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Editorial

Dear Readers and Colleagues,

Welcome to the first issue of Neurologia Croatica in 2014.

In this year, we hope to achieve our former goal of increasing national and international scientific popularity of our journal. Besides continuing to publish the journal in English exclusively (which has proved as a good decision) and having also online submissions (which has resulted in more papers submitted not only from our country, but also from abroad), our intention is to have more original scientific papers from all over the world, and more international reviewers. The greater number of collaborators (clinicians and scientists) in different roles, should eventually lead not only to identifying some new fields in neuroscience suitable for publishing in Neurologia Croatica, but also to upgrading the quality of our journal.

This issue of Neurologia Croatica brings an interesting original article about the results of a study in multiple sclerosis patients which, once again, confirmed the usefulness of tongue somatosensory evoked potentials in the evaluation of afferent trigeminal pathways in multiple sclerosis. It is followed by two very useful clinical reviews, one about difficulties in the diagnosis of vestibular migraine, which is now, with the help of the newly proposed criteria, much easier, and the other one about the problems with, very often not evidence based, complementary and alternative medicine in treating multiple sclerosis. The Case Reports section includes four unusual clinical cases. The first one presenting differential diagnostic problems in patients with neuroborreliosis, originally thought to be multiple sclerosis, and the second one being mostly neuroradiological challenge, where the usually benign posterior reversible encephalopathy syndrome mimicked paraneoplastic encephalomyelitis in a patient with subsequently discovered small cell lung cancer. There also are two case reports by our colleagues from Turkey, presenting a rare neurological clinical picture of celiac disease and two patients with limbic encephalitis. This issue, in the Case Records sections, presents a very rare consequence of poisoning with algae dinoflagellates by ingesting fish from the Adriatic Sea, which resulted in chronic fibromyalgia, and finally a case of severe relapse of multiple sclerosis due to therapy change, presented not only as clinical picture worsening, but also through impressive neuroimaging changes.

At the end, I hope we all will enjoy reading this issue and also get motivated to submit experiences and doubts from our daily clinical routine and scientific work in the form of new contributions to Neurologia Croatica.

Professor Zdravka Poljaković, MD, PhD Associate Editor Neurologia Croatica



Tongue somatosensory evoked potentials in multiple sclerosis

M. Krbot Skorić¹, I. Adamec¹, T. Gabelić¹, M. Habek^{1,2}

ABSTRACT – **Objective:** The aim of this study was to determine the efficacy of tongue somatosensory evoked potentials (tSSEP) in the evaluation of brainstem involvement in patients with multiple sclerosis (MS). **Methods:** tSSEP was performed in ten healthy volunteers and 29 patients with first clinical episode of a demyelinating event suggestive of MS. The data obtained were compared between the two groups and tSSEP findings of MS patients were correlated with their clinical and magnetic resonance imaging (MRI) data. **Results:** Multiple sclerosis patients had statistically significant prolongation of N1, P1 and N2 latencies on the left side compared with healthy controls (17.8 \pm 3.5 *vs.* 15.2 \pm 1.3, p=0.004; 23.9 \pm 3.3 *vs.* 20.8 \pm 1.0, p<0.001; 29.9 \pm 4.2 *vs.* 26.7 \pm 2, p=0.01, respectively) and of P1 and N2 on the right side (23.8 \pm 3.5 *vs.* 20.8 \pm 1.3, p=0.04; 30.3 \pm 3.8 *vs.* 27.3 \pm 1.9, p=0.01, respectively). Out of the 29 MS patients, eight (28%) had clinically evident involvement of the brainstem and 19 (66%) had brainstem lesions demonstrated on brain MRI. There were 19 MS patients with prolonged latencies of tSSEP on either side with no clinical signs of brainstem lesions in a higher percentage than MRI, it was not statistically significant (p=0.18). **Conclusion:** This study conducted on a larger number of MS patients confirmed the usefulness of tSSEP in the evaluation of afferent trigeminal pathways in MS.

Key words: tongue somatosensory evoked potentials, trigeminal afferent pathway, magnetic resonance imaging, multiple sclerosis

INTRODUCTION

The role of evoked potentials in the diagnosis of multiple sclerosis (MS) has changed over time, largely due to advances in imaging techniques. It has largely changed clinical practice with magnetic

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resonance imaging (MRI) becoming the first, and very often the only investigation performed in MS patients. This has been acknowledged in a recently published revision of McDonald's criteria, which along with clinical symptoms use only MRI in providing evidence for dissemination in time and space (1). This is not always justifiable since the information provided by evoked potentials is more related to the function, unlike the information provided by MRI, which is more related to the anatomy (2).

Evidence suggests that brainstem involvement in MS is one of the major predictive factors for future disability. A recent work demonstrates that brainstem pathology is more frequent than can be depicted either clinically or with the use of MRI, and evoked potentials have been shown to reliably predict disability in MS patients (3). Brainstem involvement in MS can be manifested with different symptoms, and from these, diplopia is by far most common, followed by facial sensory symptoms, unstable gait, vertigo, oscillopsia, facial weakness/ hemispasm, nausea and/or vomiting, trigeminal neuralgia, dysarthria (constant/paroxysmal), hypacusia, myokymia, dysgeusia, somnolence and dysphagia (4). Trigeminal nerve is the most commonly involved isolated cranial nerve in MS (5). Trigeminal involvement detected by MRI in MS is usually associated with trigeminal neuralgia or painless paresthesia in the distribution of the fifth nerve (6).

We have recently shown in a small cohort of early MS patients that the tongue somatosensory evoked potentials (tSSEP) are an efficient method for evaluating the afferent trigeminal pathway in patients with early MS (7). The aim of the present study was to determine the efficacy of (tSSEPs) in the evaluation of afferent trigeminal pathway in a larger cohort of MS patients.

SUBJECTS AND METHODS

The study included ten healthy volunteers, 5 female and 5 male, age range 27-66, mean age 33.2 years, and 29 patients with the first symptom of MS, 15 female and 14 male, age range 18-51, mean age 31.4 years. All patients underwent brain MRI and cerebrospinal fluid (CSF) analysis. Exclusion criteria for the study were molar surgery and any preexisting lesion of trigeminal nerve that could influence outcome of the study.

All participants were informed about the details of the experiment and they all signed informed consent forms. The study was approved by the Ethics Committee of the Zagreb University Hospital Center. The methods of data recording and analysis were designed according to the previously described details (8).

During the experiment, study subjects were sitting in a comfortable chair. After explaining them the experiment in detail, they were instructed to relax in order to avoid muscle tension. Electroencephalography (EEG) electrodes mounted on the plastic clip were used for stimulation and they were located on the lateral side of the first two-thirds of the tongue. The subjects opened the mouth slightly and the tongue with stimulation electrodes was held relaxed inside the mouth. Each side of the tongue (left and right) was stimulated twice with 300 trials in order to confirm the repeatability of the cortical response obtained. Stimulation was produced with a constant current stimulator (Twister, Germany). The frequency of the stimulation was 3 Hz and the duration of each stimulus was 0.2 ms. The polarity of the stimulation was alternating in order to avoid large baseline shifts.

At the beginning of each set of trials, the perceptive threshold was assessed in each subject. The intensity of stimulation during each set of trials was set at three times the perceptive threshold. It varied



Fig. 1. Superimposed tracings from two repeats of the tongue somatosensory evoked potentials (tSSEP) in the healthy control. Upper panel: tSSEP from the stimulation of the right side of the tongue; lower panel: tSSEP from the stimulation of the left side of the tongue.

Gender (M/F)	Age (yrs)	EDSS	BS FS	MRI	tSSEP	Conduction block	tSSEP_R	tSSEP_L
М	30	1.0	0	1	1	0	1	0
F	31	2.0	2	1	1	1	0	1
F	42	1.0	0	0	1	1	1	0
F	33	3.5	0	1	1	0	0	1
М	42	2.0	0	1	0	0	0	0
М	29	0	0	0	1	0	1	1
F	23	3.0	0	1	1	0	1	0
F	22	3.0	0	1	1	1	1	1
М	23	2.0	2	1	1	0	1	1
М	38	0	0	1	1	1	1	0
М	29	3.5	0	1	1	0	1	1
М	26	2.0	0	0	1	0	1	1
F	28	0	0	0	1	0	0	1
М	36	2.5	0	0	1	0	1	1
F	18	0	0	0	1	0	1	0
М	51	0	0	1	1	0	1	0
М	28	0	0	1	1	0	0	1
М	20	1	0	1	1	0	1	1
F	27	2	2	1	0	0	0	0
F	31	1	0	1	0	0	0	0
F	26	3	3	0	1	0	1	1
F	30	0	0	0	1	0	0	1
М	29	2	0	1	1	1	1	1
F	35	0	0	0	1	1	1	1
F	33	1	0	1	1	0	1	1
F	34	1	1	1	0	0	0	0
F	41	2	2	1	1	1	1	1
М	34	1	1	0	1	0	0	1
М	42	3.5	2	1	1	1	1	1

Table 1. Characteristics of study patients

EDSS = Expanded Disability Status Scale; BSFS = brainstem functional system (part of the EDSS); F = female; M = male; tSSEP = tongue somatosensory evoked potentials; R = right; L = left; 0 = negative; 1 = positive.

from 4.5 mA to 10 mA for patients and from 3.5 mA to 9 mA for healthy controls.

Cortical response was recorded from four surface disk electrodes situated at the surface of the scalp. Active electrodes were situated on the contralateral side of the scalp, according to the international 10/20 system, at the middle position between C3 and T3 for stimulation of the right side of the tongue (C5 electrode) and at the middle position between C4 and T4 for stimulation of the left side of the tongue (C6 electrode). Both electrodes were referred to the frontal electrode Fz. The electrode situated at the vertex (Cz) was used as a ground electrode.

Responses obtained with electrical stimulation of the tongue were recorded with a Brain Products Vision Recorder (Germany) and analysis of the recorded data was performed using a Brain Products Vision Analyzer (Germany). Signals were filtered with a bandpass filter from 0.1 Hz to 1000 Hz. Sampling rate was 5000 Hz. For the purpose of averaging, signals were divided in segments of 70-ms duration according to the time position of the stimulus (20 ms before the appearance of the stimulus and 50 ms after the appearance) and averaged for each set of 300 trials. The grand average was computed from two averaged sets and used for analysis.

The responses obtained consisted of three main components (N1, P1 and N2), as shown in Figure 1. Latencies and peak to peak amplitude values (N1-P1 and P1-N2) were analyzed in order to detect the difference between healthy controls and MS patients.

Statistical analysis was performed using the SPSS 17.0 software. Differences in qualitative variables were analyzed by the χ^2 -test, while differences in quantitative variables, in respect of distribution, were analyzed by the parametric t-test or non-parametric Mann-Whitney test. The p values less than 0.05 were considered statistically significant.

RESULTS

Multiple sclerosis patients had a statistically significant prolongation of N1, P1 and N2 latencies on the left side compared with healthy controls $(17.8\pm3.5 vs. 15.2\pm1.3, p=0.004; 23.9\pm3.3 vs. 20.8\pm$ 1.0, p<0.001; and 29.9±4.2 vs. 26.7±2, p=0.01, respectively), and P1 and N2 on the right side



Fig. 2. Brain magnetic resonance imaging: T2 sequences of the patient with multiple sclerosis who presented with double vision. Left figure shows demyelinating lesion present in the brainstem, Right figure shows multiple periventricular lesions.



Fig. 3. Results of the tongue somatosensory evoked potentials (tSSEP) in the multiple sclerosis patient from Figure 2. Upper panel: tSSEP from the stimulation of the right side of the tongue showing prolonged latencies. Lower panel: tSSEP from the stimulation of the left side of the tongue showing prolonged latencies.

(23.8±3.5 *vs*. 20.8±1.3, p=0.04; and 30.3±3.8 *vs*. 27.3±1.9, p=0.01, respectively).

There was no statistically significant difference in latency and amplitude values between the left and right sides. From the values of the left and right sides, the averaged values of latencies and amplitudes were calculated. There was a statistically sig-



Fig. 4. Brain magnetic resonance imaging (MRI), T2 sequences of the patient with multiple sclerosis who presented with paraparesis. Left figure shows normal MRI at the level of the brainstem. Right figure shows multiple periventricular lesions.



Fig. 5. Results of the tongue somatosensory evoked potentials (tSSEP) in the multiple sclerosis patient from Figure 4. Upper panel: tSSEP from the stimulation of the right side of the tongue showing prolonged latencies of the P1 wave; lower panel: tSSEP from the stimulation of the left side of the tongue showing prolonged latencies of the P1 wave.

nificant difference between healthy controls and MS patients in the averaged N1 latency (15.5 ± 1.4 *vs.* 17.7 ± 2.6 , p=0.003), averaged P1 latency ($20.8\pm$ 0.8 *vs.* 23.7 ± 2.6 , p<0.001) and averaged N2 latency (26.9 ± 1.6 *vs.* 30.3 ± 4.1 , p<0.001), while there was no statistically significant difference in the amplitudes.

Out of the 29 MS patients, eight (28%) had clinically evident involvement of the brainstem and 19 (66%) had brainstem lesions demonstrated on brain MRI (Table 1). There were 19 MS patients with prolonged latencies and/or complete block of tSSEP on either side with no clinical signs of brainstem dysfunction and this difference was statistically significant (p<0.0001). Although tSSEP detected brainstem lesions in a higher percentage than MRI, it was not statistically significant (p=0.18). Figures 2 and 3 present a patient with demyelinating lesions in the brainstem and prolonged latencies in tSSEP. Figures 4 and 5 present a patient with normal brainstem MRI and prolonged latencies in tSSEP.

DISCUSSION

This study confirmed our previous findings on the usefulness of tSSEP in the evaluation of afferent trigeminal pathway in MS (7). Patients with MS showed prolonged latencies compared to healthy controls and this method is more precise in detecting brainstem involvement than clinical examination. Although tSSEP were pathologic in a higher percentage than MRI, the difference was not statistically significant.

The recording of evoked potentials is a noninvasive routine clinical testing procedure in neurology. For trigeminal nerve stimulation, however, evoked potentials have not received widespread clinical attention. The main reason for this is a variety of protocols and procedures that have been used; differences encountered include the stimulation mode, site and frequency, the recording electrode position and data acquisition parameters (9). This has resulted in a diversity of recorded trigeminal somatosensory evoked potentials signals, making comparisons almost impossible.

Nevertheless, there are only few studies employing this methodology in MS.

Bergamaschi *et al.* used trigeminal somatosensory evoked potentials by surface electric pulse stimulation in 70 MS patients, 13 of whom presenting clinical trigeminal impairment. The authors observed significant prolongation of all evoked potential parameters in MS group with trigeminal somatosensory evoked potentials being abnormal in 64.3% of patients. Clinical and neurophysiological data were consistent in 36 (51%) patients on 84 (60%) sides with trigeminal somatosensory evoked potentials being able to detect clinically silent lesions 54 times (10). Similarly, another group found changes in trigeminal evoked potentials (showing distorted waveforms and/or prolonged latencies) in 69.4% of patients (11). The presence of demyelinating plaques in the brainstem often causes involvement of the trigeminal nerve, demonstrable by blink and jaw reflexes (12). Trigeminal somatosensory evoked potentials have proved to be quite informative in the evaluation of the sensory 5th nerve function but have remained underused in the workup for MS.

Compared to trigeminal somatosensory evoked potentials, tSSEP have an excellent sensitivity for pathological processes involving the somatosensory afferents of the tongue, however, they do not seem to provide further information on the nature of the lesion (8).

In conclusion, this study confirmed, in a larger number of MS patients, the usefulness of tSSEP in the evaluation of afferent trigeminal pathways in MS.

