Contents / Sadržaj

UDK 616.8

ISSN 0353-8842

Neurologia Croatica

SINCE 1953

INDEXED / ABSTRACTED IN

Science Citation Index Expanded

SCOPUS

NEUROL. CROAT. 2015 64 (3-4): 45-72

NEUROLOGIA CROATICA (Vol. 1-24 “Neuropsihijatrija”, Vol. 25-39 “Neurologija”) Journal of Clinical Neuroscience published by University Department of Neurology, Zagreb University Hospital Center, School of Medicine, University of Zagreb, Zagreb, Republic of Croatia

NEUROLOGIA CROATICA (Vol. 1-24 “Neuropsihijatrija”, Vol. 25-39 “Neurologija”) Časopis kliničkih neuroznanosti izdaje Neurološka klinika, Klinički bolnički centar Zagreb, Medicinski fakultet Sveučilišta u Zagrebu, Zagreb, Republika Hrvatska

EDITORIAL BOARD – UREDNIČKI ODBOR

Printed and typesetting by / Tisak i dizajn:

DENONA d.o.o., Getaldićeva 1, Zagreb

ADVISORY BOARD – SAVJETODAVNI ZNANSTVENI UREDNIČKI ODBOR

UDK 616.8

ISSN 0353-8842

Neurologia Croatica

SINCE 1953

OFFICIAL JOURNAL OF

Croatian Neurological Society
Croatian Neurosurgical Society

INDEXED / ABSTRACTED IN

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NEUROLOGIA CROATICA,
University of Zagreb, School of Medicine and Zagreb University Hospital Center, University Department of Neurology, Kišpatićeva 12, HR-10 000 Zagreb, Croatia;
phone/fax: +385 1 2388 176.
E-mail: neurologiacroatica@kbc-zagreb.hr
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Subscription rate: an annual volume in Croatia is 100 HRK for individuals and 200 HRK for institutions, payable to the account No. 2503007-1100007828, SPES - Društvo za pomoć neurološkim bolesnicima, KBC Zagreb, Kišpatićeva 12, 10 000 Zagreb. All other countries: 30 USD for individuals and 50 USD for institutions, payable to the account No. SWIFT VBCRHR22-4082867101, Volksbank d.d., 10 000 Zagreb, Croatia.

Ministry of Science, Education and Sports, Republic of Croatia supports regular printing of the journal.

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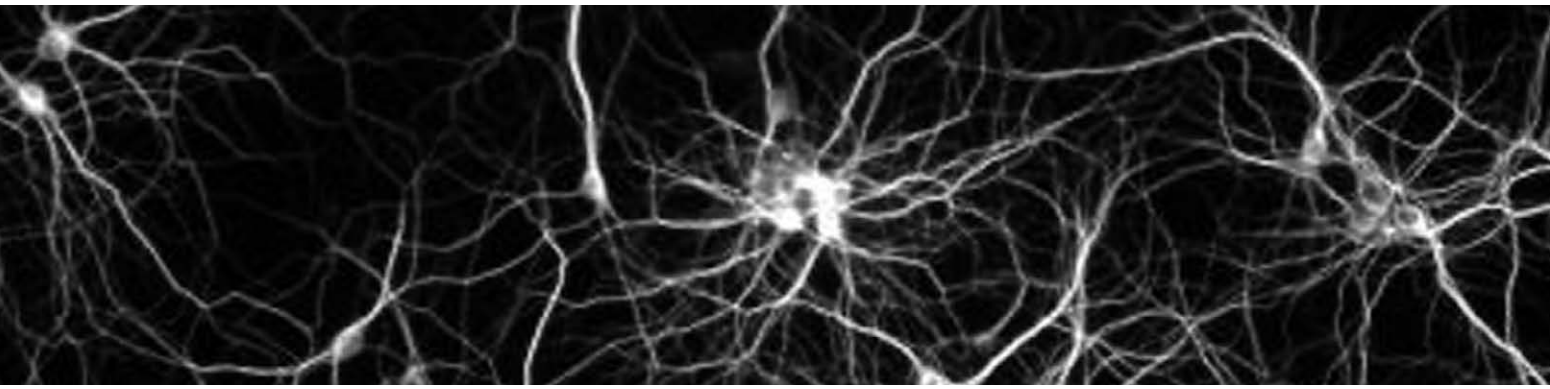


Complementary and alternative medicine use in multiple sclerosis patients

Merisanda Časar Rovazdi, Viktor Vidović, Oto Kraml, Senka Rendulić Slivar

ABSTRACT – *Objective:* The aim of the study was to determine the frequency and modality of the complementary and alternative medicine (CAM) use among patients with multiple sclerosis (MS) and to analyze the link between CAM usage and patient age, sex, clinical course of MS, disease duration, and degree of disability. *Methods:* The study included 81 patients. A questionnaire on the use of CAM was filled in with the help of medical staff. The data obtained were compared between the groups of CAM users and non-users. *Results:* Sixty-four (79.0%) respondents reported that they were currently using CAM. In the group of CAM users, there were a significantly higher proportion of patients with lower level of disability (p=0.009), relapsing-remitting disease course (p=0.015) and shorter duration of disease (p=0.002) compared with the group of non-users. There were no statistically significant between-group differences according to sex (p=0.078) and age (p=0.062). Respondents most commonly used dietary supplements (n=62; 76.5%), followed by meditation (n=9; 11.1%), special dietary regimen (n=8; 9.9%), acupuncture (n=6; 7.4%), bioenergy (n=6; 7.4%), massage (n=3; 3.7%), chiropractic (n=3; 3.7%), yoga (n=3; 3.7%), magnetic therapy (n=3; 3.7%), homeopathy (n=1; 1.2%), heliotherapy (n=1; 1.2%) and bee venom therapy (n=1; 1.2%). *Conclusion:* Study results demonstrated frequent use of CAM procedures among MS patients and a wide range of CAM treatment modalities. The frequent use of CAM by MS patients calls for additional researches on the efficacy and safety of these procedures.

Key words: multiple sclerosis, complementary and alternative medicine, dietary supplements

INTRODUCTION

Complementary and alternative medicine (CAM) refers to a group of health care systems, practices and treatments that are not considered to be part of conventional medicine (1). The USA National Center for Complementary and Alternative Medicine (NCCAM) classifies CAM into five categories (1):

Lipik Special Hospital for Medical Rehabilitation, Lipik, Croatia

1) Biological-based therapies, e.g., dietary supplements, various diets, herbs;
2) Mind-body therapies, e.g., meditation, deep-breathing exercises, tai chi, hypnotherapy, yoga;
3) Manipulative and body based systems, e.g., chiropractic, massage, reflexology, osteopathic manipulations;
4) Energy therapies, i.e. therapies that purport the existence of energy fields that surround the body, e.g., Reiki, therapeutic touch; and
5) Alternative medical systems, e.g., traditional Chinese medicine including acupuncture, homeopathy, naturopathy.

