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NEUROLOGIA CROATICA,
University of Zagreb, School of Medicine and Zagreb University Hospital Center, University Department of Neurology, Kišpatićeva 12, HR-10 000 Zagreb, Croatia;
phone/fax: +385 1 2388 176.
E-mail: neurologiacroatica@kbc-zagreb.hr
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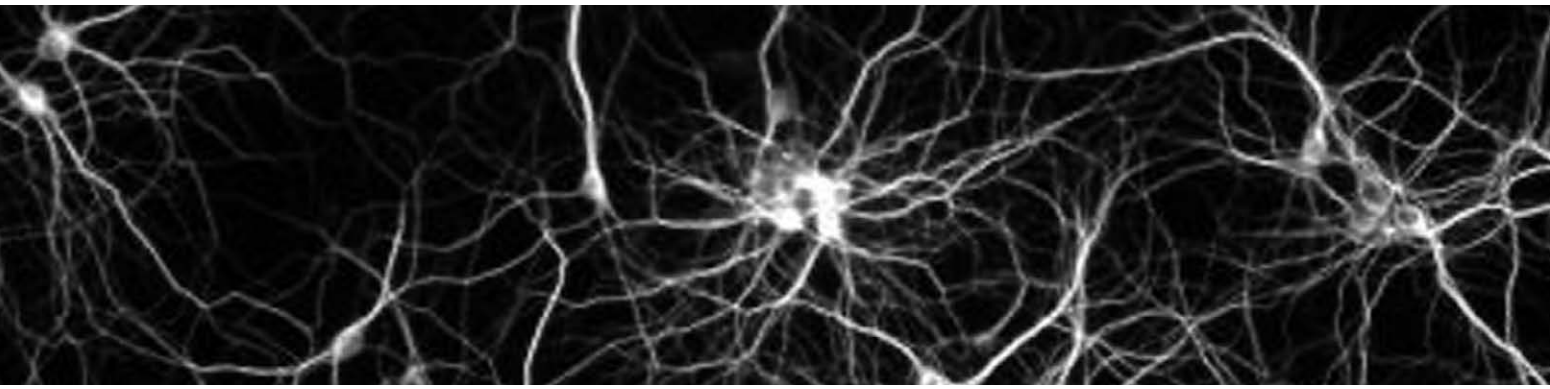

Correlation of electrodiagnostic and clinical findings in unilateral S1 radiculopathy

Seyed Mansoor Rayegani, Navid Rahimi, Elham Loni,
Shahram Rahimi Dehgolan, Leyla Sedighipour

ABSTRACT – *Objectives:* Lumbosacral radiculopathy is a challenging diagnosis and electrodiagnostic study (EDX) is a good complementary test to magnetic resonance imaging (MRI). Physical examination, MRI and electrodiagnosis have different diagnostic value in this regard. MRI can provide anatomical evidence and is useful in choosing the treatment procedure, but it may also yield false-positive results. In this study, we assessed the correlation of clinical and EDX findings in patients with L5-S1 disc herniation on MRI. *Methods:* EDX was performed in 87 patients referred for clinical and MRI diagnosis of S1 radiculopathy. The consistency of EDX results with MRI and clinical findings was evaluated by Pearson χ^2-test and odds ratio. *Results:* Disc protrusion was present in 58% and disc extrusion in 42% of patients. Physical examination revealed absent Achilles reflex in 83% and decreased S1 dermatome sensation in 65% of patients. In this study, EDX sensitivity was about 92%. The highest consistency between EDX parameters and physical examination findings was recorded between absent H-reflex and decreased Achilles reflex (OR=6.20; p=0.014), but there was no significant consistency between H-reflex and either muscular weakness or straight leg raising test result (p>0.05). There was no relationship between the type of disc herniation on MRI and H-reflex either. There was correlation between H-reflex abnormalities and absent ankle reflex in patients with unilateral L5-S1 disc herniation on MRI. *Conclusion:* Results of this study showed that in patients with L5-S1 disc herniation and S1 nerve root compression, it is still beneficial to perform EDX for selected patients.