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Somatosenzorni evocirani potencijali jezika u bolesnika s multiplom sklerozom

SAŽETAK – **Cilj:** Cilj ovoga istraživanja bio je ispitati učinkovitost somatosenzornih evociranih potencijala jezika (tSSEP) u procjeni zahvaćenosti moždanog debla u bolesnika s multiplom sklerozom (MS). **Metode:** Metoda tSSEP je provedena na deset zdravih ispitanika i 29 bolesnika s prvim kliničkim znakovima koji upućuju na MS. Dobiveni podatci uspoređeni su između dvije skupine i tSSEP rezultati dobiveni kod bolesnika s MS-om korelirani su s njihovim kliničkim podatcima i magnetskom rezonancom (MR). **Rezultati:** Bolesnici s MS-om su imali statistički značajno produžene latencije komponenata N1, P1 i N2 na lijevoj strani u usporedbi sa zdravim kontrolama (17,8±3,5 *vs.* 15,2±1,3, p=0,004; 23,9±3,3 *vs.* 20,8±1,0, p<0,001; 29,9±4,2 *vs.* 26,7±2, p=0,01) te latencija komponenata P1 i N2 na desnoj strani (23,8±3,5 *vs.* 20,8±1,3, p=0,04; 30,3±3,8 *vs.* 27,3±1,9, p=0,01). Od 29 bolesnika s MS-om osam (28 %) ih je imalo kliničke znakove oštećenja moždanog debla i 19 (66 %) ih je imalo lezije moždanog debla vidljive na MR-u. Devetnaest bolesnika s produženim latencijama nije imalo kliničkih znakova zahvaćenosti moždanog debla (statistički značajno, p<0,0001). Metoda tSSEP je otkrila lezije moždanog debla u većem postotku nego MR, ali to nije bilo statistički značajno (p=0,18). **Zaključak:** Ovo istraživanje provedeno na većem broju bolesnika s MS-om

Ključne riječi: somatosenzorni evocirani potencijali jezika, aferentni trigeminalni putovi, magnetska rezonanca, multipla skleroza



Vestibular migraine considering new diagnostic criteria

S. Maslovara, S. Butković Soldo¹, I. Pajić-Penavić², T. Alkhamis³, T. Vešligaj, A. Soldo¹

ABSTRACT – Vestibular migraine is one of the causes of spontaneous vertigo. Around 50 to 60 percent of migraine patients experience vertigo following a migraine attack, and in about half of the patients vertigo occurs unrelated to the headache. It is clinically manifested as a rotatory, positioning, visually- or head-movement-related vertigo. In more than 60% of cases, photo- or phonophobia occurs. Changes in electro-nystagmography/videonystagmography results are more common in patients with migraine than in the rest of the population, but very different and unspecific. Although accepted, the lack of universally acclaimed definition of vestibular migraine prevented clinicians and researchers to recognize it more often. In July 2012, the Bárány Society's Committee for Classification of Vestibular Disorders and Subcommittee for the Classifications of Migraine of the International Society for Headaches have co-published diagnostic criteria for vestibular migraine and probable vestibular migraine as part of the project in the classification of otoneurologic disorders. Diagnosis of vestibular migraine is based on the presence of different forms of vertigo with moderate or severe intensity, which occur often and last between 5 minutes and 72 hours, as well as on the history of migraine and exclusion of other causes of vestibular symptoms. For the first time, we are in possession of proposed criteria for the diagnosis of vestibular migraine, which will facilitate the diagnosis of this common but insufficiently diagnosed vertiginous entity.

Key words: migraine, episodic recurrent vertigo, vestibular migraine, diagnostic criteria

INTRODUCTION

The association between migraine and vestibular sense has been known since 1861, when Prosper Ménière described Ménière's syndrome in patients with migraine (1). Later, other authors also observed correlation of symptoms such as tinnitus, hearing loss and vertigo with migraine. When described, vertiginous spells that occur during mi-

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graine headaches or related to them, during a peaceful period, are called vestibular migraine (VM), migraine vertigo (MV), migraine related vertigo (MRV), and it is supposed that benign vertigo related to the position that occurs during childhood is also a form of this entity. It is the most common cause of vertigo occurring spontaneously, and according to some authors, the second most common cause of vertigo in general (2-4). Until recently, vertigo related to migraine was, similar to benign paroxysmal positional vertigo (BPPV), rarely diagnosed and frequently neglected by the clinicians. In recent years, the awareness of this phenomenon has increased significantly due to the scientific work of many authors, both worldwide and in Croatia (5-7).

ETIOPATHOGENESIS

Taking into account empirical and epidemiological arguments in favor of the existence of a common etiopathogenesis of migraine and VM (8), as well as abnormalities found in vestibular experiments during and between vertiginous episodes (9), various hypotheses have been proposed for VM, and all come from the presumed pathophysiological mechanism of migraine.

In spite of the general hypothesis on the origin of VM, which is no longer considered to be valid, and nowadays it is considered to be a primary brain disorder (10), the theory of the specific internal auditory artery vasospasm still remains a potential explanation for the peripheral vestibular and auditory symptoms of migraine (11), similar to the retinal vasospasm observed in retinal migraine (12).

Another hypothesis seeking to explain the pathophysiology of VM presents migraine aura as a probable clinical equivalent to cortical spreading depression, while vertigo is the most common manifestation of basilar migraine aura (13,14).

The development of molecular techniques has led to the new momentum in the theories on different molecular channelopathies, so neither ion channels defect should be left out as a potential contributing factor in the development of VM. The concept of ion channel disorder is particularly interesting for VM, since different mutations in the CACNA1A gene that encodes a transmembrane component of the neuronal calcium channel can provoke family hemiplegic migraine or episodic attacks of ataxia type 2 (15). In addition to calcium metabolism, potassium also has a potential role in the development of VM. Namely, a mutation in the KCNA1 gene is a common finding in family episodic ataxia syndrome, which can be presented as recurrent vertigo with migraine (16). However, analysis of patients with familial migraine with vertigo excluded mutation in the CACNA1A gene in some patients (17), leaving the question of the role of ion channel mutations in the pathophysiology of VM open.

Finally, one of the latest hypotheses when considering the pathophysiology of VM is activation of the specific neural structures. Functional positronemission tomography images during acute migraine attack identified activation of the brain stem regions in projection of the coeruleus and dorsal raphe nucleus, suggesting that these structures are involved in the induction of migraine attacks (18). Since vestibular nuclei receive noradrenergic projections from the locus coeruleus (19) and serotonergic input from the dorsal raphe nucleus (20), it is possible that activation of these structures during migraine attacks also affects the central vestibular processing (21). Observation of eye movements during and between VM attacks suggests primarily the existence of central vestibular disorders, but the possibility of a peripheral vestibular cause is not completely excluded either (22).

In conclusion, our review of current literature suggests that VM is a heterogeneous vestibular disorder, in the onset and progression of which different pathophysiological mechanisms are involved.

EPIDEMIOLOGY

Migraine is a widely spread disease, as evidenced by a comprehensive recently published survey including revision of 19 previous studies dealing with migraine in adults according to the International Classification of Headache Disorders II (ICHD-II) criteria. According to the results, the annual prevalence of migraine is 11.5%, probable migraine 7%, while their combined annual prevalence is 18.5% (23). Mostly women of reproductive age are affected (2-3 times more often than men) (24). In Germany, according to Neuhauser et al. and Neuhauser, the annual prevalence of vertigo in general population is 4.9% and of vestibular migraine 0.89% (25,26). Results of the survey conducted in Croatia have shown the annual prevalence of migraine with and without aura to be 7.5% and of probable migraine 11.3%. Joint annual prevalence of migraine and probable migraine is 13.0% and is higher in the inland part of Croatia than in coastal Croatia (27). Vertigo was by far more common in patients with migraine than in the control group of patients with tension headaches or those without headache (28). Nevertheless, the association of these two entities is still so intertwined and controversial, and the clinical manifestations are so varied that some authors speak of "a chameleon among episodic vertiginous syndromes" (29).

CLINICAL SYMPTOMS

There are a large variety of typical symptoms, which patients themselves are often not aware of. They can occur in various forms, e.g., as spontaneous rotatory (subjective or objective) vertigo or positional vertigo, as visually-induced vertigo (caused by movement of large and complex visual stimuli), as head motion-induced dizziness (taking place subsequent to the motion of the head and accompanied by nausea and loss of spatial orientation), as well as blurriness, instability, and instability while standing or walking. With a well-taken history data, one can easily distinguish between vertigo as a vestibular and dizziness as a non-vestibular phenomenon (30). The only form of non-vestibular symptoms related to VM is head motion-induced dizziness with nausea. It occurs spontaneously, periodically, and usually lasts between several minutes and several hours, but sometimes it can be measured in seconds or days. According to the results, 32% to 63% of patients with migraine have an accompanying vertigo, which in 45% of cases occurs regardless of headache (31,32). Migraine attacks occurred as vertigo in over 60% of cases, followed by photo- or phonophobia, as well as aura in some patients.

Changes in electronystagmography/videonystagmography (ENG/VNG) reports are more common in migraine patients than in healthy population, but are rather diverse and nonspecific (33).

DIAGNOSIS

There is no single pathognomonic test which can help in setting the correct diagnosis of VM. A detailed medical history is critical as in other types of vertigo (34,35). It is essential to write a diary of headache, recording all of its characteristics for at least three months. It is important to be familiar with the International Headache Society (IHS) criteria for the diagnosis of headache, which determine the type of headache very accurately (36). The findings of otoneurologic examination are normal in most cases, but sometimes in acute vertigo a spontaneous or positional, horizontal, rotatory and vertical type of nystagmus can be observed (37). Dix-Hallpike test can sometimes yield subjectively but not objectively positive results. Vestibular tests are only used to exclude other causes of vertigo. Although very varied and nonspecific, vestibular laboratory test abnormalities in patients with VM in the periods between attacks are twice as likely as in patients suffering from migraines (38).

One of the recent clinical studies indicates abnormal results in at least one of the three laboratory tests carried out in 66% of VM patients, mostly after performing the head shaking test (HST) (39). This is understandable given that these patients are very sensitive to movement, and it is characteristic that most of them (about 70%) experienced an illusion of the surrounding moving around them or themselves moving through the surrounding. Definitive diagnosis can only be set in the case of migraine with aura or vertigo that occurs simultaneously with headaches. Definitive diagnosis is often made by exclusion of other possible causes of vertigo or *ex juvantibus*, according to a positive response to antimigrainous therapy.

In July 2012, The Bárány Society Committee for Classification of Vestibular Disorders and the International Society for Headaches Subcommittee for the Classification of Migraine published diagnostic criteria for VM and probable VM jointly, as part of a larger project of otoneurologic disorders classification. The diagnosis of VM is based on the presence of various forms of vestibular symptoms with moderate or severe intensity that appear frequently and last between 5 minutes and 72 hours; the history of migraine; and exclusion of other possible causes of vestibular symptoms (40). These criteria have been incorporated in the 3rd edition of the ICHD-III, published in 2013, i.e. in an annex concerning new disorders necessitating more studies. Precisely defined, the criteria that must be met for the diagnosis of VM and probable VM are as follows:

VESTIBULAR MIGRAINE

 A) At least five episodes of migraine with vestibular symptoms¹ of moderate or severe intensity² lasting between 5 minutes and 72 hours³

¹Vestibular symptoms qualified for the diagnosis of vestibular migraine include:

⁻ spontaneous vertigo, which includes:

^{1) &}quot;subjective vertigo", an illusion of spontaneous moving through the visual surrounding, and

^{2) &}quot;objective vertigo", an illusion of visual surrounding spinning or flowing

- B) Current or previous history of migraine with or without aura according to ICHD⁴
- C) In over 50% of vestibular episodes⁵ one or more features of migraine are found:

– headache with at least two of the following features: one-sided, pulsating, moderate or severe pain, pain amplification in normal physical exertion

- photophobia and phonophobia⁶
- visual aura⁷
- D) Without better explanation within other vestibular or ICHD diagnoses⁸

- visually induced vertigo launched by complex or significant visual stimuli
- vertigo due to head motion that occurs during movement of the head
- dizziness caused by head motion, accompanied by nausea and a feeling of impaired spatial orientation.

² Severe vestibular symptoms are those that interfere with daily activities to the extent that they cannot be continued, and moderate symptoms interfere with daily activities, but to the extent that they can be resumed.

³ The length of these episodes varies: about 30% of patients have episodes lasting for several minutes, 30% have migraine attacks that last for hours, and 30% have migraine attacks lasting for several days. The remaining 10% have attacks that last for seconds and occur repeatedly during head movements, visual stimulation, or after change in head position. In these patients, the length of the episode is defined as the total period during which these brief attacks last. At the other end of the spectrum are patients who need four weeks to recover from one episode, although the main episode rarely exceeds 72 hours.

⁴Mygraine types 1.1 and 1.2 according to ICHD.

⁵One symptom is enough during a single episode. Different symptoms may occur during various episodes. Related symptoms may occur before, during or after vestibular symptoms.

⁶ Phonophobia is defined as a discomfort caused by sound. It is a temporary bilateral phenomenon and must be distinguished from the recruitment, which is unilateral and durable. Recruitment means the occurrence of heightened perception, often distortion of loud sounds in the ear with a significant hearing impairment.

PROBABLE VESTIBULAR MIGRAINE

- A) At least five episodes of migraine with vestibular symptoms of moderate or severe intensity lasting between 5 minutes and 72 hours
- B) One of the criteria B or C for vestibular migraine
- C) Without better explanation within other vestibular or ICHC diagnoses

Along with everything else, migraine attacks can be triggered by vestibular stimulation. Thus, the differential diagnosis should include other vestibular disorders further complicated by the added migraine.

DIFFERENTIAL DIAGNOSIS

The largest differential diagnostic problem is Ménière's disease or *Morbus Ménière* (MM), with a similar duration as VM, but never lasting longer than 48 hours, which is often the case with VM. In addition, MM is generally accompanied by characteristic symptoms of progressive unilateral hearing loss (mostly in lower frequencies). Hearing impairment with VM is rare and less significant, occurs mostly bilaterally and worsens over time.

The ENG/VNG findings in both diseases show unilateral labyrinth lesion, which is present in every MM case to a lesser or greater extent, while in VM it occurs in only 20%-25% of cases. VM is often (25%) accompanied by positive positional test, as well as by nystagmus finding within different searches. Tinnitus is very strong in MM, either unilaterally or bilaterally, while in VM it has lower intensity, in case it ever occurs. Photophobia is a symptom that often occurs in connection with VM and never with MM.

Finally, it should be noted that these two diseases can coexist (41,42). In this case, MM should be treated by all principles of its treatment. Concerning MM, in terms of differential diagnosis, one should always think of the possible BPPV (because a significant portion (25%) of VM patients had positive Dix-Hallpike test), as well as vestibular neuronitis, perilymphatic fistula and transient is-

⁻ positional vertigo that occurs after a change in head position

⁷ Visual auras are characterized by bright scintillating lights or zigzag lines, often with an outburst that interferes with reading. They typically intensify in 5-20 minutes and last less than 60 minutes. They are often, but not always limited to one hemisphere. Other forms of migraine aura, or somatosensory or dysphasic aura, are not included in the diagnostic criteria because their phenomenology is less specific, and most patients also have visual auras.

⁸ Medical history and otoneurologic review do not suggest a different vestibular disorder, or such a disorder is taken into account, but was rejected after an appropriate search, or such a disorder exists as a comorbid or independent case, but the episodes can be easily distinguished from one another.

chemic attack. Also, BPPV that occurs during childhood and adolescence, according to several authors, is closely associated with VM in later life (43-45).