The rate of CAM use in MS patients has been estimated to 33%-80% (2-12), predominantly among those who are female, have higher education levels, and report poorer health (2-4,8,13). In most studies, CAM users had longer duration of illness than non-users (4,7,11,13), although shorter duration of illness was also observed among users (14). The majority of MS patients using CAM perceive it as being beneficial (2,4,8,9,15,16).

The aim of the study was to determine the prevalence of CAM usage among MS patients and to analyze the relationship between CAM usage and patient age, sex, clinical course of MS, degree of disability, and time elapsed from MS diagnosis.

PATIENTS AND METHODS

The study included 81 patients with MS that underwent inpatient rehabilitation at the Lipik Hospital for Medical Rehabilitation in the period from May 1, 2015 to September 1, 2015. Patients older than 18 years and diagnosed with MS according to the revised McDonald criteria were included in the study (17). The exclusion criterion was serious cognitive impairment. Data on patient age, sex, clinical course of MS, and time elapsed from MS diagnosis were collected. The degree of disability for all study subjects was based on the Expanded Disability Status Scale (EDSS) (18), while assessment of cognitive status was performed using the Mini Mental Status Exam (MMSE) (19). A semi-structured questionnaire on the current usage of CAM was applied. Closed ended questions referred to using the following forms of treatment modalities: vitamins, minerals, vitamin/mineral combinations, special dietary regimen, meditation, yoga, biofeedback, chiropractic, massage, reflexology, bioenergy, and magnetic therapy. The questionnaire was filled in with the help of medical staff. The data obtained were compared between the groups of CAM users and non-users.

The study was approved by the Hospital Ethics Committee and patients were required to provide written consent for their participation.

Statistical analysis was performed using the SOFA Statistics for Windows. Comparison of the variables was conducted using the Student's t-test and Pearson's correlation test.

RESULTS

The study included 81 patients, 61 (75.3%) female and 20 (24.7%) male, mean age 51.6 years, age range 25 to 85 years. The mean time elapsed from MS diagnosis was 14.9 years, range 6 months to 62 years. The relapsing-remitting course of the disease (RRMS) had 36 (44.5%), secondary progressive MS (SPMS) 41 (50.6%), primary progressive (PPMS) 3 (3.7%) patients, and benign MS 1 (1.2%) patient. The mean EDSS was 5.2, range 1.5 to 9.

At the time of investigation, 64 (79%) MS patients reported that they were currently using one or more CAMs.

Patients were divided into two groups according to the usage of CAM. In the group of CAM users, there were a significantly higher proportion of patients with lower level of disability (p=0.009), relapsing-remitting disease course (p=0.015), and shorter duration of disease (p=0.002) compared with the group of non-users. There were no statistically significant between-group differences according to sex (p=0.078) and age (p=0.062). Demographic and clinical characteristics of study patients are shown in Table 1.

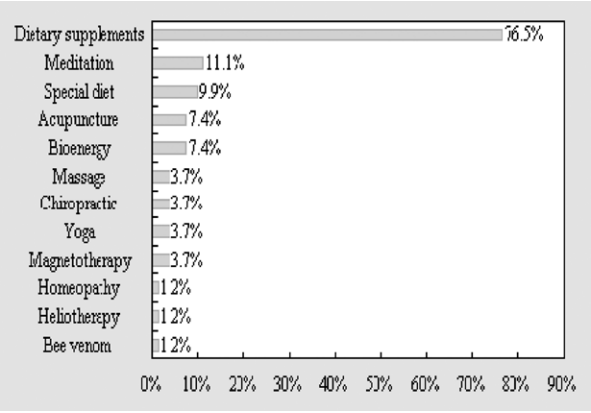
Due to the small number of patients suffering from PPMS and with benign course of disease, statistical analysis of these patients was not done.

Respondents most commonly used dietary supplements (n=62; 76.5%), followed by meditation (n=9; 11.1%), special dietary regimen (n=8; 9.9%), acupuncture (n=6; 7.4%), bioenergy (n=6; 7.4%), massage (n=3; 3.7%), chiropractic (n=3; 3.7%), yoga (n=3; 3.7%), magnetic therapy (n=3; 3.7%), homeopathy (n=1; 1.2%), heliotherapy (n=1; 1.2%) and bee venom therapy (n=1; 1.2%) (Fig. 1). Types of special diets used were Swank's diet (n=4), and Mediterranean, vegetarian, low-calorie and gluten-free diet (one patient each). Using multiple treatment modalities was reported by 39.1% of CAM users.

Table 1. *Demographic and clinical characteristics of respondents*

Characteristic		CAM users	CAM non-users
n (%)		64 (79)	17 (21)
Age (yrs), x̄±SD		50.3±11.92	56.5±11.67
Female, n (%)		51 (79.7)	10 (58.8)
Male, n (%)		13 (20.3)	7 (41.2)
EDSS, x̄±SD		4.9±1.81	6.3±1.58
MS course, n (%)	RRMS	34 (53.1)	2 (11.8)
	SPMS	27 (42.2)	14 (82.3)
	PPMS	2 (3.1)	1 (5.9)
	Benign MS	1 (1.6)	0 (0.0)
Time elapsed from MS diagnosis (yrs), x̄±SD		12.9±9.65	22.4±15.26

CAM = complementary and alternative medicine; EDSS = Expanded Disability Status Scale; MS = multiple sclerosis; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis; PPMS = primary progressive multiple sclerosis; Benign MS = benign multiple sclerosis



CAM = complementary and alternative medicine; MS = multiple sclerosis

Fig. 1. *CAM treatment modalities used by MS patients.*

Of the patients taking dietary supplements, vitamin D was most commonly reported (n=40; 64.5%), followed by vitamin B complex (n=29; 46.8%), magnesium (n=9; 30.6%), calcium (n=15; 24.2%), ready-made multivitamin/mineral preparations (n=13; 21%), hemp products (n=8; 12.9%), omega-3 fatty acids (n=7; 11.3%), vitamin C (n=4; 6.5%) and vitamin E (n=4; 6.5%). Other types of dietary supplements were taken by less than 5% of dietary supplement users (Table 2).

Hemp products were taken in the form of oil and seeds, and bee products in the form of meadow honey, propolis and royal jelly. Mushroom extract preparations consisted of *Cordyceps sinensis* mushroom and *Cordyceps sinensis/Ganoderma lucidum* mushrooms.