Key words: electromyography-nerve conduction studies, magnetic resonance imaging, H-reflex, lumbosacral, S1 radiculopathy

Physical Medicine and Rehabilitation Research Center, Shohada Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran

INTRODUCTION

Lumbosacral discopathy is one of the most common causes of low back pain. Estimated lifetime prevalence of lumbosacral radiculopathy is 3%-5% of the general population (1). The intervertebral disc between fifth lumbar and first sacral vertebrae (L5-S1) is the most susceptible point to herniation accounting for 42% of all lumbar disc herniation (2). Lumbosacral radiculopathy is a challenging diagnosis. Electrodiagnostic study (EDX) is a useful modality to help in diagnosis because the test is very specific and is therefore a good complement to lumbosacral magnetic resonance imaging (MRI), which is a highly sensitive but nonspecific test. In addition, it is the unique test to evaluate physiologic function of the spinal nerves to see if they are damaged or not. A comprehensive study can also help rule out differential diagnoses that cause pain or neurologic changes in lower extremity. In the hands of a skilled examiner, EDX is very specific and can help us rule out some differential diagnoses that are very common (3). In some studies, two limb muscles plus associated lumbar paraspinal muscle abnormality, two limb muscle abnormality, or one limb muscle plus associated lumbar paraspinal muscle abnormality on electromyography (EMG) showed 97%, 96%, and 92% specificity, respectively, for radiculopathy (4). The specificity of 85% has been reported for EDX in another study (5). There are other studies claiming that EDX could not be replaced by MRI (6). However, there is no systematic review regarding this comparison. Therefore, as there is no gold standard test for lumbosacral radiculopathy, a combination of history, physical examination, imaging, and EDX is used to confirm the diagnosis in research, as well as in clinical setting (3).

There are multiple clinical, imaging and electrodiagnostic tests to detect S1 radiculopathy (2,7). Lumbar radiculopathy is known to have various presentations. Some patients are vague historians, and physical exam is neither highly sensitive nor specific in these patients. Because of this, and because there is no gold standard test for diagnosis, it is common for patients to undergo additional work up. From the evidence based medicine perspective, it may be difficult to assess the value of these tests (3).

Imaging (especially MRI) can well depict disc degeneration and herniation. However, there is very poor consistency between imaging findings of disc herniation and clinical presentation or course. In other words, MRI is more sensitive than clinical findings and consequentially has a large amount of false-positive results (8). For example, lumbar disc protrusions can be seen in as many as 67% of asymptomatic patients older than 60 and more than 20% have lumbar central stenosis (3).

Electrodiagnostic studies including electromyography-nerve conduction studies (EMG-NCS), when performed by an expert physician, are a very valuable method to diagnose root involvement. It is especially valuable in patients whose physical examination is not reliable (7), as well as in highly suspicious patients who have negative MRI, thus a non-compressive radiculopathy such as infective or immune mediated one being suspected. EDX is very helpful in the work up of patients who have multiple level involvements, and also in patients who are at the risk of neuropathy (3). One study found the needle EMG to be highly specific in the diagnosis of lumbar radiculopathy when using appropriate EDX criteria (92% specificity). EDX for radiculopathy has a low rate of false-positive results (6).

Among EDX findings, H waves are very helpful in the diagnosis of S1 radiculopathy. In some studies, it has been characterized as a definitive sign of S1 radiculopathy, even without the need to perform needle EMG (9-12). This wave has several strengths, including the ability to detect injury to sensory fibers and, unlike needle examination, they are not dependent on a window of opportunity to discover abnormalities because they become abnormal as soon as compression occurs and the deficit can last indefinitely (12).

The aim of the present study was to describe the utility of electrodiagnostic studies in confirming clinically suspected diagnosis and investigate the consistency between clinical and paraclinical findings (EDX) in patients highly suspected of S1 radiculopathy with disc herniation on MRI.

PATIENTS AND METHODS

This prospective study was conducted at the Shohada-e-Tajrish Hospital, Shahid Beheshti University in Tehran, Iran, in 2014. Our patients were referred from neurosurgery department with a high clinical suspicion of S1 radiculopathy and disc herniation findings on MRI in the preceding 3 weeks. All 87 patients referred between 2013 June and 2014 December with a suspicious diagnosis or requiring additional evaluation for better treatment decision were consecutively included in the study. None of the patients had local soft tissue infection or other contraindication for EDX. All study pa-

tients signed their informed consent. The inclusion criteria were as follows: low-back pain radiating to one lower limb and onset of symptoms between 3 weeks to 3 months before.

Individuals with bilateral radicular symptoms, previous spine surgeries, polyneuropathies, focal neuropathies in lower limb, myopathies and known motor neuron diseases were excluded from the study.

On physical examination, the ankle reflex, straight leg raising (SLR) test, plantar flexion strength and sensory loss in S1 territory were examined. Manual muscle testing was recorded in grading system of the Medical Research Council Scale: full available range of motion (ROM) is achieved against gravity and is able to demonstrate maximal resistance (5/5); full available ROM is achieved against gravity and is able to demonstrate moderate resistance (4/5); full available ROM is achieved against gravity but is not able to demonstrate resistance (3/5); full available ROM is achieved only with gravity eliminated (2/5); a visible or palpable contraction is noted, with no joint movement (1/5); and no contraction is identified (0/5) (14). Achilles reflex was determined by taping Achilles tendon with a reflex hammer in prone position and assessed as 0 (no response), 1+ (diminished but present and might require facilitation), 2+ (usual response), 3+ (more brisk than usual), and 4+ (hyperactive with clonus).