A much larger differential diagnostic problem may arise in case of basilar migraine (in ICHD-III, migraine with brain stem aura) (36), sometimes accompanied by hearing impairment similar to that in MM. However, the hearing damage does not deteriorate over time, and the disease is usually accompanied by many neurologic symptoms, i.e. ataxia, dysarthria, visual disturbances such as diplopia and visual symptoms like spots or flashes, simultaneously in both temporal and nasal fields of both eyes, bilateral paresthesias and reduction and/ or complete loss of consciousness.

TREATMENT

There is still no specific cure for VM, so the treatment actually comes down to common migraine treatment, a disease in its surface. More precisely, it corresponds to the treatment of migraine with aura (4).

BEHAVIOR THERAPY

Behavior therapy advocates avoiding certain foods and beverages, as well as changes in lifestyle and habits. It is recommended not to eat chocolate, carob, monosodium glutamate (found in fast food, Chinese food, soy sauce, yeast, some soups and salad dressings), aged cheeses (Colby, Roquefort, Brie, Gruyere, Cheddar, Bleu, Mozzarella, Parmesan, Boursault, Romano), aspartame, red wine, sherry, scotch and bourbon. It is desirable to give up caffeine and taking unnecessary painkillers (which causes rebound phenomenon), to regulate menstrual cycle and sleep, and to avoid stress.

PHARMACOTHERAPY

The treatment of VM is primarily prophylactic because the treatment of a migraine attack itself does not show satisfactory results. Many nonspecific drugs have been used in migraine prevention with varying degrees of success. Preventive migraine treatment should be initiated if the patient has more than 3 migraine attacks a month, which last longer than 48 hours, or when acute therapy is not effective or is contraindicated. In the case of VM, prophylaxis should be performed in all patients because the disease is often not synchronous with headache, while calm periods without headaches but with episodes of vertigo can sometimes last for years.

According to the latest recommendations of the European Federation of Neurological Societies (EFNS), first-line drugs for migraine prevention and VM therapy are β -blockers (propranolol, metoprolol), the calcium channel blocker flunarizine, and the anticonvulsants topiramate and valproic acid.

As second-line therapy, they classify the tricyclic antidepressant amitriptyline, nonsteroidal anti-in-flammatory drug naproxen, root extract of the plant *Petasites hybridus* (common butterbur) in high doses, and the β -blocker bisoprolol (46).

In relation to the EFNS, the latest American Academy of Neurology and American Headache Society's guidelines, based on several important clinical studies (47), also recommend *Petasites hybridus* as Level A (48,49).

Guidelines of the Canadian Headache Society partly coincide with those guidelines, but they also recommend the tricyclic antidepressant amitriptyline, mineral magnesium and vitamin riboflavin (B2), as the clinical studies confirm their efficacy (50).

Recommendations of the Croatian Society for Neurovascular Disorders, Croatian Medical Association, from 2012 are generally consistent with the relevant European and international guidelines. As the first group of drugs in the prevention of migraines, there are tricyclic antidepressant amitriptyline, serotonin antagonists pizotifen and dihydroergotamine and antiepileptic gabapentin. Monotherapy or a combination of β -blockers and tricyclic antidepressants is recommended (51,52).

Treatment should be strictly individual considering the particularities of each individual patient, the side effects of certain medications, other diseases of which the patient is suffering, and the availability as well as the cost of the drug. The selected drug should be prescribed by introducing it through the lowest effective doses, which are then gradually increased and given over a period of at least three months to show its full effect. Patient should be warned that the drug will have its full effect only after a period of at least 6 weeks. If the drug is successful, the patient should continue taking it for a year.

VESTIBULAR REHABILITATION

When it comes to the application of vestibular rehabilitation, opinions are divided as in the case of VM there is an unstable deficiency of one or both labyrinths. In such cases, central nervous system cannot decide and recognize which of the deficits to compensate since they are very fast and constantly changing. Vestibular rehabilitation has proved useful in uncommon VM, if quiet periods between attacks last for at least several weeks. In this case, treatment should be intensive and repeated after each subsequent attack (53). Some authors even claim that vestibular rehabilitation should only be used in cases of complications such as loss of patient's confidence in his/her own balance and visual dependence (54).

CONCLUSION

Although awareness of a significant proportion of VM among the causes of vertigo has been present for years, clear and generally accepted criteria for diagnosis have not been made until now. Today, we have proposed criteria for the diagnosis of VM, which greatly facilitate the diagnosis of this common, but unfortunately, underdiagnosed vertiginous entity. Further development of diagnostic criteria as well as nomenclature and classification of vertigo is necessary because they have been noted and shown in many different ways, which creates significant difficulties for researchers attempting a comparative analysis.

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Vestibularna migrena u svjetlu novih dijagnostičkih kriterija

SAŽETAK – Vestibularna migrena je jedan od uzroka spontano nastalih vrtoglavica. Javlja se kod 50 %-60 % bolesnika s migrenom, a kod oko polovine njih vrtoglavica se javlja nevezano uz napadaj glavobolje. Klinički se manifestira kao kružna, položavajuća, vidno ili pokretima glave potaknuta vrtoglavica. U preko 60 % slučajeva praćena je foto- ili fonofobijom. Promjene u elektronistagmografskom i ostalim laboratorijskim nalazima češće su kod bolesnika s migrenom nego kod ostale populacije, ali dosta raznolike i nespecifične. Usprkos priznatosti, manjak univerzalno prihvaćene definicije vestibularne migrene onemogućava kliničare i istraživače u češćem prepoznavanju. U srpnju 2012. godine Odbor za klasifikaciju vestibularnih poremećaja Bárányjeva društva i Pododbor za klasifikaciju migrena Međunarodnoga društva za glavobolje zajednički su objavili dijagnostičke kriterije za vestibularnu migrenu i vjerojatnu vestibularnu migrenu kao dio većega poduhvata za klasifikaciju otoneuroloških poremećaja. Dijagnoza vestibularne migrene temeljena je na prisutnosti različitih oblika vrtoglavice umjerenoga ili jakog intenziteta koji se učestalo pojavljuju, u trajanju između 5 minuta i 72 sata, anamnestičkim podatcima o migreni i isključenju ostalih uzroka vestibularnih simptoma. Prvi put posjedujemo kriterije za dijagnozu vestibularne migrene, što će uvelike olakšati dijagnostiku toga ne tako rijetkog, ali nažalost nedovoljno dijagnosticiranoga uzroka vrtoglavice.

Ključne riječi: migrena, epizodična povratna vrtoglavica, vestibularna migrena, dijagnostički kriteriji



Is complementary and alternative medicine in multiple sclerosis evidence based?

I. Zadro

ABSTRACT – The use of complementary and alternative medicine (CAM) is common in multiple sclerosis (MS). It includes approaches to MS that are not generally considered as part of conventional medicine. There is very limited research evaluating the safety and effectiveness of CAM in MS. CAM therapies in MS exhibit a broad range of risk-benefit profiles; some of these therapies are low risk and possibly beneficial, whereas others are ineffective, dangerous, or unstudied. However, in recent years, much effort has been invested in research in this very important area. Health professionals who provide objective, evidence based and practical information about the risks and benefits of CAM therapies may improve the quality of care for those with MS.

Key words: alternative therapy, complementary therapy, multiple sclerosis

INTRODUCTION

Multiple sclerosis (MS) is a chronic, often disabling disease, which affects mainly young people. Given the fact that the etiology and pathogenesis of MS are not completely understood, conventional therapy is more or less effective in individual patients, and there are limitations in terms of high prices, side effects, and so far, no proven efficacy in primary progressive form of the disease. These are the reasons why a large number of MS patients use complementary and alternative medicine (CAM) despite an approved and registered effective conventional therapy. CAM is growing in popularity and prevalence, but the problem is that patients mostly use various types of CAM therapies without consulting a neurologist. Due to the insufficient information because of a small number of randomized controlled clinical trials of CAM therapies in MS and an even smaller number of those that have proven their effectiveness, the uncontrolled use of CAM therapies in MS is not safe and may be harmful (1). Despite polarization of attitudes among neurologists about CAM therapies in MS, on counseling patients are required to follow only evidence based facts. Some forms of therapy are promising, others are ineffective and potentially harmful, and most of them require randomized controlled clinical trials.

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DEFINITION OF COMPLEMENTARY AND ALTERNATIVE MEDICINE

The National Center for Complementary and Alternative Medicine (NCCAM), which was established in 1998 by the US Congress as a new institute of the National Institutes of Health (NIH), defines CAM as "a group of diverse medical and health care systems, practices, and products that are not presently considered to be part of conventional medicine" (2). Complementary is defined as a pool of all therapeutic approaches that are used together with and alternative instead of evidence based medicine (EBM). The NCCAM classifies CAM into five categories (2):

- Biological-based therapies: natural and biologically based products, practices and interventions, e.g., herbs, supplements, diet therapy;
- Mind-body therapies: behavioral, social, psychological and spiritual approaches to health, e.g., yoga, meditation, hypnosis;
- 3) Manipulative and body-based systems: systems based on manipulation and/or movement of the body, e.g., massage, reflexology, chiropractic, osteopathic manipulative treatment;
- 4) Energy therapies: systems that use energy fields in and around the body, e.g., therapeutic touch, Reiki; and
- 5) Alternative medical systems, e.g., homeopathy, naturopathy, traditional Chinese medicine-acupuncture.

FREQUENCY AND FACTORS INFLUENCING THE UTILIZATION OF CAM

There have been a number of studies reporting the prevalence of CAM use by MS patients, and the range of prevalence is 33%-70% (3-5). The age, duration of illness and severity of MS influence CAM utilization. It seems that MS patients are turning towards CAM when the disease proceeds and conventional medication is less effective (6). Patient characteristics that are predictive of CAM use in MS are reported to be similar to those reported in the general population and include female sex, high education and patient reports of poor health status (7-9).

DIETARY SUPPLEMENTS IN MULTIPLE SCLEROSIS

VITAMIN D

Vitamin D is a group of fat-soluble prohormones, the two major forms of which are vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol). Vitamin D regulates immune function (10-13). A latitude gradient in the prevalence of MS was recognized first in the 1920s (14,15) with the MS prevalence increasing with distance from the equator in both the northern and southern hemispheres. The latitude gradient might be caused by reduction in exposure to UV radiation and thus lower vitamin D status as latitude increases. A strong correlation with ambient UV radiation levels during the first trimester of pregnancy suggests that this pattern could be linked to reduced maternal vitamin D status in winter as a result of lower ambient UV radiation during this time and people with MS are more likely to be born in late spring in both the southern (November) and northern (May) hemispheres compared to the general population (16,17). Epidemiologic studies have found that low vitamin D intake and low serum vitamin D levels may increase the risk of MS (18,19).

Despite the accumulating evidence to support a role of vitamin D in MS, only a few studies have directly measured the effect of vitamin D supplements on MS activity, but the interest is growing after publications of recent study results.

A study of the safety and efficacy of vitamin D3 as an add-on therapy to interferon β -1b (IFNB) in MS patients showed that once weekly dose of 20,000 IU (500 µg) of vitamin D3 as add-on treatment to IFNB reduces magnetic resonance imaging (MRI) disease activity in MS. Patients in the vitamin D group showed fewer new T2 lesions (p=0.286) and a significantly lower number of T1 enhancing lesions (p=0.004), as well as a tendency to reduced disability accumulation (p=0.071) and improved timed tandem walk (p=0.076) (20).

A recent study has reported that every 50 nmol/L increment in average serum 25-hydroxyvitamin D levels observed at baseline translated into a 57% lower rate of new active MS defining lesions (p=0.0009). It was found that higher baseline differences in 25-hydroxyvitamin D levels were associated with a 57% lower relapse rate (p=0.03), 25% lower increase in T2 lesion volume (p=0.00004), 0.41% lower yearly loss in brain volume (p=0.07) from 12 to 60 months and fewer active lesions on

MRI (hazard ratio 0.73, p=0.002). Lower disability demonstrated by small reduction in the Expanded Disability Status Scale (EDSS) score (mean difference 0.17 points, p=0.004) was also found (21).

Daily supplement of 4000 IU of vitamin D in late fall and winter and 1000-2000 IU in spring and summer seems warranted for people who do not get a lot of exposure to sunlight in summer months. It is considered that a dose of 4000 IU is safe and because of the potential adverse effect on kidney, serum calcium levels and kidney function needs to be controlled from time to time. However, a number of studies looking at the effect and optimum doses of vitamin D supplements in MS are currently underway or planned: vitamin D as an add-on to injectable disease modifying treatments (SOLAR study (22), CHOLINE trial (23)), vitamin D as a treatment to reduce relapse rate in relapsing remitting MS (EVIDIMS study (24)) or to prevent the diagnosis of MS following the person's presentation with the first episode of symptoms - people with clinically isolated syndrome (PREVANZ study (25)).

ANTIOXIDANTS

Theoretically, antioxidants should be beneficial for MS because they neutralize free radicals, which may be involved in myelin and axonal damage (26). However, antioxidants stimulate the immune system, which could offset any benefits and even be harmful (27). Nevertheless, various antioxidants, including lipoic acid and the combination of selenium and vitamins C and E, have been well tolerated in small, short-term studies in MS. Whether antioxidants have disease-modifying effects has not been verified. Association of the intake of carotenoids, vitamin C and vitamin E with the risk of MS was assessed prospectively in two cohorts of women, one including 81,683 women (Nurses' Health Study I) followed-up for 12 years, and the other one (Nurses' Health Study II) including 95,056 women followed-up for 6 years (28). The findings in this study do not support the hypotheses relating higher intakes of dietary carotenoids, vitamin C and vitamin E to a reduced risk of MS in women.

Another study examined alpha-tocopherol concentrations and their relationship to disease activity in Norwegian MS patients. The prospective cohort study included 88 relapsing-remitting MS (RRMS) patients followed-up for two years, originally included in a randomized placebo-controlled trial of omega-3 fatty acids (the OFAMS study), before and during treatment with IFNB (29). During treatment with IFNB, increasing serum concentrations of alpha-tocopherol were associated with reduced odds for MRI disease activity in RRMS patients. New T1 gadolinium enhancing lesions two months later were reduced by 65.4% (p=0.019), and new T2 lesions by 61.0% (p=0.023).

Despite promising results in animal models, there is limited and conflicting evidence for the potential therapeutic effects of antioxidants such as vitamins C and E in treating MS.

VITAMIN B

Studies have reported a significantly higher rate of vitamin B12 deficiency in people with MS than in people without MS, which is suspected to be due to the problems with binding and transport of vitamin B12 (30). People with vitamin B12 deficiency have destruction of both the myelin and the underlying axon, which can cause MS-like symptoms. There are no large studies using vitamin B12 in people with MS. A placebo-controlled study of injected vitamin B12 (combined with lofepramine and l-phenylalanine) showed small (but statistically nonsignificant) beneficial effects in the treatment group (31).

LOW FAT DIET

Fat is an essential nutrient for the body. While some fats are deemed 'bad', others, such as polyunsaturated fats, actually help lower cholesterol and the risk of heart disease. These polyunsaturated fats were the focus of MS studies with some evidence pointing to effect on inflammation and benefits for RRMS (32). The Swank diet is a low saturated fat diet proposed for the treatment of MS and introduced by Roy L. Swank (33). There is no medical evidence to support the claims made for the Swank diet because his work was methodologically insufficient (34).