Table 2. *Prevalence of dietary supplement usage among multiple sclerosis patients*

Dietary supplement	n	%
Vitamin D	40	64.5
Vitamin B complex	29	46.8
Magnesium	19	30.6
Calcium	15	24.2
Multivitamin/mineral	13	21.0
Hemp products	8	12.9
Omega-3 fatty acids	7	11.3
Vitamin C	4	6.5
Vitamin E	4	6.5
Evening primrose oil	3	4.8
Bee products	3	4.8
Chokeberry extract	2	3.2
Mushroom extract	2	3.2
Beta carotene	2	3.2
Cranberry syrup	2	3.2
Fish oil	1	1.6
Olive oil	1	1.6
Coenzyme 1	1	1.6
Copper	1	1.6
Ginkgo extract	1	1.6
Black cumin oil	1	1.6
Klamath algae	1	1.6
Noni juice	1	1.6
Zinc	1	1.6
Sesame oil	1	1.6

Of the patients taking dietary supplements, 15 (24.2%) were taking monotherapy (including B complex preparations) and 47 (75.8 %) different combinations (including ready-made poly-vitamin/mineral preparations).

DISCUSSION

Studies on the use of CAM have documented the popularity of CAM for the treatment of health problems that lack definitive cures (20). The possible reasons for this are dissatisfaction with the currently available treatments and anecdotal reports of CAM guide (21,22). Active coping strategies such as searching for information also seem to stimulate CAM utilization (23,24), as well as determination for more personal involvement in the healing process (25).

The present study showed a widespread use of CAM treatments among people with MS, as well as large variation of CAM modalities. These findings support the results of other studies (3-6,9,15,26-29).

Regarding the types of CAM treatment used, we found dietary supplements, meditation, special diets, acupuncture and bioenergy to be the CAM treatment modalities most commonly used, which is in concordance with other studies (4,8-10). In the majority of studies, the use of CAM was more prevalent in women (4,8,13), however, others report no sex difference in CAM usage (6). We found no statistically significant sex difference between CAM users and non-users.

In the study by Skovgaard *et al*. (30), CAM users were more likely to be 18-40 years of age, while Harirchian *et al*. (11) found no age difference between the users and non-users. To our knowledge, there is no study analyzing other factors that may affect difference in the rate of CAM usage depending on age or sex, so the reason for diverse findings remains obscure. In our study, there was no statistically significant age difference between the two groups of patients either.

Our results showed shorter MS duration to be a predisposing factor for the usage of CAM. The same findings were obtained in the study by Kochs *et al*. (14), but longer disease duration was recorded in other studies (4,7,11,13). CAM usage in the early stage of the disease could be the patient's attempt to slow down the progression of the disease and thus to prevent serious disability, and may be influenced by regional and cultural differences.

According to the EDSS score, CAM users were less severely affected by MS than non-users. While some researchers showed higher CAM usage among patients with mild and moderate disease (9,14), others showed higher CAM usage in more severely affected patients (6,7). The possible explanation for lesser CAM usage among patients in an advanced stage of the disease is that they have resigned for being aware of suffering from an incurable disease (14). However, heterogeneous findings reported in the literature could also be due to different definition of CAM, small sample size, and differences in the length of CAM usage (8).

The frequency of RRMS was significantly higher in the group of CAM users. In the study by Campbell *et al*. (31), CAM use was more likely among patients with progressive-relapsing MS, while other studies did not analyze the relationship between CAM usage and disease course.

A limitation of the study is the fact that it was conducted in MS patients having undergone inpatient rehabilitation. These patients are also under conventional neurological care, so we could not estimate the prevalence of exclusive CAM use as an alternative to conventional therapies. Furthermore, we did not evaluate the use of cannabinoids because in our country preparations of cannabis were not registered at the time of investigation.

CONCLUSION

Study results pointed to frequent use of CAM among MS patients, with a broad range of CAM treatment modalities. CAM users were more likely to be patients with a lower level of disability and shorter disease duration as compared with CAM non-users. Respondents most commonly used dietary supplements as a CAM modality. The frequent use of CAM by MS patients calls for additional research on the efficacy and safety of these procedures.

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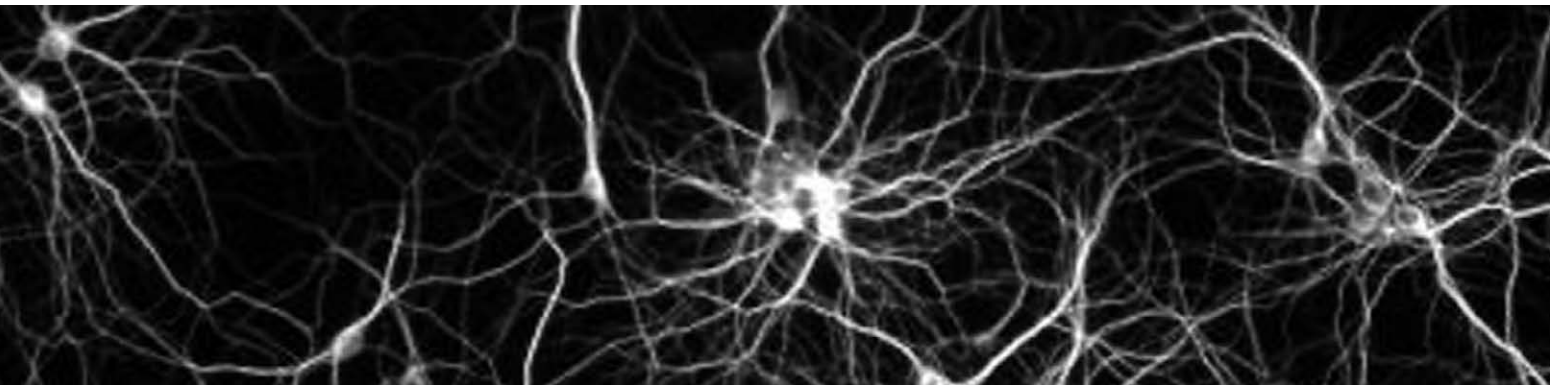
Address for correspondence: Merisanda Časar Rovazdi, MD, Lipik Special Hospital for Medical Rehabilitation, Marije Terezije 13, HR-34551 Lipik, Croatia; E-mail: merisanda.casar@bolnica-lipik.hr

Uporaba komplementarne i alternativne medicine kod oboljelih od multiple skleroze