We performed EDX studies to confirm diagnosis and to determine the severity of progressive axonal loss.

PARACLINICAL EVALUATION

Electrodiagnostic (EDX) test was performed by a two-channel synergy electrodiagnostic instrument (Medelec™ Synergy T-EP). Needle EMG with a concentric needle electrode was performed by an experienced physiatrist, professor of physical and rehabilitation medicine.

Multiple muscles within the appropriate myotome and adjacent myotomes (above and below) were examined (13,14).

NERVE CONDUCTION STUDIES (NCS)

Standard EDX techniques (13) were used for sural, saphenous and superficial peroneal nerve sensory conduction studies. Sensory action potentials (SNAPs) and nerve conduction velocities (NCVs) of the above nerves were calculated. Surface electrodes were used for NCS.

Motor conduction studies were also performed for tibial and deep peroneal nerves and compound motor nerve action potentials (CMAPs) were recorded from the abductor muscle of great toe and short extensor muscles of toes. NCVs of both tibial and deep peroneal nerves were also measured.

Patients with impaired nerve conduction studies including patients with peripheral nerve injury, lumbosacral plexopathy or polyneuropathy were excluded from the study. Patients with a history of radiation, immune or infectious disease, which could induce postirradiation radiculitis, plexopathy, infective or immune mediated radiculopathy were also excluded.

Standard EMG techniques were followed for six muscles in S1 myotome (*gastrocnemius, soleus, abductor hallucis, gluteus maximus, peroneus longus, flexor hallucis longus*) and paraspinal muscles. Also, muscles innervated by L4 and L5 were examined for diagnosing S1 radiculopathy and ruling out differential diagnoses. The criteria for neurogenic EMG included membrane instability, defined as fibrillation potentials and/or positive sharp waves, polyphasic (>4 phases) and/or long-duration motor unit action potentials (MUAPs) (≥13 ms), reduced recruitment, and/or reduction in interference pattern (14).

H-reflex was recorded from gastro-soleus muscle using Braddom's technique by submaximal stimulation over the tibial nerve (14). We also adjusted these values for patient leg length and age. All these electrodiagnostic tests were done in both limbs.

STATISTICS

Statistical analysis was conducted using the SPSS version 20. Association between EDX parameters and clinical findings was calculated by odds ratios with the level of significance determined by Pearson χ^2-test. Paired T-test was used to assess changes in continuous variables. The level of statistical significance was set at $p<0.05$.

RESULTS

During this 18-month study, 102 patients with high suspicion of clinical and imaging findings indicating unilateral S1 radiculopathy were referred to our EDX lab. Of these patients, 15 patients were excluded as they had other diagnoses leading to

their symptoms: nine patients had sensorimotor polyneuropathy, and three patients had sciatic nerve injury and lumbosacral plexopathy each. Finally, 87 patients with S1 lumbosacral radiculopathy remained in the study. Demographic and clinical characteristics of these patients are shown in Table 1.

According to patient MRI results, 51 (59%) patients had protruded and 36 (41%) patients extruded disc herniation. Physical examination revealed absent Achilles reflex in 83%, decreased S1 dermatome sensation in 65%, positive SLR test in 47%, and prominent muscular weakness in only 2.3% of patients. In this study, EDX sensitivity was high (92%, positive result in 80 patients). There was no association between the type of disc herniation and Achilles tendon reflex (p=0.47, OR=0.65, 95%CI 0.2-2.0); there was no association between the type of disc herniation and either H-reflex (p=0.769, OR=0.82, 95%CI 0.23-2.94) or EMG result (p=0.13).