The most common dietary interventions are supplementation with polyunsaturated fatty acids (PUFA), omega-3 and omega-6 fatty acids. Omega-3 PUFAs (e.g., α -linolenic acid) are primarily derived from fish oils, whereas omega-6 PUFAs (e.g., linoleic acid) are obtained from plant sources, including sunflower, safflower, corn, wheat germ, soybean oils and evening primrose oil. In 2012, the Cochrane Collaboration conducted a systematic review into dietary therapies for MS (35). Six randomized controlled trials that investigated PU-FAs in a total of 794 randomized patients met the

inclusion criteria in terms of methodological quality. PUFAs did not have a significant effect on disease progression at 24 months. Neither omega-6 fatty acids nor omega-3 fatty acids showed any benefit in MS patients. Slight potential benefits in relapse outcomes were associated with omega-6 fatty acids in some studies, however, these findings were limited by the reduced validity of the endpoints, and the trial quality was rated as poor.

GINSENG

Ginseng is one of the herbal medicines possessing antifatigue properties, and its administration in MS for such a purpose has been evaluated. A randomized placebo controlled double blind study of ginseng efficacy and safety in the treatment of fatigue and quality of life of MS patients was conducted recently. This study has indicated that 3month ginseng treatment can reduce fatigue and has a significant positive effect on the quality of life (36). Further studies are needed to confirm the efficacy of ginseng in this field.

GINKGO BILOBA

Ginkgo biloba is an herb and popular supplement that some believe can help in MS symptoms, especially cognitive functions. A new randomized placebo controlled trial has provided Class I evidence that treatment with ginkgo 120 mg twice a day for 12 weeks does not improve cognitive performance in people with MS (37).

CARNITINE

Some research suggests that acetyl-L-carnitine can improve fatigue associated with MS. Acetyl-L-carnitine is a form of L-carnitine, an amino acid that is found in nearly all cells of the body and plays a critical role in the production of energy from longchain fatty acids. In addition, it increases the activity of certain nerve cells in the central nervous system. A recent systematic review published in 2012 concludes that there is still insufficient evidence that carnitine offers therapeutic advantage over placebo or other medications (38).

CRANBERRY

Bladder dysfunction occurs at some time in most MS patients and these patients are prone to recurrent urinary tract infections. Cranberry has been traditionally used for the treatment and prophylaxis of urinary tract infections. A recent trial has shown that taking cranberry extract *versus* placebo twice a day did not prevent the occurrence of urinary tract infections in MS patients with urinary disorders (39).

CANNABINOIDS

Multiple sclerosis is associated with chronic symptoms, including muscle stiffness, spasms, pain and insomnia. The Cannabinoids in Multiple Sclerosis (CAMS) study included 657 people with MS. Study subjects received either cannabis oil, synthetic tetrahydrocannabinol (THC, active ingredient in marijuana) or inactive placebo for 13 weeks. Following the treatment period, those on active treatment had no objective improvement in muscle spasticity as measured by a standardized scale. However, treated subjects reported improvements in walking speed, spasticity, muscle spasms, sleep and pain (40). To test the effectiveness and long term safety of cannabinoids in MS, in the CAMS study follow up (41), a total of 630 MS patients with muscle spasticity were randomized to receive oral Δ 9-tetrahydrocannabinol (Δ 9-THC), cannabis extract, or placebo for 12 months and showed evidence of a small treatment effect on muscle spasticity as measured by Ashworth score and on some aspects of disability. These data provide limited evidence for a longer term treatment effect of cannabinoids. A long term placebo controlled study is now needed to establish whether cannabinoids may have a role beyond symptom amelioration in MS.

Results of the Multiple Sclerosis and Extract of Cannabis (MUSEC) double blind, placebo controlled, phase III study had a screening period with a 2-week dose titration phase from 5 mg to a maximum of 25 mg of THC daily and a 10-week maintenance phase (42). The rate of relief from muscle stiffness after 12 weeks was almost twice as high with cannabis extract as with placebo. Laboratory evidence indicated that cannabinoids might have a neuroprotective action. The CUPID study examined the effect of oral dronabinol (Δ (9)-THC) on slowing the course of progressive MS. The results showed that dronabinol had no overall effect on the progression of MS in the progressive phase (43).

LOW-DOSE NALTREXONE (LDN)

Naltrexone is approved in the United States for the treatment of alcohol and opioid addictions. The postulated mechanism of naltrexone is mediating prevention of oxidative damage to neuronal cells and oligodendrocytes (44). A sixth-month phase II multicenter-pilot trial with a low dose of the opiate antagonist naltrexone (LDN) was carried out in 40 patients with primary progressive multiple sclerosis (PPMS). A significant reduction of spasticity was measured at the end of the trial (45).

GENERAL NUTRITION IN MULTIPLE SCLEROSIS

Maintenance of general good health is very important for persons with MS or any chronic disorder. Obesity and malnutrition are frequently observed in MS. Weight gain has been related to reduced mobility and fatigue. Weight loss has been related to dysphagia, reduced cognition and poor appetite. In patients with MS, malnutrition has been associated with impairment of the immune system, which can exacerbate the MS symptoms. These findings emphasize the need of nutritional support in MS patients. A number of nutritional screening tools can be helpful for nutritional status screening, for instance, the Subjective Global Assessment (SGA), Mini Nutritional Assessment (MNA), Malnutrition Universal Screening Tool (MUST), and Nutritional Risk Screening 2002 (NRS 2002) (46). These screening tools combine a number of questions with or without anthropometric measurements and helps identify patients at risk of malnutrition early. It is important to obtain thorough history, anthropometric measures and laboratory tests such as complete blood count (hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin, lymphocytes) and serum albumin or prealbumin concentration, before initiation of nutrition therapy. In patients with good nutritional status, a 'healthy diet' is recommended, which is in concordance with current healthy eating recommendations.

CAUTION WITH HERBS

Herbs should be used with caution by people with MS. There are many herbs with no well-documented benefits, which may potentially worsen MS or interact with MS medications. There are many immunostimulatory herbs including alfalfa, arnica, astragalus, boneset, calendula, cat's claw, celandine, drosera, echinacea, garlic, Asian and Siberian ginseng, licorice, mistletoe, reishi mushroom, saw palmetto, shiitake mushroom, and stinging nettle, which needs to be avoided because of the already overactive immune system in MS (47). CYP3A4 liver enzymes play a major role in drug breakdown and detoxification by the liver. Echinacea, milk thistle and chamomile all interfere with this enzyme and thus increase or decrease the effects of some medications, leading to increased side effects or reduced benefit from taking these drugs. Echinacea can decrease the efficacy of immunosuppressant and increase toxicity of corticosteroids, ephedra can increase toxicity of sympathomimetics and decrease efficacy of corticosteroids, St John's wort decreases the efficacy of tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), benzodiazepines and cyclophosphamides, and kava and yeast red rice increase the toxicity of benzodiazepines (48). Dosing is an important factor with vitamin or mineral supplements. Vitamins or minerals taken at a certain dose may be beneficial. However, taken at a higher dose, the same vitamin or mineral may be harmful.

OTHER CAM THERAPIES

COOLING THERAPY

Cooling demyelinated nerves can reduce conduction block, potentially improving symptoms of MS. The therapeutic effects of cooling in patients with MS have not been convincingly demonstrated because prior studies were limited by uncontrolled designs, non-blinded evaluations, reliance on subjective outcome measures, and small sample sizes. Patients reported less fatigue during the month of daily cooling, concurrently on the Rochester Fatigue Diary and retrospectively on the Modified Fatigue Impact Scale. Cooling therapy was associated with objectively measurable but modest improvements in motor and visual function as well as persistent subjective benefits (49).

HYPERBARIC OXYGEN THERAPY

It has been suggested that Hyperbaric Oxygen Therapy (HBO(2)T) may slow or reverse the progress of the disease. In 2004, the Cochrane Collaboration conducted a systematic review of clinical evidence for the use of HBO(2)T in the treatment of MS (50). In 2010, a literature review appeared on HBO(2)T, focused on the interaction of hyperbaric oxygenation and MS. There were 12 randomized studies in the field, all of which were performed between 1983 and 1987. A meta-analysis of this evidence suggests that there is no clinically significant benefit from the administration of HBO(2)T. No plausible benefit of HBO(2)T on the clinical course of MS was identified in this review (51). At this time, the routine treatment of MS with HBO(2)T is not recommended.

BEE VENOM THERAPY

Bee venom contains proteins that affect the immune system. However, the exact mechanism remains unknown. This therapy can produce rare but potentially serious adverse effects, including severe allergic reactions and death. A recent clinical trial demonstrated that bee venom was no better than placebo for treating MS (52).

MIND-BODY INTERVENTIONS

The evidence for mind-body medicine (yoga, mindfulness, relaxation and biofeedback) in MS is limited. Mind-body modalities appear safe, can be prescribed as an adjunct to conventional care (53), and can be effective for treating common MS symptoms, including fatigue, anxiety, depression, incontinence and quality of life. The placebo effect demonstrates the powerful influence that the mind may have over the body (or brain). This mind-body effect may be underutilized in conventional medicine and may be an important component of some forms of CAM.

MANIPULATIVE AND BODY BASED THERAPY

Manipulative and body-based therapy and psychological counseling seem to improve depression, anxiety and self-esteem. Massage and bodywork are among alternatives recommended by the National Multiple Sclerosis Society, but research in these areas is minimal. In a small study of MS patients, it was found that massage lowered anxiety, improved depressed mood, and increased self-esteem and body image (54). Another study in 53 MS patients showed the effectiveness of reflexology for improving spasticity, paresthesias (numbing and tingling sensations), and urinary symptoms (55). A study of Feldenkrais bodywork in 20 MS patients showed benefits of decreased perceived stress and lowered anxiety, but no improvement in physical functioning (56). Aromatherapy massage showed improvements in sleep, mobility and sense of wellbeing, but yet there is no comprehensive review of evidence for MS. There is no evidence that chiropractic can alter the underlying disease process or the disease course in MS. While there is anecdotal

evidence that people with MS have experienced some symptom relief, there are no controlled clinical trials demonstrating treatment safety or efficacy in MS (57). In a pilot study, osteopathic manipulative treatment combined with maximal-effort exercise showed beneficial effects in the activities of daily living in female patients with MS (58).

ENERGY THERAPY

Magnetic field therapy and neural therapy appear to have a short-term beneficial effect on the physical symptoms of MS (59).

ALTERNATIVE MEDICAL SYSTEM

Homeopathic substances are mostly natural but there is no evidence that homeopathy can prevent MS progressing or cure the MS symptoms. In a pilot study, naturopathy, stimulation of self-healing capacities of the individual by using clinical nutrition/diet counseling, herbs, nutritional supplements, homeopathy, physical medicine, and psychological counseling combined with usual care for MS showed a trend of improvement in the General Health subscale of the SF-36, Timed Walk and EDSS (60). There is little medical research to back up the claims of any specific benefits of acupuncture in MS. Acupuncture is generally well tolerated and appears to be associated with benefits for a proportion of patients with fatigue who are resistant to conventional drugs such as amantadine (61) and can provide relief of MS-related symptoms like pain, spasticity, fatigue, numbness, tingling, bowel and bladder issues, anxiety and depression.

CONCLUSION

Conservative estimate is that at least one-third of MS patients use CAM therapies. Results from large clinical trials are needed to determine whether vitamin D supplementation and what dosage is a potential treatment for MS. For now, 4000 IU is considered safe with serum calcium and kidney function control. Vitamin B12 did not show benefit in MS treatment. While the majority of MS patients who use CAM report benefit from diet, polyunsaturated fats and antioxidant supplements, these treatments have not been investigated with the rigor required to determine whether or not they are effective. Ginseng extract may reduce fatigue and improve quality of life but further studies are needed to shed light on the efficacy of ginseng in this field. A recent study has shown that Ginkgo biloba

does not improve cognitive performance in people with MS. Cannabis may improve spasticity in MS, although most trials show improvements in patient self-report and not in the objective measures of spasticity, and no overall effect on the progression of MS in the progressive phase. A low dose naltreloxone may have a positive effect of reducing spasticity but larger trials are needed. Therapeutic effects of cooling in patients with MS have not been convincingly demonstrated, but may have some efficacy in fatigue. Studies have repeatedly demonstrated that hyperbaric oxygen is not an effective treatment for MS. Nutritional support in MS patients is necessary only if the patient has malnutrition, otherwise healthy nutrition is recommended. Herbs should be used with caution by people with MS because some may actually worsen MS or interact with MS medications. Other CAM therapies like manipulative and body-based therapy, mindbody therapies, energy therapy and alternative medical systems can improve some MS symptoms like fatigue, depression, anxiety, sleep disorders, stress, pain, and improve the quality of life with limited evidence. It is very important to follow evidence based facts when choosing complementary and alternative treatments, but also to be aware of the placebo or nocebo effects and the costs of that kind of therapy.

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Je li komplementarna i alternativna terapija u multiploj sklerozi zasnovana na dokazima?

SAŽETAK – Primjena komplementarne i alternativne terapije je učestala u bolesnika s multiplom sklerozom. To uključuje terapiju koja nije dio konvencionalne medicine. Istraživanja sigurnosti i učinkovitosti komplementarne i alternativne terapije u multiploj sklerozi su vrlo ograničena. Ako se u obzir uzmu rizici i dobrobit pojedinih metoda komplementarne i alternativne medicine u multiploj sklerozi, postoji širok raspon: neke su moguće korisne, druge su neučinkovite i potencijalno štetne, a najveći broj zahtijeva randomizirana kontrolirana klinička ispitivanja. Međutim, u posljednjih nekoliko godina je mnogo truda uloženo u istraživanja u ovom važnom području. Zdravstveni radnici koji pružaju objektivne, znanstveno utemeljene i praktične informacije o rizicima i prednostima komplementarne i alternativne terapije mogu poboljšati kvalitetu skrbi za osobe s multiplom sklerozom.

Ključne riječi: alternativna terapija, komplementarna terapija, multipla skleroza



Neuroborreliosis: diagnostic problem in distinguishing from multiple sclerosis

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ABSTRACT - **Objectives:** To present the importance of additional diagnostic procedures in differential diagnosis of multiple sclerosis and neuroborreliosis, exemplified by a case of our patient. Neurological manifestation of Lyme disease varies and sometimes can imitate multiple sclerosis, especially in the early disseminated or late phase when there are no data on clinical infection. **Case report:** We present a patient with neuroborreliosis, initially considered as multiple sclerosis. Positive serology for *Borrelia burgdorferi* is an indicator of a past infection. However, the presence of specific IgG and IgM antibodies in the CSF confirms the diagnosis. In our case, magnetic resonance imaging (MRI) of the brain showed normal findings, whereas during spinal cord MRI, edema and hyperintense lesions of the thoracic spinal cord were found. Visually evoked potentials revealed prolonged latencies of the P wave on the left side. CSF analysis showed proteinorrhachia and distinct pleocytosis, with positive serology for specific antibodies to *Borrelia burgdorferi.* **Conclusion:** The clinical symptoms, MRI and CSF findings in combination with good response to antibiotic therapy confirmed the diagnosis of neuroborreliosis.