SAŽETAK – *Cilj rada:* Cilj rada bio je ispitati učestalost i oblike liječenja komplementarnom i alternativnom medicinom (CAM) kod bolesnika s multiplom sklerozom (MS) i odrediti povezanost uporabe postupaka CAM-a s dobi ispitanika, spolom, tipom MS, trajanjem bolesti i stupnjem onesposobljenosti. *Metode:* Ispitivanje je uključilo 81 bolesnika. Upitnik o uporabi CAM-a ispunjen je uz pomoć medicinskog osoblja, a dobiveni podatci uspoređeni su između skupina bolesnika koji su koristili i onih koji nisu koristili liječenje CAM-om. *Rezultati:* U vrijeme istraživanja liječenje CAM-om koristilo je 64 (79,0%) ispitanika. U skupini koja se liječila CAM-om utvrđena je statistički značajno veća zastupljenost bolesnika s manjim stupnjem onesposobljenosti (p=0,009), relapsno-remitirajućim tijekom bolesti (p=0,015) i kraćim trajanjem bolesti (p=0,002) u odnosu na skupinu koja se nije liječila CAM-om. Nije nađena statistički značajna razlika u odnosu na spol (p=0,078) i životnu dob (p=0,062). Ispitanici su kao oblik liječenja najčešće koristili dijetalne nadomjestke (n=62; 76,5%), potom meditaciju (n=9; 11,1%), poseban dijetetski režim (n=8; 9,9%), akupunkturu (n=6; 7,4%), bioenergiju (n=6; 7,4%), masažu (n=3; 3.7%), kiropraktiku (n=3; 3,7%), jogu (n=3; 3,7%), magnetoterapiju (n=3; 3,7%), homeopatiju (n=1; 1,2%), helioterapiju (n=1; 1,2%) i terapiju pčelinjim otrovom (n=1; 1,2%). *Zaključak:* Rezultati istraživanja pokazali su učestalo liječenje postupcima CAM-a kod oboljelih od MS-a, kao i širok spektar oblika liječenja. Potrebna su daljnja istraživanja o učinkovitosti i sigurnosti primjene postupaka CAM-a s obzirom na visoku učestalost korištenja navedenih postupaka kod oboljelih od MS-a.

Ključne riječi: multipla skleroza, komplementarna i alternativna medicina, dijetalni nadomjesci



Chronic inflammatory demyelinating polyneuropathy superimposed on hereditary neuropathy with liability to pressure palsy

Ervina Bilić[1], Slobodan Apostolski[2], Bruna Sanader[3], Branimir Anić[4], Marija Žagar[1], Ernest Bilić[5], Marija Baković[6]

ABSTRACT – *Objective:* Herein we present a case of deterioration of hereditary neuropathy with liability to pressure palsy (HNPP), which presented with clinical and electrophysiological signs of chronic inflammatory demyelinating polyneuropathy (CIDP). *Case report:* A 31-year-old man with a former diagnosis of HNPP developed slowly progressive motor and sensory deficit five months after influenza vaccination. Clinically, it presented as distal symmetric muscle weakness of both legs, areflexia, and ataxic and peroneal gait. Nerve conduction studies revealed signs of demyelination and conduction blocks (CB) in motor fibers of upper and lower limbs. Sensory nerve action potentials (SNAP) were normal and no CB in sensory fibers was detected. *Results:* The diagnosis of CIDP was established according to the European Federation of Neurological Societies (EFNS) guidelines. The patient was submitted to prolonged prednisone treatment (60 mg *per* day) and impressive improvement of clinical and neurographic parameters occurred after 9 months. We assumed that HNPP in our patient was associated with superimposed immune mediated affection of the same target tissue. *Conclusion:* Peripheral nerves in patients suffering from hereditary polyneuropathies may be highly susceptible to secondary immune damage due to antigenic variation or alteration in the blood-nerve barrier. Unusual and sudden deterioration of chronic hereditary neuropathy may be explained

[1] School of Medicine, University of Zagreb, Zagreb University Hospital Centre, Department of Neurology, Zagreb, Croatia

[2] Outpatient Neurologic Clinic, Belgrade, Serbia, School of Medicine, University of Skopje, Macedonia

[3] Ludwig Maximilian University of Munich, Department of Psychiatry and Psychotherapy, Munich, Germany

[4] School of Medicine, University of Zagreb, Zagreb University Hospital Centre, Department of Clinical Immunology and Rheumatology, Zagreb, Croatia

[5] School of Medicine, University of Zagreb, Zagreb University Hospital Centre, Department of Pediatric Oncology and Hematology, Zagreb, Croatia

[6] School of Medicine, University of Zagreb, Institute of Forensic Medicine and Criminalistics, Zagreb, Croatia

by sudden, immune mediated inflammation, i.e. by superimposed autoimmune polyneuropathy. In order to prevent future damage to the peripheral nervous system, immunosuppressive or immunomodulatory treatment should be considered in these patients.

Key words: autoimmunity, chronic inflammatory demyelinating polyneuropathy, hereditary neuropathy with liability to pressure palsy

INTRODUCTION

Hereditary neuropathy with liability to pressure palsy (HNPP) is a disease with autosomal dominant inheritance. The prevalence is estimated to 2-5 *per* 100 000 people, and both sexes are equally affected. HNPP is associated with mutation or deletion of PMP22 gene on chromosome 17p11.2. There is no specific therapy. Intensive physiotherapy should be applied immediately after the onset of nerve palsy. Preventive measures include avoiding compression of peripheral nerves by abnormal positions and movements. The condition can sometimes be revealed later in life when individuals develop an acquired unrelated neuropathy due to autoimmunity (1).

Chronic inflammatory demyelinating polyneuropathy (CIDP) is common acquired autoimmune neuropathy with variable presentation and clinical course. At present, most acquired demyelinating neuropathies of otherwise unknown etiology are considered to be a form of CIDP (2). The prevalence of 1 to 7.7 *per* 100,000 is reported (3). The symptoms of motor and sensory deficits develop insidiously with progressive or relapsing phase of over 8 weeks. An acute onset resembling Guillain-Barré syndrome can develop in the minority of patients. Acute-onset CIDP in a patient initially diagnosed as Guillain-Barré syndrome is likely if deterioration continues for more than two months of the onset (4). The clinical and electrodiagnostic criteria proposed by the European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) have been successfully used in clinical trials, and according to Rajabally *et al.*, these criteria have 81% sensitivity and 90% specificity (5,6). Based on the EFNS/PNS clinical criteria, typical CIDP should be considered in any patient with progressive, stepwise, or recurrent symmetric proximal and distal weakness, generalized areflexia without wasting, and sensory dysfunction with preferential loss of vibration or joint position sense developing over at least two months. Electrodiagnostic tests for primary demyelination are mandatory and include prolongation of motor distal latencies, reduction of motor conduction velocities, prolongation of F-wave latencies, absence of F-waves, partial motor conduction blocks, abnormal temporal dispersion, and increased duration of distal compound muscle action potentials.

Hereditary neuromuscular disorders may be associated with immune response against primary affected target tissue antigens (7,8). The first report of prednisone responsive hereditary neuropathy drew attention to the possibility of association of hereditary and acquired autoimmune peripheral neuropathy (9). The subgroup with stepwise progression of Charcot-Marie-Tooth disease (CMT) may include patients in whom an autoimmune response against released hidden myelin antigens occurs. In these patients, myelin proteins and glycolipids could be recognized as altered self-antigens and induce production of autoantibodies (10). If deterioration of clinical presentation in a patient with CMT indicates possible autoimmune reaction, it is reasonable to consider immunosuppressive therapy which may prevent progression of polyneuropathy and severe disability.

