selected systematically for inclusion in the review and critically evaluated, and the selection process should be described in the paper. Maximum length: the same as for original contributions.
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