Key words: neuroborreliosis, Lyme borreliosis, encephalomyelitis, multiple sclerosis

INTRODUCTION

Neurological manifestation of Lyme disease is very diverse and can resemble multiple sclerosis (MS) (1). Acute Lyme disease is caused by a spirochete called *Borrelia burgdorferi* (Bb). Clinical features of Lyme disease (LD) can be divided into three phases: early localized LD (phase I), early disseminated LD (phase II) and late LD (phase III). In the early phase of LD, more common manifestations include redness of the skin at the site of the tick bite (*Ixodes*)

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ricinus), which appears 5-10 days to a few weeks later, spreading around the bite (erythema migrans). This can be followed by more general symptoms like headache, lymphadenopathy, conjunctivitis, fever and myalgia. In rare cases, manifestations in the early phase include lymphocytoma benignum cutis, also called Borrelia lymphocytoma. Spreading of spirochete through the blood or lymph system causes the second phase. Symptoms depend on the affected organs and more common ones are multiple erythema migrans, neuroborreliosis and arthritis. Neuroborreliosis includes central (CNS) or/and peripheral nervous system (PNS) symptoms that occur after several weeks to months after the tick bite and include meningitis, polyradiculitis, encephalitis and neuritis. If LD is not treated properly, it evolves to the late phase, commonly presenting with arthritis, but in some cases also in the form of acrodermatitis chronica atrophicans or chronic meningoencephalitis. This chronic neurologic disease presents a differential diagnostic problem on distinguishing it from MS, particularly if there are no data on clinical infection. Magnetic resonance imaging (MRI) can show disseminated lesions within the CNS white matter (2). Positive serologic findings in Bb are only an indicator of a past infection and may not be relevant to the exclusion of other causes of the CNS infection (3,4). The intrathecal synthesis of specific antibodies against Bb in the cerebrospinal fluid (CSF) is a more reliable indicator to which extent the CNS is involved (5).

However, positive specific antibodies against Bb in CSF may be present in patients with MS (3,6,7). Therefore, the diagnosis of neuroborreliosis is based on the identification of typical acute symptoms/ signs, migrating erythema and antibodies against Bb in high concentrations in the serum and CSF, as well as on the isolation of spirochetes (8-10).

CASE REPORT

We present a case of a female patient who, at the age of 42, experienced acute vision impairment on her left eye, accompanied by pain on any eyeball movement. Neurologic findings showed increased tendon reflexes of her right hand, highly exhaustive cutaneous abdominal reflexes and absence of the musculus triceps surae reflex on both sides. Fundus findings and radiologic analysis of the optic canal and sella turcica were normal. The report of visually evoked potentials showed slightly streamlined latency P wave to the left (128 ms) and the ophthalmologist diagnosed left optic neuritis.

Three years later, at the age of 45, the patient suffered paresthesias of both legs, followed by difficulties in walking. Disturbing sensation expanded to the chest level, with retention of urine. Physical findings showed red, rounded efflorescence of the left shoulder and chest. Neurologic examination revealed horizontal nystagmus, ataxia with left intention tremor, increased tendon reflexes of the left hand, absence of cutaneous abdominal reflexes and extinct left plantar reflex. It also revealed subjective hypoesthesia below the Th3-Th4 dermatomes. MRI of the brain was normal. CSF analysis showed distinct proteinorrhachia (0.85 g/L; normal range 0.15-0.45 g/L) and pleocytosis (127x10⁶/L; normal range 0-4x10⁶/L), with predominant monocytes and lymphocytes. Also, an increased local synthesis of IgG was found, with dysfunction of the blood-brain barrier, including a disproportionate increase of IgG quotient. Serology for neurotrophic viruses including tick-borne encephalitis, herpes simplex virus type 1 and 2, rubella, measles, mumps and varicella zoster virus in CSF was negative. As we recorded the red efflorescence on the left shoulder and chest, indicative of migrating erythema, as well as inflammatory findings of CSF, we tried empirical therapy with intravenous ceftriaxone, 2 g b.i.d. for three weeks and oral methylprednisolone every other day in a dose of 32 mg for two weeks. On the fifth day of therapy, the CSF findings showed decreased lymphocytic pleocytosis (50x106/L) and blood-brain barrier dysfunction, with a proportional increase of the IgG quotient. After eighteen days of treatment, the CSF findings revealed mild proteinorrhachia (0.48 g/L) and dysfunction of the blood-brain barrier with a proportional increase of IgG.

After two years, the patient was readmitted for disease deterioration. Neurologic examination revealed mild spastic paraparesis with hyperesthesia of the band type in the central part of the chest. Basic laboratory tests were normal. A year later, the patient was re-hospitalized due to mild worsening of the disease. On admission, she was subfebrile and complained of a feeling of chest tightness, or, as she put it "armor-like sensation". Neurologic examination revealed mild ataxia, paraparesis with sensation disturbance below the level of Th4, static and intentional hand tremor, and the "yes-no" motion of the head, dysdiadochokinesia to the left, positive Babinski's reflex on the left, and the need of urgent urination. Ultrasound of the abdomen showed diffuse damage to the liver and pancreas. Serum testing revealed the presence of IgG titers to Bb at 1:5120 and IgM titers at 1:320 (ELISA method), positive IgG (310.2 AU/mL; positive >15) and



Fig. 1. Magnetic resonance image of the spinal cord (*T1*, gadolinium) showing contrast enhanced lesion in the thoracic segment of the spinal cord.

IgM (67.2 AU/mL; positive >22) with CLIA method. Specific IgG antibodies (74.4 AU/mL; positive >5.5) and IgM (22.1 AU/mL; positive >3.5) were positive in the CSF (CLIA method). Serologic analysis of neurotrophic viruses (tick-borne encephalitis, herpes simplex virus type 1 and 2, rubella, measles, mumps and varicella zoster virus) in CSF was negative. The patient was treated with ceftriaxone, receiving a dose of 2 g on a daily basis, intravenously, for a period of three weeks. Repeated antibiotic therapy resulted in remarkable recovery of the neurologic deficit, with only thoracic dysesthesias persisting. At this point, MRI of the spinal cord was performed and showed edema and hyperintense lesions of the spinal cord thoracic segment (Fig. 1), while repeated brain MRI findings were normal. Even though our patient was initially treated as a case of MS, the development of clinical symptoms, the CSF and MRI findings, along with a good response to the antibiotic therapy administered confirmed that it was a case of neuroborreliosis, even though there was no information on tick bite.

DISCUSSION

Neuroborreliosis can sometimes clinically mimic MS (11,12). There may be various neurologic deficits such as spastic paraparesis, hemiparesis, cross-myelitis, cerebellar ataxia, cranial or/and peripheral nerve damage, encephalitis, making it difficult to distinguish these two diseases (13). In the case of neuroborreliosis, MRI shows periventricular white matter damage, just like MS (1). As with other types of meningitis, MRI enhanced with contrast shows meningeal adhesions, which are not typical

for MS (2,14,15). It is difficult to diagnose neuroborreliosis using laboratory analysis. Serologic tests for the detection of antibodies to Bb can be useful, but they could be positive in other CNS diseases like MS (16). When it comes to MS and neuroborreliosis, lymphocytic pleocytosis, intrathecal synthesis of IgM and IgG immunoglobulins and IgG oligoclonal bands in isoelectric focusing on polyacrylamide gel are present in the CSF. For neuroborreliosis, intrathecal synthesis of specific antibodies against Bb is characteristic, but it can be found in patients with MS (3,4). In patients with neuroborreliosis, IgM values were significantly higher compared to those suffering from MS, and the number of cells was significantly higher in the majority of patients in the acute stage of the disease. In the case of specific IgG, IgM, especially in CNS, without the virus-specific immune response, we can, with great certainty, speak about Lyme disease (5). However, specific antibodies against Bb can be found in patients with MS. Additional diagnostic parameters are significant damage to the blood-brain barrier and positive findings of Bb in CSF culture. During the last few years, a lot of discussion has been conducted about the possible causal relationship between the Bb infection and the appearance of MS. The finding of specific antibodies for spirochetes in the CSF of MS patients confirms this assumption. Findings of the synthesis of specific antibodies are not confirming that the neurologic symptoms are the result of Bb infection (17,18).

CONCLUSION

A large number of patients with neuroborreliosis are still found within the groups of patients erroneously diagnosed with MS. This is due to the similarity of clinical symptoms and MRI findings of CNS (19,20), as well as to the fact that the concentration of specific IgG oligoclonal bands depends on the duration of disease. In the case of intrathecal synthesis of specific IgG and IgM antibodies, especially for *Borrelia burgdorferi*, without the virus-specific immune response, we can with high certainty claim that it is a case of Lyme disease. Additional diagnostic indicators are significant damage to the bloodbrain barrier, as well as the presence of *Borrelia burgdorferi* in the CSF culture (21).

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Neuroborelioza: dijagnostički problemi razlikovanja od multiple skleroze

SAŽETAK – **Ciljevi:** Prikazom slučaja ukazati na sličnost kliničke slike i rezultata neuroradiološke obrade u neuroboreliozi i multiploj sklerozi te istaknuti važnost dopunskih pretraga u postavljanju završne dijagnoze. Neurološka prezentacija lajmske bolesti je raznolika i katkad može oponašati multiplu sklerozu, osobito u ranoj diseminiranoj fazi i kasnoj fazi bolesti ako ne postoji podatak o kliničkoj infekciji. **Prikaz slučaja:** Prikazujemo slučaj bolesnice s neuroboreliozom, od početka shvaćenog kao multipla skleroza. Pozitivna serologija na bakteriju *Borrelia burgdorferi* je indikator infekcije u prošlosti. Ipak, prisutnost specifičnih IgG i IgM protutijela u središnjem živčanom sustavu može potvrditi dijagnozu neuroborelioze. U našem slučaju MR mozga je bio uredan, dok je MR leđne moždine pokazao edem i hiperintenzivno oštećenje grudnog odsječka. U vidnim evociranim potencijalima evidentiran je produžen P val lijevo. Analiza cerebrospinalnog likvora (CSL) pokazala je zamjetnu proteinorahiju, izrazitu pleocitozu, pozitivan nalaz specifičnih protutijela te negativnu serologiju na neurotropne viruse. **Zaključak:** Razvoj kliničke slike, nalaz MR i CSL u kombinaciji s dobrim odgovorom na antibiotsku terapiju potvrdili su dijagnozu neuroborelioze.

Ključne riječi: neuroborelioza, lajmska borelioza, encefalomijelitis, multipla skleroza



Posterior reversible encephalopathy syndrome in a patient with paraneoplastic extralimbic encephalitis and small cell lung cancer

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ABSTRACT - **Background:** Paraneoplastic encephalomyelitis (PEM) is a multifocal inflammatory disorder of the central nervous system (CNS) associated with remote neoplasia. **Case report:** We describe a 41-year-old female patient with subacute development of dysarthria, dysphagia, tetraparesis, ataxia, breathing difficulties and cognitive deterioration. Brain magnetic resonance imaging revealed multiple confluent hyperintense lesions in cortical and subcortical white matter consistent with the posterior reversible encephalopathy syndrome. Ultimately, she was diagnosed with anti-Hu positive paraneoplastic extralimbic encephalitis and small cell lung cancer. Treatment with intravenous corticosteroids and immunoglobulins led to minimal clinical improvement, while significant regression of bilateral symmetric cortical edema and edema of subcortical white matter was seen on follow up brain magnetic resonance imaging. **Conclusion:** The paraneoplastic extralimbic encephalitis and posterior reversible encephalopathy syndrome are rare first manifestations of small cell lung cancer.

Key words: posterior reversible encephalopathy syndrome, extralimbic paraneoplastic encephalomyelitis, small cell lung cancer

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INTRODUCTION

Paraneoplastic encephalomyelitis (PEM) is a multifocal inflammatory disorder of the central nervous system (CNS) associated with remote neoplasia. The most frequently recognized focal paraneoplastic disorders of the CNS are limbic encephalitis, cerebellar degeneration and brainstem encephalitis. Although PEM can affect any part of CNS, involvement of extralimbic brain structures is not often reported in the literature (1). We describe a female patient who had reversible large T2 and FLAIR hyperintensities on magnetic resonance imaging (MRI) consistent with the diagnosis of posterior reversible encephalopathy syndrome (PRES) in a setting of PEM and small-cell lung carcinoma (SCLC).

CASE REPORT

A 41-year-old female presented with a ten-month history of nonspecific muscle pain in legs and hands, walk and speech difficulties accompanied with general weakness. She was seen by a neurologist in a local hospital, brain MRI was performed and showed multiple small T2 and FLAIR hyperintensities in the deep white matter bilaterally (MRI not available). No further work up was taken.

However, the patient's condition worsened and she presented to our emergency department. On admission, neurological examination revealed dysarthria, facial myoclonic jerks, gaze apraxia, downbeat nystagmus, tetraparesis, limb and truncal ataxia, and short-term memory impairment. Cerebrospinal fluid (CSF) analysis showed mild pleocytosis, 13 white cells *per* cubic millimeter, a slightly elevated protein level of 0.51 g/L (normal values 0.17-0.37 g/L), positive oligoclonal bands and normal level of protein 14-3-3. Serologic analysis of serum and CSF for HIV, syphilis and neurotropic viruses was negative. Electroneurography showed axonal neuropathy. Although lung oncomarkers and chest x-ray were normal, chest computed tomography (CT) revealed enlarged mediastinal lymph nodes. Bronchoscopy and transthoracic biopsy of the lymph nodes verified SCLC. Paraneoplastic anti-Hu antibodies in serum were positive. The diagnosis of PEM was established.

The patient's clinical condition continued to deteriorate. During the first week after admission, par-



Fig. 1. Axial brain magnetic resonance images: T2-weighted images showing multiple confluent hyperintense lesions in the cerebellum, subcortical white matter, predominantly in posterior regions, but also present in frontal lobes (A-C); FLAIR image showing hyperintense lesions in deep and subcortical white matter in frontal and parietal lobes (D); several small foci in the cerebellum and left occipital lobe enhanced with contrast media (E, F); diffusionweighted image with minimal T2 shine-through (G); lesions exhibit vasogenic edema, seen on the map of apparent diffusion coefficient, with ADC of 196.5x10⁻⁵ mm²/s (H).



Fig. 2. Control magnetic resonance imaging (MRI): axial T2-weighted images (A, B) and post-contrast T1-weighted image 4 weeks after initial examination; complete resolution of previous T2-hyperintense lesions (A, B); no contrast enhancement on control T1-weighted MRI image (C).

tial motor epileptic seizures with secondary generalization were observed, for which she was treated with methylphenobarbital and levetiracetam. Electroencephalography (EEG) showed focal slowed activity in frontal and temporal regions. In the first 10 days of hospitalization, the patient's blood pressure fluctuated from hypotension to normotension (systolic min-max/diastolic min-max 77-132/33-79 mm Hg), measured by cuff-style, biceps monitor. Afterwards, hypertension occurred with blood pressure mostly 150-188/91-116 mm Hg. Only occasionally, blood pressure measurements were greater than 200/110 mm Hg. Angiotensin-converting-enzyme inhibitors and hydrochlorothiazides were introduced in therapy. These great fluctuations in blood pressure, with simultaneous fluctuations in cardiac rhythm and respiratory rate were considered a manifestation of autonomic nervous system dysfunction. Follow up brain MRI performed at that point (3 weeks after admission) revealed large multiple confluent hyperintense lesions in subcortical white matter, predominantly in posterior regions, but also present in frontal lobes, with minimal involvement of temporal lobes. Lesions exhibited vasogenic edema, seen on the map of apparent diffusion coefficient. Several small foci in the cerebellum and left occipital lobe showed post-contrast enhancement (Fig. 1). The patient developed bilateral pneumonia that eventually led to respiratory arrest for which she was intubated, mechanically ventilated for 5 days, and treated with intravenous antibiotics.

At that point, the patient's general condition was too poor for active cancer treatment, so she received treatment with 1000 mg of intravenous methylprednisolone for 5 days, without any clinical improvement. In order to further improve the patient's condition, treatment with intravenous immunoglobulins was initiated (0.4 g/kg/day for five days). There were minimal clinical changes, although follow up brain MRI showed significant regression of earlier described lesions (Fig. 2). Despite intensive therapy, the patient died after two months without receiving specific cancer treatment.

Postmortem examination was not performed due to religious reasons.