In this case report, we present a patient with deterioration of HNPP after vaccination, with clinical and electrophysiological signs that met the CIDP diagnostic criteria.

CASE REPORT

A 31-year-old man complained of low back pain after physical exercise. On neurological examination, Lasegue sign was bilaterally positive and ankle reflexes were symmetrically reduced. The electroneurographic parameters indicated only mild prolongation of deep peroneal nerve motor latencies and mild reduction of sural nerves conduction velocities (NCV) (Table 1). Blood cell count, serum biochemistry (Fe, CK, HbA1c, UIBC, ferritin, Cu, B12), tests for viral and bacterial infections (HbsAg, HCV, HIV, *Borrelia burgdorferi*) and tumor antigens (CEA, Ca 19-9, AFP, PSA) showed no abnormality. Genetic analysis revealed PMP22 gene deletion and the diagnosis of HNPP was estab-

Table 1. *Electroneurographic parameters*

Nerve	Site	Parameter	Visit 1	Visit 2	Comment	Visit 3	Normal values (11)
Motor nerves							
Left median	Wrist	mDL	3.25	3.45		3.0	<3.8
		CMAP	4.6	2.1		6.3	>5.2
		CMAP d	9.7	16.9		10.2	<16.3
	Elbow-wrist	CV	52.7	6.0		51.1	>47
		CMAP	4.0	0.2	CB	6.0	>5.2
		CMAPd	8.8	24.8		11.9	<16.3
Left ulnar	Wrist	mDL	3.4	3.09		3.8	<3.7
		CMAP	8.2	4.9		4.3	>7.9
		CMAPd	8.2	19.9		15.6	<17.3
	Elbow-wrist	CV	52.3	7.4		48.1	>52
		CMAP	8.6	1.2	CB	4.2	>7.9
		CMAPd	7.8	24.3		16.9	<17.3
		F	17.8	31.5		14.3	<25
Left common peroneal	Ankle	mDL	9.1	11.9		8.15	<2.5
		CMAP	5.4	5.2		4.8	>5.1
		CMAPd	11.8	1.2	CB	13.8	<14.3
	Below head of fibula	CV	53.6	19.8		44.9	>40
		CMAP	5.4	5.2		3.9	>5.1
		CMAPd	12.5	19.9		12.7	<14.3
		F	40.3	59.8		43.6	<50
Sensory nerves							
Left median	Wrist-digit	SNAP	9.2	0.34		6.9	>19
		CV	63.5	32.1	CB?	48.3	>44
Left ulnar	Wrist-digit 2	SNAP	7.2	2.04		4.6	>20
		CV	63.2	40.0		47.4	>44
Left sural	Distal third of lower leg-ankle	SNAP	8.5	0	CB?	7.0	>1.9
		CV	48.1			47.2	>46
Motor nerves							
Right median	Wrist	mDL	3.35	2.9		4.55	<3.8
		CMAP	5.8	3.3		4.8	>5.2
		CMAP d	6.3	18.2		14.1	<16.3
	Elbow-wrist	CV	57.2	8.5		47.5	>47
		CMAP	5.9	0.2	CB	3.6	>5.2
		CMAPd	7.2	20.8		12.2	<16.3
Right ulnar	Wrist	mDL	3.09	2.75		3.35	<3.7
		CMAP	7.9	9.7		6.4	>7.9
		CMAPd	9.2	20.3		14.3	<17.3
	Elbow-wrist	CV	55.4	9.4		66.7	>52
		CMAP	7.7	2.0	CB	6.3	>7.9
		CMAPd	9.3	22.9		12.5	<17.3
		F	21	36.5		23.6	<25
Right common peroneal	Ankle	mDL	11.55	11.55		9.,11	<2.5
		CMAP	5.1	3.0		3.4	>5.1
		CMAPd	11.2	19.9		13.2	<14.3
	Below head of fibula	CV	48.0	20.7		44.6	>40
		CMAP	4.9	0.4	CB	3.9	>5.1
		CMAPd	10.8	23.8		14.8	<14.3
		F	42.5	62.5		45.2	<50
Sensory nerves							
Right median	Wrist-digit 2	SNAP	9.2	0	CB	6.2	>19
		CV	66.7			46.9	>44
Right ulnar	Wrist-digit 2	SNAP	9.8	1.0	CB	9.5	>20
		CV	65.3	32.1		44.9	>44
Right sural	Distal third of lower leg-ankle	SNAP	7.3	0	CB	8.2	>1.9
		CV	47.9			45.8	>46

SNAP = sensory action potential-orthodromic study (micro V); CMAP = compound muscle action potential (mV); mDL = motor distal latency; CV = conduction velocity (m/s); CMAPd = CMAP duration (ms); F = minimal F wave latency (ms); CB = conduction block; Visit 1 = hereditary neuropathy with liability to pressure palsy diagnosed; Visit 2 = chronic inflammatory demyelinating polyneuropathy diagnosed; Visit 3 = after CIDP treatment

lished. He was very well and without any sensory or motor alteration on neurological examinations in the following years.

Six years later, five months after influenza vaccination, he gradually started developing progressive motor and sensory deficit in lower limbs. Neurological examination revealed reduced deep tendon reflexes in upper limbs, hypotrophy and weakness of both tibial anterior muscles with foot drop, diminished deep tendon reflexes and reduced vibration sense in lower limbs. The gait was peroneal and slightly ataxic. Nerve conduction study disclosed multiple conduction blocks (CB) in motor fibers in four analyzed nerves of upper and lower extremities with prolonged F-wave latencies, prolonged and time-dispersed M potentials and decreased sensory nerve conduction velocity. CBs were observed at non-entrapment sites. Sensory nerve action potentials (SNAP) were normal and no CB in sensory fibers was detected (Table 1).

Blood cell count and serum biochemistry were normal. ELISA test for anti-ganglioside antibodies (GD1b) were highly positive. According to the EFNS guidelines, the CIDP diagnosis was established and immunosuppressive treatment was started with administration of prednisone at a daily dose of 60 mg (5). After 9 months of corticosteroid treatment, full recovery of clinical and electroneurographic parameters was achieved and slow tapering of prednisone for the next 10 months was performed.

DISCUSSION

A superimposed immune mediated neuropathy developed in the patient with HNPP. It occurred five months after influenza vaccination. The clinical and electrophysiological presentation of immune mediated neuropathy was recognized as a symmetric distal, predominantly motor form of CIDP. Slow progression of the disease over two months excluded the possibility of Guillian-Barré syndrome, whereas reduced vibration sense and full response to steroid treatment excluded multifocal motor neuropathy (12).