Table 1. *Demographic characteristics and physical examination findings in patients with S1 radiculopathy*

Sex Male/female	Male 48 (55%)	Female 39(45%)
Age (years) Mean Range	 41.2 19-65	
Duration of patient symptoms, range (months)	6-24	
Physical exam findings:		
Straight leg raising test	Positive 41 (47%)	Negative 46 (53%)
Ankle reflexes	Absent or decreased 73 (84%)	Normal 14 (16%)
Sensation in S1 dermatome	Decreased 47 (65.5%)	Normal 30 (34.5%)
Plantar flexor muscle strength	Weak 2 (2%)	Normal 85 (98%)

Calculated sensitivity of H-reflex to diagnose S1 radiculopathy was 87.4% (76 patients had decreased or absent H-reflex) and only 11 (12.6%) subjects had normal H-reflex. There was no association between H-reflex and SLR test results (p=0.58, OR=1.08, 95%CI 0.3-3.8), between H-reflex and plantar flexor muscle weakness (p=0.23, OR=0.133, 95%CI 0.008-2.30), or between H-reflex and decreased sensation in S1 dermatome (p=0.12, OR=2.6, 95%CI 0.7-9.3) but H-reflex and ankle jerk were strongly associated (p=0.014, OR=6.2, 95%CI 1.5-24.5) and were seen together in 77% of all patients and 91% of patients with decreased Achilles reflex (Table 2).

Electromyography showed neurogenic pattern (neurogenic MUAPs or active denervation) in 92% of subjects. Only seven patients were normal on EMG exam and 80 patients had positive findings, as shown in Figure 2 (92% total sensitivity). The highest sensitivity was recorded for active denervation (37.9%), followed by chronic neurogenic pattern (27.6%) (Table 3). There was no correlation between the type of disc herniation on MRI and type of EMG abnormalities in electrodiagnostic study (p=0.13).

Table 2. *Physical examination and H-reflex findings in patients with S1 radiculopathy*

	Ankle reflex		Straight leg raising test		Sensory examination	
	Normal	Decreased	Negative	Positive	Normal	Decreased
Normal H-reflex	5 (45.5%)	6 (54.5%)	6 (54.5%)	5 (45.5%)	5 (45.5%)	6 (54.5%)
Prolonged/absent H-reflex	9 (11.8%)	67 (88.2%)	40 (52.6%)	36 (47.4%)	9 (11.8%)	67 (88.2%)
Significance	p=0.014; OR=6.20 Pearson χ^2=8.04		p=0.582; OR=1.08 Pearson χ^2=0.014		p=0.124; OR=2.60 Pearson χ^2=2.24	

Table 3. *Needle electromyography (EMG) findings in patients with S1 radiculopathy*

Electromyographic finding	n (%)
Normal	7 (8%)
Denervation potentials	33 (38%)
Chronic neurogenic process	24 (26%)
Decreased interference	17 (18%)
Denervation potentials & neurogenic pattern MUAPs	6 (7%)
Total abnormal EMG	80 (92%)

MUAP = motor unit action potential

DISCUSSION

Low-back pain with radiating pain to the lower limb is the most common reason for referral to

EDX lab. EDX has been used to assess for lumbosacral radiculopathy diagnosis, determine the involved roots, physiologic function of nerve, and severity of lesion. It can also serve as an adjunct to clinical history and physical examination, and to confirm neuroimaging result (15). In our study, the sensitivity of EMG and H-reflex in diagnosing lumbosacral radiculopathy was 92% and 87%, respectively, and the two most common physical exams were decreased Achilles reflex and S1 dermatome abnormality. In another investigation, sensory loss in the painful dermatome was the most frequent finding on physical examination (56% of cases) and EMG was abnormal in at least one myotome in 42% of cases (16).

Recently, some evidence has been reported for the role of EDX before surgery to know which patients have better prognosis, but it is beyond the scope of this article. H-reflex is routinely used to evaluate S1 radiculopathy diagnosis. The H-reflex diagnostic criteria are latency difference between two sides, prolonged latency, and absence of H-reflex (12,13). Diagnostic sensitivity and specificity vary widely among studies. The sensitivity and specificity of 50% and 91% are reported for H-reflex, respectively (8). In the present study, ankle jerk reflex abnormalities were followed by H-reflex latency abnormality in 91% of patients. In similar investigations, H-reflex study was abnormal in 88% of subjects (17). Bobinac-Georgijevski *et al*. report that EMG abnormalities indicating S1 radiculopathy were followed by H or F wave latency abnormality in 63% of patients. The rest of patients (37%) showed mild EMG abnormalities, followed by normal H or F wave (11). Our study revealed similar results; there was significant association between EMG findings and H-reflex (p=0.066). Normal EMG finding was followed by normal H or F wave in 64% of patients. In a study performed by Katirji and Weissman, the maximal H-reflex amplitude and maximal H/maximal M amplitudes were associated in a positive slope with ankle jerk (18). In most of the previous studies, H-reflex abnormalities including H-reflex latency or its absence were strongly associated with ankle reflex.