DISCUSSION

We describe a patient with anti-Hu positive PEM and large reversible T2 and FLAIR hyperintensities on the MRI consistent with PRES. The patient was later diagnosed with SCLC. Rapid neurological deterioration, cognitive changes, mild pleocytosis, slightly elevated protein level and positive oligoclonal bands in the CSF, along with the detection of highly specific paraneoplastic anti-Hu antibodies in serum supported the diagnosis of PEM (2,3).

Positive paraneoplastic anti-Hu antibodies are present in 23% of patients with SCLC and their significance in patient outcome has not yet been completely clarified. Some studies show that SCLC patients with PEM have a more severe neurological deficit, are most refractory to treatment, and survival from the time of diagnosis is significantly worse (4-8). On the other hand, there are studies showing that SCLC patients with PEM have a higher probability of survival at 30 months compared

Patient sex/age (Ref. no.)	Brain MRI	Clinical presentation	Tumor	Therapy	Outcome
M/66 (11)	T2 lesions in F and T lobes	Epilepsia partialis continua	SCLC	AED	Death
W/63 (10)	T2 extralimbic lesions	Hemiparesis, hemianopia	Brest adenocarcinoma	MPL, CP	Progressive dementia
W/79 (10)	F and PO lesions	Epilepsia partialis continua, monoparesis	Brest adenocarcinoma	DX	Improvement
M/65 (10)	Left hippocampus and amygdala	Sensory neuropathy, limbic encephalitis	Squamous cell lung carcinoma	PE, CP	Good
W/55 (12)	T2 lesions P and T lobes and insula	Seizures, aphasia	Thymoma	R, Th	Good
W/33 (13)	Multiple cortical and limbic T2 and DWI lesions with gadolinium enhancement	Seizures	Thymoma	Th, R, AED	Good
M/18 (14)	Bilateral F and T diffuse T2 lesions, brainstem involvement	Tetraparesis, seizures, coma	Hodgkin's lymphoma	PE, R, AED	Good

Table 1. Paraneoplastic encephalomyelitis cases described in the literature

M = magnetic resonance imaging; M = man; W = woman; F = frontal; PO = parieto-occipital; T = temporal; AED = antiepileptic drugs; MPL = methylprednisolone; CP = cyclophosphamide; DX = dexamethasone; PE = plasma exchange; R = radiotherapy; Th = thymectomy.

with those without PEM (9). Low anti-Hu titers without PEM or sensory neuronopathy are associated with more indolent tumors (10).

However, paraneoplastic antibodies are not always present in a patient with paraneoplastic neurologic syndrome, and their absence should not repel the diagnosis (11).

As our patient's condition deteriorated, follow up brain MRI showed large lobar T2 and FLAIR hyperintensities bilaterally in the frontal, parietal and occipital lobes and cerebellum with minor involvement of the temporal regions. Brain MRI in PEM usually shows changes in temporal lobes, limbic part of the CNS and cerebellum. Abnormal MRI contrast enhancement is not a typical feature of PEM but it can be present (12). The extralimbic abnormalities in MRI are rarely reported and there are only few described cases in the literature (12-16) (Table). The PRES is exceptionally associated with SCLC; when present, it is usually associated with chemotherapy (17). Its occurrence is well described in hypertensive patients where it is postulated that failure of cerebral blood flow autoregulation and hyperperfusion leads to cerebral edema. The appearance of PRES in normotensive patients

as its absence in many hypertensive patients suggests a more complex underlying mechanism besides blood pressure autoregulation failure (18,19). In a patient like ours who had high blood pressure in the third week of hospitalization, merely a coincidence of PRES in a setting of PEM has to be considered. Besides hypertension, the clinical conditions usually associated with PRES are preeclampsia/eclampsia, infection, sepsis, shock, autoimmune diseases, cancer chemotherapy and organ transplantation. A similar immune process in these conditions with T-cell activation, production of inflammatory cytokines, endothelial activation could lead to endothelial injury (20). Although histologic studies in PRES are rare, there are data describing chronic vessel injury (21). This would be in concordance with brain MRI and CT studies in PRES that show involvement of watershed zones and this could explain involvement of other brain regions besides the posterior one (18). In our patient, watershed zones were seen in the cerebellum (Fig. 1A) and semioval center bilaterally (Fig. 1D).

As the name PRES implies, the lesions are predominantly occipital, however, extraoccipital lesions should not exclude this diagnostic possibility. Lesions in the frontal lobe, basal ganglia, cerebellum or brainstem can be found in about one-third of cases, but there are only a few case reports with isolated atypically located lesions (22). Patients with extensive lesions on T2 weighted imaging tend to have a worse prognosis (23).

Paraneoplastic encephalomyelitis is a rare first manifestation of SCLC and there are no established protocols for its treatment. Removal of the underlying tumor and suppression of the immune response are two usual approaches (24,25). Immunotherapy can be helpful in PEM treatment, but improvement is mild or not sustained unless the underlying tumor is controlled (26). Our patient received immunosuppressive therapy with steroids and intravenous immunoglobulins for PEM treatment with minimal clinical improvement, while there was almost complete regression of MRI lesions, supporting the diagnosis of PRES in the setting of PEM.

CONCLUSION

The PEM and PRES are rare first manifestation of SCLC. In the absence of known malignancy the right diagnosis is very difficult to make, especially when clinical picture and radiological findings are not typical.

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Sindrom posteriorne reverzibilne encefalopatije u bolesnice s paraneoplastičnim ekstralimbičnim encefalitisom i malostaničnim karcinomom pluća

SAŽETAK – **Cilj:** Pokazati kako raznovrsna klinička prezentacija i tijek bolesti mogu otežati postavljanje dijagnoze i liječenje paraneoplastičnog sindroma. **Prikaz slučaja:** Opisujemo slučaj 41-godišnje bolesnice s postupnim razvojem dizartrije, disfagije, tetrapareze, ataksije, otežanog disanja i kognitivnih smetnji. Magnetska rezonancija mozga pokazala je multiple konfluirajuće hiperintenzivne lezije kortikalne i sub-kortikalne bijele tvari koje upućuju na sindrom posteriorne reverzibilne encefalopatije. Bolesnici je dijagno-sticiran anti-Hu pozitivan paraneoplastični ekstralimbični encefalitis i malostanični karcinom pluća. Liječenje intravenskom primjenom kortikosteroida i imunoglobulina rezultiralo je tek minimalnim kliničkim oporavkom, dok je kontrolna magnetska rezonancija mozga pokazala značajnu regresiju ranijeg simetričnog bilateralnog kortikalnog edema i edema subkortikalne bijele tvari. **Zaključak:** Paraneoplastični ekstralimbični encefalitis i sindrom posteriorne reverzibilne encefalopatije rijetka su prva manifestacija malostaničnog karcinoma pluća.

Ključne riječi: sindrom posteriorne reverzibilne encefalopatije, ekstralimbični paraneoplastični encefalomijelitis, malostanični karcinom pluća



A rare neurological presentation of celiac disease

S. V. Shetab-Boushehri^{1,2}, R. Khodabandehlou³

ABSTRACT – **Background:** Celiac disease (CD) is an autoimmune disease of the small intestine due to sensitivity to gluten, a protein which is present in wheat, rye, and barley. The most common clinical findings in CD are gastrointestinal complications but neurological presentations are also seen in some patients. **Case report:** A case is described of a 40-year-old man who presented CD-related optic neuropathy, a very rare neurological manifestation of CD. He reported sudden right upper visual field blindness upon awakening in the morning without pain. He was treated with intravenous methylprednisolone for five days, followed by two-year azathioprine and methotrexate administration. His case is presented with magnetic resonance imaging, clinical history, and laboratory findings. **Conclusion:** It is reasonable that CD patients be evaluated for neurological symptoms even in the clinically stable long-term course. In addition, CD needs to be considered when making a differential diagnosis for patients presenting neurological symptoms of unknown primary cause.

Key words: celiac disease, optic neuropathy

INTRODUCTION

Celiac disease (CD) is an autoimmune disease of the small intestine due to sensitivity to gluten, a protein which is present in wheat, rye, and barley (1). The most common clinical findings in CD are gastrointestinal complications but neurological presentations are also seen in some patients (2,3). The most common gastrointestinal symptoms in symptomatic celiac patients are diarrhea, weight loss, abdominal distension, malaise, and anemia (1). Neurological manifestations in celiac patients can be seizures, dementia, or psychiatric illness but the most common manifestations are ataxia and peripheral neuropathy. Also, multifocal encephalopathy can be the neurological manifestation of CD (2). Because approximately half of adult-onset celiac patients lack prominent gastrointestinal symptoms, patients with

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neuropathy should be accurately examined regarding CD (2). The present case represents a rare neurological complication of CD.

CASE REPORT

A 40-year-old male, a toxicologist, actually the first author, presented with chief complaint of right visual loss. He reported sudden loss of the upper half of the visual field on the right eye upon awakening in the morning without pain. He did not smoke cigarettes or drink alcohol, did not have high blood pressure, diabetes mellitus or hyperlipidemia. The patient had been diagnosed with CD three years before, and the disease was well controlled by simple dietary manipulation. At that time, he underwent an endoscopic (stomach and duodenum) examination by a gastroenterologist. A biopsy from the duodenum was obtained and sent for pathological examination. The results were consistent with the diagnosis of CD. His first symptoms of CD were hematochezia, intestinal cramping, refractory hiccups, anal fissure, malabsorption, heartburns and stomachache. He reported that he had stopped dietary restriction for about one year. After each meal containing wheat products, he experienced massive hematochezia accompanied with fever. His past medical history contained only properly treated brucellosis at the age 23. His two uncles had CD.

Except for Marcus Gunn's sign and loss of the upper half of the visual field on the right eye, which was detected by Goldmann visual field testing, his neurological status was normal, including funduscopy of optic discs and retinal angiography. Brain magnetic resonance imaging (MRI) showed two hyperintense lesions on T2WI and FLAIR images, one in the left periventricular region in the frontal part of lateral ventricle and another one in the left occipital juxtacortical region without enhancement.

Serologic examination revealed high titer of antigliadin Ab IgG (AGA) (39 U/mL, normal <12 U/ mL) obtained by ELISA, high blood IgE (424 IU/ mL, normal <100 IU/mL) and mild anemia with anisocytosis. Cerebrospinal fluid (CSF) oligoclonal bands were negative (Fig. 2), as well as serum immunologic tests (CRP, ANA, RF, ANCA, anti SSA Ab, anti SSB Ab, anti ds DNA, anti phospholipid Ab (lupus anticoagulant (LA) antibodies, cardiolipin IgG and IgM antibodies), anti-endomysial antibody (anti-EMA)). CSF protein (42 mg/dL, normal 15-45 mg/dL) and cells (WBC $2/\mu$ L, RBC 0/ μ L) were normal.

His CSF angiotensin-converting enzyme (6.0 IU/ L) was a little above the normal value of <4.0 IU/L. Sarcoidosis was ruled out by chest computed tomography scan. We performed Goldmann visual field testing that showed loss of vision in the upper half of the visual field on the right eye. He was diagnosed as AGA induced neuropathy and treated with intravenous methylprednisolone 1 g daily for 5 days, with good recovery of his vision. Then, he was treated by azathioprine 3 mg/kg/day for 3 months but, due to diarrhea and stomachache, azathioprine was replaced by methotrexate 7.5 mg weekly for 15 months. After two-year follow up,



Fig. 1. *Magnetic resonance images without contrast enhancement before treatment showing a juxtacortical plaque* (*A*) *and periventricular plaque* (*B*).

OCB location





Fig. 2. Cerebrospinal fluid oligoclonal bands.

there were no new plaques or contrast enhancement on MRI images (Fig. 3).

Juxtacortical plaque disappeared completely and his AGA returned to the normal value. During

two-year follow up, he had a gluten-free diet and experienced no hematochezia and his gastrointestinal symptoms relieved as well.

DISCUSSION

Celiac disease is a common condition that affects up to 1% of the population worldwide (2). It is an autoimmune disorder of the small intestine that occurs in genetically predisposed people of all ages, from middle infancy onward (1). Several case reports have highlighted the occurrence of various neurological disorders, including neuropathy, ataxia, dementia, chorea, and epilepsy, in patients with established CD but optic neuropathy mimicking first attack of multiple sclerosis is rare. The mechanism of neuronal damage is unclear and may be immune or related to trace vitamin deficiency, especially vitamin E and some elements like copper (1).

Atypical forms of CD, i.e. without prominent gastrointestinal symptoms and with frequent extra-intestinal manifestations, are being increasingly recognized, especially over the past decade, both in adult and pediatric patients (3). CD is around 10 times more frequent than multiple sclerosis. CD and multiple sclerosis are considered as T-cell-mediated autoimmune diseases. An immune-mediated pathogenesis, initiated by gluten, is considered in patients affected by neurologic disorders, with positive AGA and immune abnormalities of the central and peripheral nervous systems, especially if some have a favorable response to gluten-free diet with lower AGA titers (4).



Fig. 3. Magnetic resonance images without contrast enhancement after treatment: the juxtacortical plaque had healed (A); the periventricular plaque was still present (B).

In the patient presented, MRI showed two plaques, which had some resemblance to multiple sclerosis plaques, but they were not ovoid lesions perpendicular to the ventricles (Dawson fingers) and did not completely fulfill the revised McDonald criteria (5) for dissemination in time even after 2-year follow up.

Although MS lesion plaques can be found throughout the brain, they have a predilection for periventricular white matter and juxtacortical region; they tend to have an ovoid configuration with the major axis perpendicular to the ventricular surface. At the initial stage, the lesions are typically thin and appear to be linear (Dawson fingers), which is probably associated with the inflammatory changes around the long axis of the medullary vein that create the dilated perivenular space (6).

In our patient, one of the plaques that was juxtacortical disappeared completely on T1W and T2W images after 2-year follow up, indicating remyelination without axonal loss, but the persistent periventricular one showed black hole on T1W images indicating axonal loss (both inflammatory and neurodegenerative nature of the plaques).

This case had some characteristics of optic neuritis (which is painful, subacute and central or cecocentral, or total visual field loss that improves completely or near completely) and some characteristics of ischemic optic neuropathy (which is sudden, painless, usually altitudinal field defect and not improving completely) (7). The patient was diagnosed with AGA induced demyelinating optic neuropathy. Gluten-free diet has been the most important treatment for CD, but it could be potentially useful for both CD and its neurological manifestations in our patient (8). The main difficulty for these patients is to follow a strict gluten-free diet for the rest of their lives.

The early detection of CD neurological manifestations caused by neuronal demyelination and their subsequent treatment with gluten-free diet and immunosuppressive drugs could be beneficial for patients who suffer from it.

CONCLUSION

Anti-gliadin antibodies may be directly or indirectly neurotoxic or a marker of neurotoxic autoimmune process. Neurological complications of CD presenting to gastroenterologists have been considered rare, but the findings of a high incidence of CD in patients with neurological disease of unknown cause emphasize that clinicians need to be vigilant for the atypical presentation and complications of CD (9). Therefore, it is reasonable that celiac patients should be evaluated for neurological symptoms even in the clinically stable long-term course. In addition, CD needs to be considered when making a differential diagnosis for patients presenting neurological symptoms of unknown primary cause, especially when revised McDonald criteria are not completely fulfilled and even in the absence of gastrointestinal symptoms (10).