Many genetic neuromuscular disorders are caused by mutations or deletions of ubiquitously expressed genes that play critical roles in RNA metabolism, leading to their dysfunction (13-15). A change in these proteins may lead to the loss of immune self-tolerance. Inherited neuromuscular disorders may be associated with immune mediated superimposed affection of the same target tissue. If not recognized, this association presents as deterioration of the primary, inherited, disease (8). Early observations of inflammatory myopathy with facioscapular distribution were the basis for the hypothesis of polymyositis superimposed on facioscapular muscular dystrophy (8). The majority of patients with polymyositis/dermatomyositis (PM/DM) and other systemic autoimmune diseases produce organ-specific autoantibodies. Survival motor neuron 1 (SMN1) is well known as a causative gene for spinal muscular atrophy (SMA), whereas mutations of glycyl- and tyrosyl-tRNA synthetases are identified as a cause of distal SMA and CMT 1A. However, at the same time, SMN complex is an autoantigen recognized in patients with PM (16). In addition, mutations of the common autoantigens in PM/DM, aminoacyl tRNA synthetases, cause another genetic neuromuscular disorder, distal SMA, or CMT 1A (16).

The subgroup with stepwise progression of CMT may include patients in whom an autoimmune humoral response directed against myelin proteins occurs (7). There are several possible explanations for this scenario. It could be that these patients have additional immunosusceptibility to inflammatory demyelinating polyneuropathy. In case of CMT 1A, they have overexpressed PMP22, which already renders their peripheral nerves liable to demyelination and superimposed inflammatory demyelinating disorder, thus it may be more likely to occur in these individuals than in genetically normal subjects (7,10,16,17). Inherited polyneuropathy may expose myelin antigens or the gene duplication may contain genes that modify the immune response in some patients. In mice heterozygously deficient in the myelin protein zero gene, T cells show enhanced reactivity to myelin components and immune deficiency results in less severe peripheral nerve disease (18). Of course, it remains possible that these CMT patients with a stepwise disease progression simply have coincidental inflammatory neuropathy and CMT, but immunology research in this field suggests that, in this group of patients, immune mediated mechanisms relate the two conditions (7,8).

The term autoantigenesis is defined by Doyle and Mamula as the change that arises in self-proteins as they break self-tolerance and trigger autoimmune B and/or T cell response (19). Between 50% and 90% of proteins in the human body acquire post-translational modification. Those post-translational modifications can create new self-antigens by altering immune processing and presentation. This kind of modification can arise either by enzymatic

modification or can occur spontaneously. Many aspects of protein chemistry are then altered, including primary and tertiary structure, biological function and proteolytic degradation. Any of these can be a case of failure of self-tolerance. Certain cellular processes such as aging, disease, inflammation and trauma are known to increase the frequency of post-translational modifications (19,20). Among the most apparent post-translational protein modifications are the myriad of phosphorylation events that communicate signals originating at the cell surface through the cytoplasm and eventually to the nucleus (21). Other well-studied protein modifications include methylation and glycosylation, which are required for the biological function of various proteins. Classical biochemistry tells us that 20 amino acids make up most proteins in nature. Closer examination reveals a number that by far exceeds 20 original structures. Indeed, when post-translational modifications are considered, more than 140 unique amino acids compose proteins (19,22). A number of other modifications that arise in proteins after their synthesis might influence the central and peripheral mechanisms of tolerance of lymphoid cells, as well as the induction of autoimmune responses. The common post-translational modifications associated with autoimmune responses are described in multiple sclerosis, rheumatoid arthritis, celiac disease and atherosclerosis (20,23,24). One explanation for the lack of tolerance is that these post-translationally modified proteins are not present in the thymus during T cell development and the modifications may arise in the periphery due to different biochemical conditions (e.g., pH, inflammation, etc.). Moreover, upon initial stimulus by modified proteins, the response may then be amplified to other sites on the protein (intramolecular epitope spreading) (19).

Influenza vaccine triggered CIDP in our patient with primary HNPP, causing stepwise worsening of the clinical and EMG signs of polyneuropathy. It is possible that immune autoreactivity caused disease progression after post-translational change in myelin proteins or vaccination heightened subclinical immune response to these proteins. The same possibility is open for CMT patients with severe toxic polyneuropathies after vinca alkaloids (vincristine) administration. The breakdown of tubuline components may be the only underlying mechanism, but secondary damage *via* autoreactivity to post-translationally changed proteins is also possible. These processes result in neo self-antigens and they could be presented to T cells and immune system can lose tolerance. It is not clear when the tolerance to newly arising self-proteins is maintained and when it is not (19). To our knowledge, there are few reports of deterioration of CIDP after influenza vaccination and one case report of CIDP associated with HNPP (12).

CONCLUSION

It is clear that post-translational protein modifications can profoundly affect the recognition of autoantigens and self-tolerance of the immune system. Recent studies have suggested that there are times when the presence or absence of post-translational alterations in self-proteins can profoundly affect antigen recognition in immune functions. This is of special interest in the field of inherited neuromuscular diseases where congenital change in various proteins may lead to additional susceptibility to the immune response to the same target tissue. The pathways that control post-translational modifications may become targets of immunotherapeutic strategies to alter the states of autoimmunity *versus* immune tolerance (18).

The stepwise worsening in patients with inherited neuromuscular disorders may be a representation of additional underlying autoimmune process and immunosuppressive/immunomodulatory therapy may be a valuable treatment option to prevent future damage to the peripheral nervous system.

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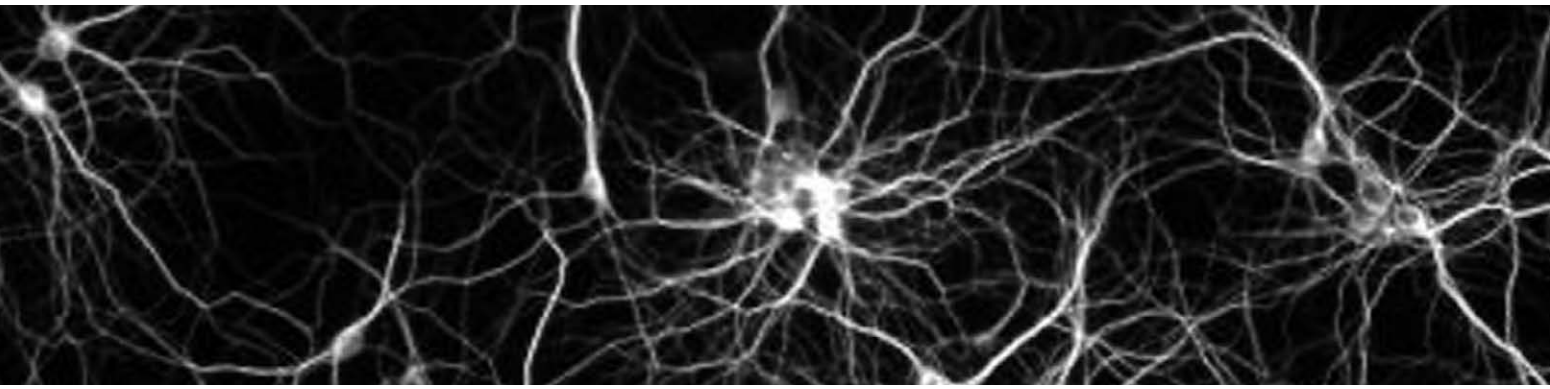
Address for correspondence: Marija Baković, MD PhD, School of Medicine, University of Zagreb, Institute of Forensic Medicine and Criminalistics, Šalata 11, HR-10000 Zagreb, Croatia; E-mail: mbakovic@mef.hr

Kronična upalna demijelinizirajuća polineuropatija superponirana na nasljednu neuropatiju sa sklonošću kompresivnoj kljenuti

SAŽETAK – *Cilj:* U članku prikazujemo bolesnika u kojeg je nastalo pogoršanje prethodno dijagnosticirane nasljedne motorne neuropatije sa sklonošću kompresivnim kljenutima (HNPP), koje je bilo uzrokovano superpozicijom stečene polineuropatije koja temeljem elektroneurografskih parametara i dinamike kliničke slike odgovara kroničnoj upalnoj demijelinizirajućoj polineuropatiji (CIDP). *Prikaz slučaja:* Muškarac u dobi od 31 godine s ranije postavljenom dijagnozom HNPP-a razvio je sporo napredujući motorni i senzorni deficit pet mjeseci nakon cijepljenja cjepivom protiv gripe. U kliničkoj slici bila je vidljiva simetrična mišićna slabost obje noge s nedostatkom refleksa, ataksijom i peronealnim hodom. Analiza parametara perifernih živaca uputila je na znakove demijelinizacije i blokova provođenja u motoričkim vlaknima živaca u gornjim i donjim udovima. Osjetni živčani akcijski potencijali bili su normalni, bez zabilježenih blokova provođenja u osjetnim vlaknima. *Rezultati:* Dijagnoza CIDP-a postavljena je na temelju smjernica Europskog udruženja neuroloških društava (EFNS). Bolesnik je podvrgnut dugotrajnoj terapiji prednizolonom (60 mg na dan), što je nakon 9 mjeseci dovelo do značajnog oporavka kliničkih i neurografskih pokazatelja. Pretpostavili smo da je pogoršanje kliničke slike HNPP-a u našeg bolesnika bilo barem dijelom povezano sa superponiranim, imuno posredovanim oštećenjem istog ciljnog tkiva. *Zaključak:* Moguće je da su periferni živci u bolesnika s nasljednim polineuropatijama, zbog antigenski izmijenjene strukture ili poremećaja barijere periferni živac-krv, naročito osjetljivi na sekundarna imuno oštećenja. Neočekivano i iznenadno pogoršanje kronične nasljedne neuropatije može se objasniti iznenadnom, imuno potaknutom upalom, odnosno superpozicijom autoimune polineuropatije. Kako bi se spriječila nova oštećenja perifernog živčanog sustava u tih bolesnika treba razmotriti primjenu imunosupresivnog ili imunomodulacijskog liječenja.

Ključne riječi: autoimunost, CIDP, HNPP



Traumatic cerebellar hematoma with good outcome

Antonija Krstačić[1], Goran Krstačić[2], Silva Butković Soldo[3]

ABSTRACT – A 26-year-old man was admitted to trauma department with head trauma due to fall from a ladder. He presented with a several-day history of progressive headache with vomiting. Glasgow Coma Scale (GCS) was 15 and detailed neurological examination was normal. Computed tomography (CT) scan demonstrated occipital skull fracture with traumatic cerebellar hematoma measuring 11 mm (Figs. 1 and 2). Traumatic cerebellar hematomas are rare, reported in <1% of all head injuries. Although rare, they are an important cause of morbidity and mortality. CT scan is the initial and gold standard investigation to evaluate traumatic cerebellar hematomas (1). Initial GCS score at the time of admission is the most important factor predicting the outcome. Patients with GCS >8 have good outcome, either managed conservatively or surgically. In our patient, surgery was not indicated. According to current guidelines, the patient was conservatively treated with good recovery. The patient was discharged home after follow up CT scan that showed regression of hematoma. In conclusion, conscious, small hemispheric hematomas can be serially followed up with widely and easily available CT scan and regular neurological status monitoring, thus avoiding unnecessary surgical evacuation.

Key words: trauma, occipital skull fracture, traumatic cerebellar hematoma

[1] Sestre milosrdnice University Hospital Center, Clinical Hospital of Traumatology, Zagreb, Croatia; Faculty of Medicine, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia

[2] Polyclinic for Cardiovascular Disease and Rehabilitation, Zagreb, Croatia

[3] Osijek University Hospital Center, University Department of Neurology, Osijek, Croatia

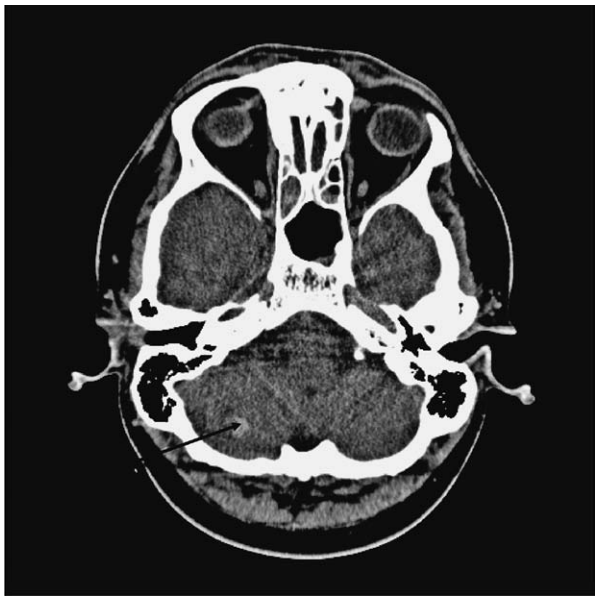


Fig. 1. *Computed tomography scan demonstrates traumatic cerebellar hematoma measuring 11 mm.*