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Rijetka neurološka prezentacija celijakije

SAŽETAK – **Uvod:** Celijakija je autoimuna bolest tankog crijeva koja nastaje kao posljedica osjetljivosti na gluten, protein koji je prisutan u pšenici, raži i ječmu. Celijakija se najčešće manifestira simptomima probavnog sustava, ali se u određenom postotku bolesnika mogu javiti i neurološki simptomi. **Prikaz slučaja:** U ovom prikazu opisuje se slučaj muškarca starog 40 godina koji se prezentirao vrlo rijetkom manifestacijom celijakije, optičkom neuropatijom. Prvi simptom bolesti je bio nagli ispad desne gornje polovice vidnog polja koji nije bio praćen bolovima. Liječen je intravenskim metilprednizolom tijekom 5 dana uz dobar klinički oporavak, a zatim azatioprinom i metotreksatom. U ovom radu prikazani su klinički simptomi, nalazi magnetske rezonancije te laboratorijski nalazi bolesnika. **Zaključak:** Iz prikazanog slučaja te podataka iz literature kod bolesnika s celijakijom bi trebalo aktivno tražiti neurološke simptome. Također na celijakiju treba misliti u diferencijalnoj dijagnostici bolesnika s neurološkim simptomima nepoznatog uzroka.

Ključne riječi: celijakija, optička neuropatija



Two limbic encephalitis cases with potassium channel antibodies

F. Kurtuluş, A. Yaman, Y. Biçer Gömceli, N. Uzun, A. Tıltak

ABSTRACT – **Background:** Autoimmune limbic encephalitis is presented with the involvement of limbic structures. It is a different entity rather than a component of paraneoplastic limbic encephalitis. In recent years, limbic encephalitis cases with immune-mediated voltage gated potassium channel antibody that respond to immunotherapies have been described. **Case reports:** We present two male patients aged 45 and 59. Both patients had elevated levels of potassium channel antibodies and presented with short-term memory impairment, psychiatric symptoms, and the first case had epileptic seizures additionally. Their radiological findings were typical for limbic encephalitis and both responded to immunotherapy. **Conclusion:** In this report, we emphasize that limbic encephalitis should be suspected in patients with subacute cognitive impairment, psychiatric symptoms and epilepsy resistant to therapy. Since the disorder is mostly reversible, early diagnosis and treatment is important.

Key words: autoimmune limbic encephalitis, potassium channel antibody

INTRODUCTION

Limbic structures such as mesial temporal lobe and amygdala bilaterally are involved in limbic encephalitis. Less commonly extralimbic structures such as hypothalamus and basal frontal cortex may be involved. Up to the mid-1990s, it was thought that the non-viral limbic encephalitis cases were paraneoplastic. Recently, limbic encephalitis cases with immune-mediated voltage dependent potassium channel antibodies and responsive to immunotherapy have been described. Symptoms of limbic encephalitis are short-term memory impairment, epileptic seizures, behavior and personality alterations, confusion, irritability, depression, alterations in sleep, hallucinations and psychosis.

We present two cases that are relevant to limbic encephalitis clinically and radiologically with positive potassium channel antibodies.

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CASE REPORTS

CASE 1

Our patient was a 45-year-old right handed male working as an accountant. He was admitted with complaints of behavioral alterations, memory loss, tremor and intermittent episodes of fear for two or three months. His complaints aggravated especially in the past week. His wife defined behavioral changes of the patient as obsessive thoughts and personality features. Levetiracetam (2x1000 mg), pregabalin (1x150 mg) and valproic acid (2x250 mg) were prescribed by another physician 2 months before. His wife described two kinds of seizures, i.e. one as complex partial seizures during which the patient was staring and had oral automatisms such as lip smacking and licking, and the other type were generalized tonic clonic seizures. His wife stated that these seizures subsided upon treatment. His personal and family history was unremarkable. On neurological examination, he was conscious but disoriented in time, space and person. He had minimal ataxic tandem gait, shortterm memory impairment and bizarre behavior. Mini Mental State Examination (MMSE) could not be performed because of attention deficit. Laboratory findings were normal except for hyponatremia (131 mEq/L). The patient was hospitalized with the pre-diagnosis of nonconvulsive status epilepticus or encephalitis (viral/autoimmune?). Cranial magnetic resonance imaging (MRI) was performed. Hyperintense signal changes were present in both medial temporal regions in T2 and FLAIR sections (Fig. 1 a, b, c, d).

Lumbar puncture was performed. Cerebrospinal fluid (CSF) was clear with normal pressure and without cell. Protein, glucose and other biochemical parameters of CSF were normal. CSF was investigated for herpes simplex virus (HSV) IgG, M, HSV polymerase chain reaction (PCR). CSF HSV IgG was positive, so, acyclovir treatment was also started (10 mg/kg three times a day). Acyclovir treatment was discontinued after the CSF HSV PCR was found to be negative. CSF cultures were negative. Electroencephalogram (EEG) revealed diffuse slowing (Fig. 2).

Possible autoimmune encephalitis was diagnosed with MRI and CSF findings and treatment with intravenous immunoglobulin (IVIG) 0.4 g/kg for five days was initiated. Serum onconeural antibodies and neuronal antibody screening for limbic encephalitis were performed. For malignancy screening, thorax computed tomography (CT) and abdominal CT were performed and tumor markers were investigated. There were no findings suggestive of malignancy. NMDA receptor antibody (NMDAR ab), anti-glutamate types AMPA 1 (gl 1), anti-glutamate types AMPA 2 (gly 2), anti-CASPR 2, anti-GABA B were negative but anti LGL 1 was found positive. Onconeural antibodies for paraneoplastic study were checked; anti-hu/anna-1, antiyo/pca-1, anti-riski/ANNA 2, anti-MA in 2/T, antiamphiphysin and anti-CV2.1 were found to be negative. Potassium channel antibody was positive (1172 pmol/L (negative <85) (Euroimmun Laboratory, Germany). The patient's sodium levels and serum osmolarities were low during the course of disease; Na: 123-131 Meq/L, serum osmolarity: 264-270 mOsm/L.

In the follow up, after IVIG therapy for 5 days, the patient's clinical symptoms partially improved within 15 days. IVIG was preferred as the first choice of treatment because of the need of immediate treatment in the period when the central nervous system (CNS) infection could not have been excluded yet. After the exclusion of CNS in-



Fig. 1. Case 1: cranial magnetic resonance image shows hyperintense signal changes in both medial temporal regions in axial FLAIR (fluid-attenuated inversion recovery) (a, b, c) and hypointense signal changes in axial T1 (d) sections.



Fig. 2. Case 1: interictal electroencephalography revealed diffuse slowing.

fection and because of the inadequate response, high dose steroid was started intravenously (1000 mg/day) for 8 days and continued with oral steroids (1 mg/kg/day). Three weeks later, there was no significant difference in the lesions on MRI (Fig. 3 a, b).

Generalized and focal seizures were observed during hospitalization. Since the patient was already taking three antiepileptic drugs (AEDs) with inappropriate doses before admission, we regulated the doses of these drugs. Levetiracetam and valproic acid doses were increased to 3000 mg/day and 2000 mg/day, respectively. Pregabalin therapy was discontinued. Lamotrigine (with weekly 25 mg increments) 75 mg/day was added. Although he used three AEDs, his seizures responded significantly to steroid treatment. A nephrologist was consulted because of hyponatremia. Inappropriate antidiuretic hormone (ADH) syndrome was considered and fluid restriction was proposed. On the day 15 of steroid therapy, the Montreal Cognitive Assessment scale (MOCA) was performed, yielding a score of 20/30. He had mild attention deficit and short-term memory impairment, with partial improvement. The patient was discharged with oral steroid therapy and AEDs. Two months later, the level of serum potassium channel antibodies decreased significantly (286 pmol/L). This finding was consistent with the patient's clinical response. After eight months, MOCA test was repeated and the score was 22/30. The seizures were not observed anymore and the doses of AEDs were reduced on



Fig. 3. Follow up axial FLAIR magnetic resonance imaging (MRI; three weeks after the first MRI): there was no significant difference in the lesions (a, b).

follow up visits. He received oral steroid 1 mg/kg/ day for three months and then steroid dose was gradually reduced. Significant improvement was observed in the patient's daily activities. Follow up MRI (9 months after the first MRI) revealed disappearance of hyperintense lesions of the medial temporal regions and atrophy was observed (Fig. 4 a, b, c).

CASE 2

A 59-year-old right handed male working as a curtain seller was admitted to the hospital with complaints of headache and memory impairment. The patient reported that severe headache in the frontal region had started two months before. He also complained of amnesia and occasional dizziness. He



Fig. 4. Case 1: follow up magnetic resonance imaging (MRI; 9 months after the first MRI) showed disappearance of hyperintense lesions in medial temporal regions (axial FLAIR) (a, b) and atrophy (axial T1) (c).



Fig. 5. Case 2: cranial magnetic resonance imaging showed hyperintense signal changes on axial FLAIR images in the left inferior, middle and superior temporal gyrus, anterior insular cortex, inferior frontal gyrus and frontal operculum, both amygdala and the right hippocampus (a, b, c) and slightly hypointense lesions in the same regions on axial T1 images (d).

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Fig. 6. Case 2: electroencephalography was normal.



Fig. 7. Case 2: follow up cranial magnetic resonance imaging showed that the lesions decreased significantly in axial FLAIR sections (a, b), with hippocampal atrophy in T1 section (c).

had short-term memory loss, asking the same things over and over again, and thoughtfulness. Also, he was mushy, had obsessive thoughts and was crying continuously for six weeks. The patient was first evaluated at psychiatry department and escitalopram was initiated. Because of accompanying complaints, he was referred to neurology department. In his past medical history, septoplasty (in 2005) and inguinal hernia (in 2008) operation were described. His family history was unremarkable. His neurological examination was normal except for cognitive impairment. There were orientation, attention, and memory impairments. MMSE test score was 24. Laboratory findings were as follows: fasting blood sugar mildly elevated (127 mg/ L), other serum biochemical parameters, complete blood count and erythrocyte sedimentation rate were normal. Cranial MRI revealed slightly hypointense lesions in T1 images and hyperintense signal changes in T2 images in the left inferior, middle and superior temporal gyrus, anterior insular cortex, inferior frontal gyrus and frontal operculum. There was no contrast enhancement and minimal diffusion restriction was observed in diffusion weighted images. T1 hypointense, T2 hyperintense signal changes were detected in both amygdala and the right hippocampus (Fig. 5 a, b, c, d).

Lumbar puncture was performed. Protein (45 mg/ dL, normal range: 15-40 mg/dL), chloride and glucose levels were normal. No cell was detected in the CSF and cultures were negative. The result of herpes PCR was negative. EEG was normal (Fig. 6).

The probable diagnosis of autoimmune limbic encephalitis was considered. CSF was tested for neuronal antibodies and onconeural antibody. Then, IVIG therapy was started (0.4 g/kg for 5 days). For the purpose of malignancy screening, abdominal ultrasound, abdominal and thorax CT, tumor markers, and protein and immune electrophoresis were performed. Abdominal ultrasound revealed bladder diverticulum. Thorax and abdominal CT was normal. No changes in the lesions were observed on control MRIs. NMDA receptor antibody (NMDAR ab), anti-glutamate type AMP 1 (GL 1), anti-glutamate type AMP 2 (GL 2), anti-CASPR 2 and anti-GABA B in the CSF were negative. For paraneoplastic screening, the onconeural antibodies anti-hu/anna-1, anti-yo/pca-1, anti-risk / ANNA 2, anti-MA in 2/Ta, anti-amphiphysin and anti-CV2.1 were checked and found negative. Potassium channel antibodies were positive (103 pmol/L (negative <85) (Euroimmun Laboratory, Germany) (this result could be obtained after IVIG therapy). Herpes virus PCR in the CSF for viral encephalitis was negative. Meanwhile, because of his anxiety and depressive symptoms and insomnia, the patient had psychiatric consultation. The dose of escitalopram dose was increased (20 mg/day) and alprazolam was added to the treatment. IVIG therapy was administered for the possible diagnosis of autoimmune limbic encephalitis, however, with only minor improvement. Because of this, intravenous high dose (1000 mg/day) steroid treatment for 5 days was introduced and then continued with oral steroids (1 mg/kg/day). Because of the high level of blood glucose, insulin was started on endocrinologist's suggestion. Follow up MOCA test score and MMSE test score were 18/30 and 23/30, respectively. Although no significant differences were observed on follow up MRI, the patient's clinical symptoms improved significantly. The patient was followed up at the outpatient clinic after discharge from the hospital. On the last follow up visit (at 3.5 months of discharge), his memory impairment improved significantly, he could drive

and do shopping again, his depressive symptoms decreased and his sleep was better. MOCA test score was 22/30 and MMSE test score 27/30. On follow up cranial MRI, the lesions decreased significantly, whereas hippocampal atrophy was still observed (Fig. 7 a, b, c).

DISCUSSION

We present two cases of limbic encephalitis with potassium channel antibodies, which responded to immunotherapy. In the first case, clinical presentation included behavioral abnormalities, impairment of memory and epileptic seizures lasting for 2-3 months. Similarly, the second case presented with forgetfulness, psychiatric symptoms and headache. These signs and symptoms are consistent with the clinical presentation of limbic encephalitis (1,2). Diagnostic approach is based on structural and functional imaging (MRI, PET), CSF analysis, EEG and clinical signs and symptoms in limbic encephalitis cases.

Unilateral or bilateral medial temporal hyperintensities are especially important in T2 and FLAIR sections in cranial MRI. MRI can be normal as well. Hyperintensities in extralimbic areas like frontobasal region may also be detected. Contrast enhancement of the lesions is rarely seen (1-3). Both of our two cases had T2 and FLAIR (Figs. 1 and 5) medial temporal hyperintensities. Hyperintensity in the frontobasal region was also present in our second case (Fig. 5). EEG shows unilateral or bilateral epileptic activity, focal or diffuse slowing in most cases of limbic encephalitis (3). In our first case, EEG showed generalized slowing (Fig. 2), whereas the second case had normal EEG (Fig. 6).

Some of the antibodies causing limbic encephalitis target intracellular antigens (anti-Hu, anti-CV2, anti-Ma2, anti-Ri), while others target ion channels [anti-VGKC (voltage gated potassium channel) and N-methyl-D aspartate receptor, which is associated with teratoma in young females presenting with psychiatric symptoms]. Additionally, some other antibodies are defined in a limited number of patients. However, any anti-neuronal antibodies could not be detected in 30%-40% of the limbic encephalitis cases. Since VGKC is found widely in the nervous system, patients that have antibodies against this channel may present with various clinical pictures such as neuromyotonia, Morvan's syndrome, epileptic seizures and limbic encephalitis. Most of the VGKC antibodies are LGI 1, less commonly CASPR-2 (1,2). Our first patient had significantly high levels

of VGKC antibody related to LGI 1. The second patient had slight elevation. Our first patient had accompanying hyponatremia, which has been reported as an accompanying sign in limbic encephalitis cases with VGKC (2-4). Also, it has been reported that a decrease in antibody levels is related to clinical improvement after treatment, similar to our first case (5).

Pleocytosis with the predominance of lymphocytes and elevated protein levels can be detected in CSF samples of limbic encephalitis cases. However, CSF study is usually within the normal limits in limbic encephalitis cases related to VGKC antibodies (3). In our two patients, CSF investigation revealed no cells, while protein level was normal in the first patient and slightly elevated in the second patient.

Association with underlying tumor has been reported to be as low as 20%-30% in cases with VGKC antibodies (mostly lung cancer and thymoma) (2,6,7). Tumor was not detected in either of our patients.

Most of the cases with antibodies against intracellular antigens are associated with tumor and response to immunotherapy is worse. On the other hand, cases with antibodies against cell membrane surface antigens respond better to immunotherapy (2,6).

High dose intravenous followed by oral steroids, IVIG, plasma exchange (PE) and combinations (PE before IVIG) are the recommended treatment regimens. Most of the patients respond in weeks. Rituximab, cyclophosphamide or a combination of both can be tried in non-responders (if the paraneoplastic study is negative) (2). We treated our patients with IVIG as first line treatment. However, response to IVIG was insignificant in both of our patients, so we administered high dose intravenous steroid followed by oral steroid. In our first patient who was under treatment with three antiepileptic drugs seizures decreased significantly after steroid therapy, which is consistent with literature data (5).