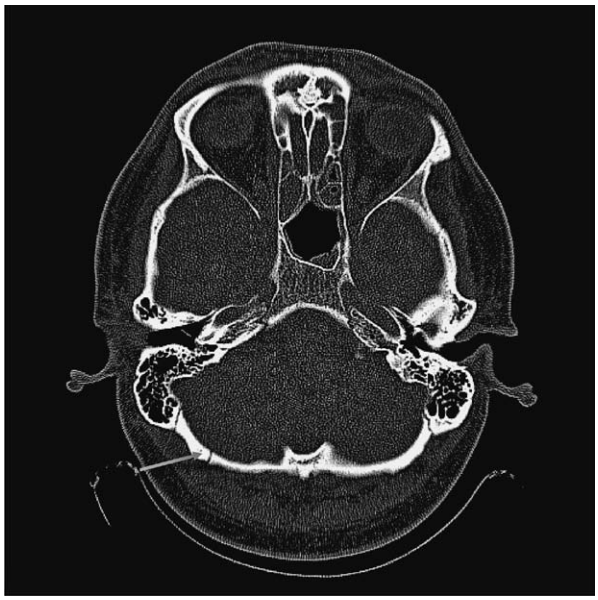


Fig. 2. *Computed tomography scan demonstrates occipital skull fracture.*

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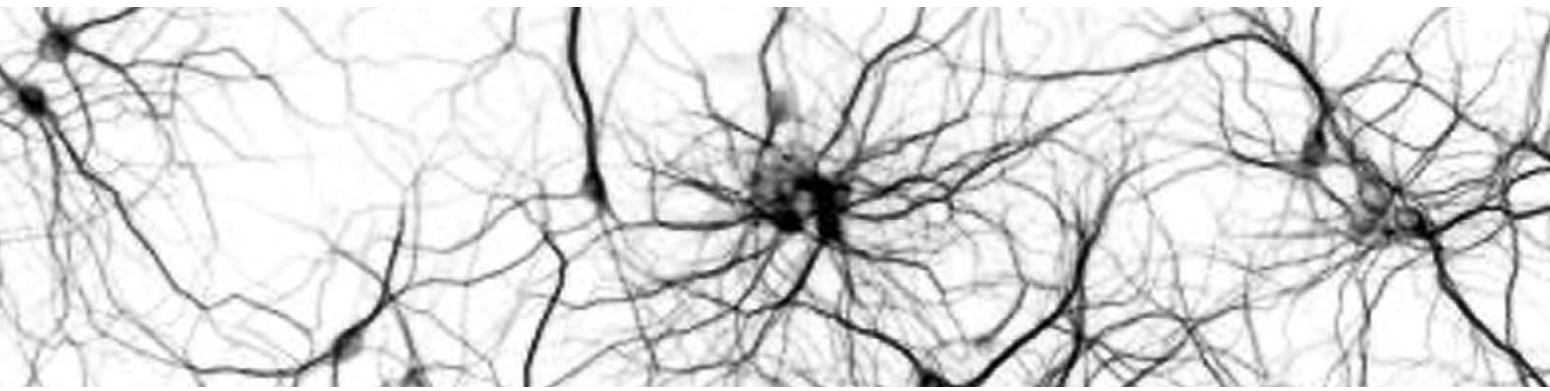
Address for correspondence: Antonija Krstačić, MD, PhD, Clinical Hospital of Traumatology, Sestre milosrdnice University Hospital Center, Draškovićeva 19, HR-10000 Zagreb, Croatia; e-mail: akrstacic@gmail.com



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The complete manuscript, including text, figures, tables and references, should be typed on one side of a paper only, double-spaced, with 3 cm left margin and right margin not justified. Each paragraph should be indented by five spaces. Author should mark in the margin where figures and tables are to be inserted. Each section should start on a new page (i.e. title page, abstract, figures, tables, legends and references).

The **title page** should comprise: 1) title of paper; 2) full name of each author followed by their highest academic degrees and institutional affiliations (all institutional names should be written in English); 3) name, accurate address, phone & fax number and e-mail of the author responsible for correspondence, galley-proofs and reprints; 4) short title, not longer than 30 characters including spaces; and 5) acknowledgement of source(s) of support.

Abstracts should be no longer than 250 words. Original contributions should have structured abstracts with the following headings: objectives, methods, results and conclusions. Abstract for Neurological reviews should not be structured. Case reports should have structured

abstract with the following headings: objectives, case description, results, conclusion. Images in neurology and letters to the editor do not require an abstract. It should only present the main results and avoid general formulations and well-known facts. Three to ten key words, from Index Medicus, should be supplied in alphabetical order immediately following the abstract. Please search for the key words at the web page http://www.ncbi.nlm.nih.gov/pubmed/, link MeSH Database.

Text should be divided, when appropriate, into sections: Introducion, Material and Methods, Results, Discussion, and Conclusion. Scientific papers, including list of references, should not exceed 12 pages (32 lines with 60 characters each *per* page), and brief communications 3 pages.

Tables should be typed on separate sheets, not to be submitted as photographs. Illustrations should be provided unmounted, in the form and condition suitable for reproduction. Freehand drawings, raw laboratory material, e.g. strip charts, roentgenograms, etc., should be photographed in B/W. Photographs should not be larger than 20x25 cm. If the attachements are in colour (tables, photographs, etc.), the author should pay for the expenses of printing that page in agreement with the Denona Printing-House. For every photograph of a recognizable patient written permission is required. On the back of each photograph indicate its number and top of the photograph. Beside that, the set of illustrations accompanying master copy should have the name of the first author written on the back. The author(s) should be aware that the size of illustrative material may be reduced if needed. Tables and figures should be numbered in Arabic numerals in the order they are mentioned in the text. Legends for each of them should be typed separately, each legend on a separate sheet. The number of figures should not exceed 6.

List of **references** should include only those works that are cited in the text and that have been accepted for publication or already published. The list should be arranged according to the order of appearance in the text and then numbered. Several works of the same first author should be listed chronologically by the year of publication. Index Medicus abbreviations for journal names should be used.

Journals

All authors to be listed in case there are six or less:

Mubrin Z, Kos M. Assessment of dementia. Flow chart approach to clinical diagnosis. Neurol Croat 1992; 41: 141-156.

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.

Citations of works in text should be indicated by numbers in brackets.

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Prof. Sanja Hajnšek, MD, PhD, Editor-in-Chief, NEUROLOGIA CROATICA, University Hospital Center Zagreb, Department of Neurology, University of Zagreb School of Medicine, Kišpatićeva 12, HR-10 000 Zagreb, Croatia; e-mail: predstojnik.nrl@kbc-zagreb.hr

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:

1. **Izvorni znanstveni rad**: Maksimalna duljina: 3000 riječi, bez tablica, opisa slika i literature. Uza svaki tekst potrebno je navesti i ukupan broj riječi (ukljujući sažetak, cijeli tekst, tablice, opise slika i literaturu).
2. **Neurološki pregled**: Pregledi su obično zatraženi od strane urednika, no i spontane prijave su dobrodošle. Svi pregledani članci i izvori podataka bi trebali sadržavati informaciju o specifičnoj vrsti studije ili analizi, populaciji, intervenciji, izlaganju i testu ili rezultatima. Svi članci i izvori podataka bi trebali biti sustavno odabrani za uključivanje u pregled i kritički evaluirani, te bi proces odabira trebao biti opisan u članku. Maksimalna duljina: jednako kao i za izvorne znanstvene radove.
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4. **Izvještaji o slučajevima Klinike za neurologiju Kliničkog bolničkog centra Zagreb** će biti zatraženi od strane urednika.
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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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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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