Despite the lower level of antibody in our second case, we interpreted both cases as autoimmune limbic encephalitis with clinical picture, MRI and CSF findings, presence of neuronal antibodies and response to immunotherapy (2).

It is known that antibody mediated non-viral limbic encephalitis cases with surface membrane antibodies are reversible or have good response to treatment (8,9). In this report, we emphasize that limbic encephalitis should be suspected in patients with subacute cognitive impairment, psychiatric symptoms and epilepsy resistant to therapy. Since the disorder is mostly reversible, early diagnosis and treatment is important. In conclusion, if the clinical and radiological signs are consistent, autoimmune encephalitis should be suspected after exclusion of infectious encephalitis. These patients should be treated with immunotherapy in the early stage, even before the results of antibody investigations in serum and CSF are obtained.

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Dva slučaja limbičnog encefalitisa s protutijelima kalijevih kanala

SAŽETAK – **Podloga:** Autoimuni limbični encefalitis očituje se zahvaćanjem limbičnih struktura. To je zaseban entitet, a ne sastavnica paraneoplastičnog limbičnog encefalitisa. Posljednjih godina opisuju se slučajevi limbičnog encefalitisa s protutijelima kalcijevih kanala, koji dobro odgovaraju na imunoterapiju. **Prikazi slučajeva:** Prikazuju se dva slučaja muških bolesnika u dobi od 45 i 59 godina. Obojica su imali povišene razine protutijela kalijevih kanala, a bolest se očitovala poremećajem kratkotrajnog pamćenja, psihijatrijskim simptomima te u prvom slučaju i epileptičnim konvulzijama. Njihovi radiološki nalazi bili su tipični za limbični encefalitis i obojica su dobro odgovorili na imunoterapiju. **Zaključak:** Naglašava se potreba sumnje na limbični encefalitis u bolesnika sa subakutnim kognitivnim poremećajem, psihijatrijskim simptomima i epilepsijom otpornom na terapiju. Kako je bolest uglavnom reverzibilna, od velike je važnosti rana dijagnoza i liječenje.

Ključne riječi: autoimuni limbični encefalitis, protutijelo kalijevih kanala



Neurotoxin-induced fibromyalgia or fibromyalgia after ciguatera (tilapia fish) poisoning?

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ABSTRACT – **Background:** Global climate change and the consequent increase in seawater temperatures have not spared the Adriatic Sea, leaving trace on its flora and fauna. Due to rises in seawater temperatures over the last few years, the dinoflagellatae algae that contain a potent neurotoxin, ciguatera, can now be found in the Adriatic Sea. The chronic form of ciguatera poisoning is characterized by chronic fatigue, chronic pain and diffuse sensory disturbances. Diagnosis of fibromyalgia is based on clinical signs and diagnostic criteria, with pain in the characteristic trigger points being the leading symptom. The clinical presentations of fibromyalgia and the chronic form of ciguatera poisoning largely overlap, and it is known that fibromyalgia may develop after infections with neurotrophic viruses or bacteria, as well as after certain poisonings. **Case reports:** This paper presents two patients with ciguatera poisoning that developed the chronic pain syndrome, the characteristics of which meet the criteria for the diagnosis of fibromyalgia. In both patients, excellent results were achieved using antidepressants in the treatment of their pain. **Conclusions:** Clinical studies are needed to assess the efficacy of antidepressants in pain treatment in the chronic form of ciguatera poisoning and in the Adriatic Sea, we believe that this paper may help in the understanding and differential diagnosis of acute and chronic neurological syndromes that develop after the ingestion of fish from the Adriatic Sea.

Key words: fibromyalgia, ciguatera poisoning, global warming, antidepressants

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INTRODUCTION

Ciguatera toxin poisoning (CP) is the most commonly reported disease caused by a toxin of marine origin and caused by the ingestion of contaminated coral fish (1,2). Interest in CP in Europe has risen in the last few years because of climate change and increase in seawater temperatures as well as the growth of dinoflagellates in the Adriatic Sea. The dinoflagellatae algae contain a potent ciguatera toxin (CTX) that causes acute and chronic neurological symptoms. It activates voltage-gated Na⁺ channels (VGSC) increasing the permeability to Na⁺ ions and depolarizing neurons (3-5). It is assumed that this depolarization of neurons causes the neurological signs associated with acute CP. Neurological symptoms in CP include paresthesia, numbness and itching, myalgia, arthralgia and fatigue (1,6). Fibromyalgia is a condition of prolonged, extended, chronic pain that changes in location and strength, and may be associated with disorders of sleep and mood. The pain in fibromyalgia is frequently associated with symptoms such as chronic fatigue, irritable bowel, interstitial cystitis, temporomandibular pain, depression, cognitive dysfunction and insomnia, and it is often more convenient to refer to it as fibromyalgia syndrome (FMS) (2). Environmental factors that contribute to the development of fibromyalgia are emotional stress, physical trauma and infections with neurotropic viruses and bacteria (7). Dual antidepressants prevent the reuptake of norepinephrine and serotonin, thereby reducing pain in syndromes of central neuropathic pain, as well as regulating sleep and reducing the anxious-depressive component of the clinical picture in chronic pain syndromes (8,9). Pregabalin is the first US Food and Drug Administration approved drug for the treatment of fibromyalgia; it has also been proposed as a possible treatment for pain in acute and chronic forms of CP. The pain in the chronic form of CP (CCP) has some characteristics of central neuropathic pain, is not dependent on movement or load, is associated with sleep disorders, and can be controlled with the use of antidepressants and pregabalin, highly resembling the pain of FMS.

CASE REPORTS

CASE 1

A 47-year-old female was admitted to the Department of Neurology due to chronic fatigue syndrome, diffuse paresthesias, ataxia, myalgia and arthralgia, which had developed after short-term gastrointestinal symptoms of nausea and abdominal pain. Paresthesia was described as a "feeling of cold and warm water flowing down the limbs" or as a "splash of cold water". She complained of perceiving a cold sensation on the soles of her feet as hot. Upon clinical neurological examination, a disturbance in temperature sensation was recorded (i.e. temperature sensation reversal), as well as a mildly attenuated triceps reflex, excessive sweating of the face, and mild fatigability and pelvic muscle pain on repeated squatting. An underlying cause was not found after an extensive diagnostic workup. Lumbar puncture was normal, and there were no signs of a recent neurotrophic viral or bacterial infection. Electromyoneurographic (EMNG) findings suggested a mild polytopic radiculopathy. The repetitive nerve stimulation test was normal. Antibodies to muscle specific kinase (MuSK) and nicotinic acetylcholine receptor (NAChR) were negative. Pyridostigmine bromide (2x60 mg) therapy was initiated with a modest therapeutic effect. History data indicated that clinical manifestations had developed after the ingestion of fish during the patient's stay in Maldives (Republic of Maldives, Indian Ocean). Altogether, her clinical symptoms and medical history pointed to CP. The diagnosis of CCP was made based on her clinical presentation, medical history and the results of the laboratory, neuroradiological, immunological and electrophysiological workup.

The patient was monitored over a period of two years, and gradual improvement of the neurological symptoms was noted. In the meantime, the patient developed an allergy to milk, wheat, eggs, chicken and propolis. Antidepressant therapy (duloxetine 60 mg daily) has been introduced with significant pain reduction and regulation of sleep disturbances, but allergies to the mentioned antigens have persisted.

CASE 2

A 54-year-old female was referred to the Center for Neuromuscular Diseases due to paresthesias in the extremities, pain in the muscles, joints and extremities, sleep disturbances and depression, as well as chronic fatigue syndrome that remained after an acute episode of fever, sore throat and abdominal pain. The first symptoms appeared during a trip to Texas, six months prior to the checkup, and after the ingestion of a raw tropical fish, tilapia, caught on the northern coast of the Gulf of Mexico. During the patient's first neurological examination, a disturbance in temperature sensation in the feet, muscle weakness, and pain in the shoulder and pelvic area were noted, as well as painful acroparesthesia. Myotatic reflexes were normal, and mild radiculopathy of L5-S1 was detected in her EMNG findings. No other cause of the syndrome was found upon diagnostic workup. A diagnosis of CCP was made based on her medical history and clinical presentation. Given the associated chronic fatigue syndrome, depression, sleep disturbances and pain in the characteristic points, fibromyalgia syndrome was also diagnosed. Duloxetine (60 mg daily) was introduced and resulted in excellent clinical response.

DISCUSSION

The symptoms of CCP largely overlap with the clinical picture of FMS. In this paper, we present two patients with CCP that developed a chronic pain syndrome, with the characteristics meeting the criteria for FMS and showing significant pain reduction after duloxetine administration. It is well known that infections with neurotropic viruses and bacteria can lead to FMS, and it is possible that the chronic pain found in CCP is neurotoxin-induced fibromyalgia (7). The mechanism of action of ciguatoxin is fairly well understood. However, CCP is substantially more complex and goes beyond the initial toxic damage to peripheral nerves. Many similarities between FMS and CCP have been noted as a result of studies on chronic inflammatory response syndrome (10,11). Some less frequent laboratory abnormalities found in CCP have helped identify a complex syndrome characterized by the host response to inflammation, autoimmune disease, and coagulopathy. HLA-DR haplotype is predictive of other chronic diseases sharing similar characteristics with CCP (12). Abnormalities in the following parameters have been noted in CCP: visual contrast sensitivity (VCS) deficits, HLA-DR, melanocyte stimulating hormone abnormalities (MSH), vasoactive intestinal peptide (VIP), C4A, TGFβ1, matrix-metalloproteinase-9 (MMP9), ACTH/cortisol and ADH/osmolality. Ciguatoxins are extremely potent activators of VGSC, which exhibit their effects predominantly in the peripheral nervous system. VGSC have now been found in various types of non-excitable cells and these channels contribute to the activation of inflammatory pathways in many immune cells (3). The first patient presented developed an allergic response to multiple allergens during the sub-chronic stage of the disease. A deficit of VIP and MSH, two neuropeptide regulators of the inflammatory response, has been observed in patients with CP indicating a lack of inflammatory regulation in those suffering from CCP (13). Increased activity of MMP9 is characteristic of several inflammatory and autoimmune conditions. TGF β 1, an anti-inflammatory cytokine, up-regulates MMP9, which can promote the progression of CCP (3,12). The differentiation between acute illness and the development of chronic disease can be made according to HLA genotype, dysfunction of antigen presentation or regulation of auto-reactive T cells. Inflammation is an important step in the development of various forms of neuropathic pain, both central and peripheral. There is convincing evidence that proinflammatory cytokines present in chronic inflammation promote the development of neuropathic low back pain, complex regional pain syndrome and fibromyalgia (14-16). Other than a constitutional predisposition to the development of disease, abnormal regulation of neuropeptides and immune response, CCP and FMS share several clinical features: chronic fatigue, chronic pain, depression, and sleep disturbances. A positive therapeutic response to pregabalin in the treatment of chronic pain in both conditions is another common feature (17). In this paper, we have presented two patients with CCP whose symptoms fulfilled the diagnostic criteria for FMS, and who showed an excellent response to duloxetine in the treatment of their pain (18). The overlap of neurological symptoms present in these two syndromes may indicate the possibility of common pathophysiological mechanisms and suggests that ciguatera toxin may be a possible environmental cause of FMS. It is possible that changes in the host immune response occur in genetically predisposed individuals, as well as a wide range of changes to immunoregulatory molecules and neuropeptides, setting the basis for the development of fibromyalgia. The chronic pain syndrome in CCP is likely triggered by initial nociceptive damage to peripheral nerves, although in constitutionally predisposed individuals chronic neuropathic pain, as seen in fibromyalgia, can also develop. Although the patients have exhibited an excellent response to duloxetine in the treatment of chronic pain in CCP, a substantially larger sample group is needed to evaluate the efficacy of duloxetine in the treatment of CCP. Future research on the association between chronic inflammation and stress as the underlying basis for the development of CCP and FMS may provide new therapeutic options in the treatment of FMS, as well as other chronic pain syndromes such as CCP.

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Fibromialgija nakon otrovanja ciguaterom ili neurotoksinom izazvana fibromialgija?

SAŽETAK - **Podloga:** Globalne klimatske promjene s posljedičnim porastom temperature mora utjecale su na floru i faunu Jadrana. Zbog porasta temperature mora u posljednjih nekoliko godina alge dinoflagelata koje sadrže snažan neurotoksin ciguateru sada se mogu naći i u Jadranskom moru. Kronični oblik otrovanja ciguaterom obilježava kronični umor, kronični bolovi i difuzni poremećaj osjeta. Klinička dijagnoza fibromialgije temelji se na bolovima u karakterističnim točkama-okidačima kao vodećem simptomu. Klinička slika fibromialgije i kroničnog oblika otrovanja ciguaterom je vrlo slična. Također je poznato da se fibromialgija može razviti nakon infekcije neurotropnim virusima i bakterijama, kao i nakon određenih vrsta otrovanja. **Prikazi slučajeva:** U ovom radu prikazujemo dvije bolesnice kod kojih se nakon otrovanja ciguaterom razvio kronični bolni sindrom sa značajkama fibromialgije. U obje bolesnice izvrstan analgetski učinak postignut je upotrebom antidepresiva. **Zaključak:** Za procjenu učinka antidepresiva u liječenju boli u bolesnika s kroničnim oblikom otrovanja ciguaterom neophodna su daljnja klinička istraživanja. S obzirom na to da je ciguatera neurotoksin trenutno prisutan i u flori Jadranskoga mora vjerujemo da će ovaj rad pomoći u razumijevanju i diferencijalnoj dijagnostici akutnih i kroničnih neuroloških poremećaja nastalih nakon konzumacije ribe iz Jadranskog mora.

Ključne riječi: fibromialgija, otrovanje ciguaterom, globalno zatopljenje, antidepresivi



Severe relapse after stopping natalizumab for multiple sclerosis

M. Habek^{1,2}

A 19-year-old female was diagnosed with multiple sclerosis (MS) in 2008, after she had developed double vision. In the next year, she suffered four relapses, after which therapy with subcutaneous interferon beta 1a was introduced. In the next 2.5 years, she suffered seven more relapses with good



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recovery after steroid treatment. At that point, her Expanded Disability Status Scale (EDSS) was 3.5. Because of the disease progression, therapy with natalizumab 300 mg i.v. monthly was initiated. During the next 12 months, the patient was stable, without new relapses and her EDSS improved to 1.5. Her magnetic resonance imaging (MRI) 6 months after starting natalizumab (Fig. 1 a, b, c, T2 sequences) showed several infra- and supratentorial lesions without postcontrast enhancement (postcontrast T1 sequences not shown). Because the patient wanted to become pregnant, therapy with natalizumab was stopped after 12 months. Three months after discontinuation, the patient experienced severe relapse with ataxia and spastic paraparesis (muscle strength of the left leg was 3/5 and of the right leg 0/5). Brain MRI performed at that point (Fig. 1 d, e, f, T2 sequences) showed

Key words: multiple sclerosis, natalizumab, relapse

many new T2 and FLAIR lesions, predominantly in the medulla oblongata, pons and supratentorial regions, without postcontrast enhancement (postcontrast T1 sequences not shown). Treatment with methylprednisolone 1 g for 10 days led to moderate to good recovery. Treatment with natalizumab was initiated again, and after three monthly doses the patient was stable with an EDSS of 3.5.

This case highlights the problem of the disease course after natalizumab discontinuation because of pregnancy planning.

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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.

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

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

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

Books

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

Chapter in a book

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

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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.

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Knjige

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Poglavlje u knjizi

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