In a study conducted by Lauder *et al*. to determine the extent to which the history and physical examination predicted the outcome of EDX evaluation in patients with suspected lumbosacral radiculopathy, the history and physical examination could not reliably predict electrodiagnostic outcome (2). However, there was strong association between the presence of an abnormality in the respective reflex and radiculopathy at that level. For example, subjects with an abnormal Achilles reflex were more than eight times more likely to have S1 radiculopathy than those with normal Achilles reflex (19). These findings are almost consistent with the results of our study.

Finally, we should say that imaging can be considered complementary to electrodiagnostic medicine. It depicts disc degeneration and disc herniation, and can also suggest the presence of discogenic abnormality, but the lack of the gold standard obviates any definitive conclusions. As we know, there is very poor correlation between imaging findings of disc herniation and the clinical presentation or course (9). In our study, EDX findings were used to confirm the diagnosis of disc herniation but there was no significant correlation between the pattern of disc herniation (extrusion *vs*. protrusion) and electrodiagnostic results including EMG findings, H-reflex latency, etc.

In conclusion, in the population of patients with suspected lumbosacral radiculopathy referred for an EDX study, generally physical examination may not be reliable in predicting EDX outcome. However, ankle reflex can be assessed and considered as a H-reflex study in electrodiagnostic testing. This study also showed that in a patient with L5-S1 disc herniation on MRI, in the presence of an EMG expert, it is still beneficial to perform EDX study, in particular in patients that are candidates for surgery intervention or those with negative MRI results. However, MRI and EDX are complementary to each other. MRI investigates the anatomic change of discovertebral complex and electrodiagnostic studies provide physiologic information. EDX could reveal nerve root compression, its progress and its stage, i.e. acute or chronic lesion, but imaging and other investigations may be necessary to determine the exact cause of spinal nerve damage other than disc herniation.

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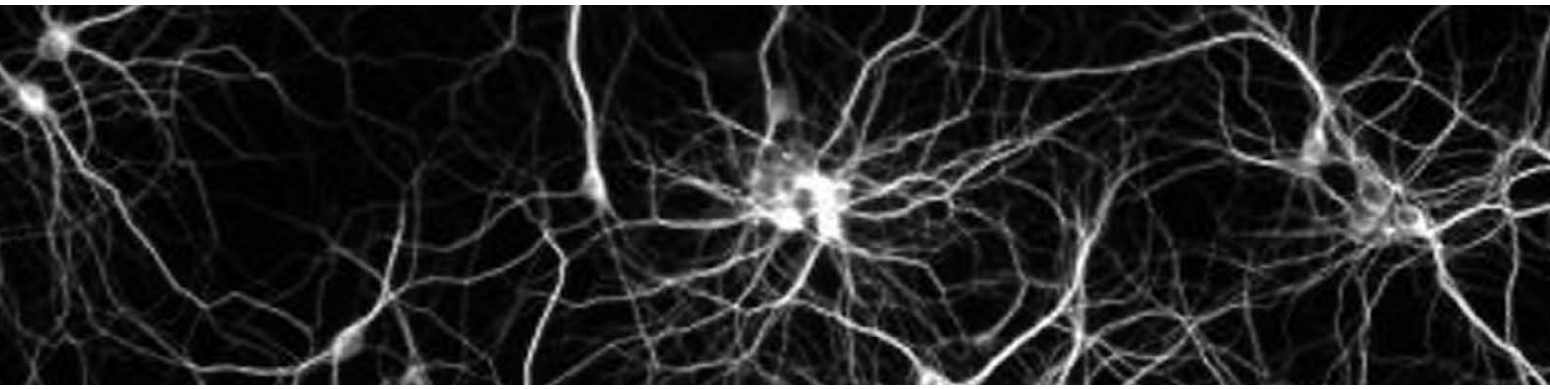
Address for correspondence: Assist. Prof. Leyla Sedighipour, MD, Physical Medicine and Rehabilitation Research Center, Shohada Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran; e-mail: lsedighy@yahoo.com

Korelacija elektrodijagnostičkih i kliničkih nalaza kod jednostrane S1 radikulopatije

SAŽETAK – *Ciljevi:* Lumbosakralna radikulopatija je zahtjevna dijagnoza, a elektrodijagnostičko ispitivanje (EDX) je valjana dopunska pretraga magnetskoj rezonanci (MRI). Fizikalni pregled, MRI i elektrodijagnostika imaju različitu dijagnostičku vrijednost u ovom području. MRI pruža anatomske dokaze i korisna je za odabir terapijskog postupka, ali isto tako može dati lažno-pozitivne rezultate. U ovom istraživanju procjenjivali smo korelaciju kliničkih i EDX nalaza u bolesnika s hernijom diska L5-S1 na MRI. *Metode:* EDX je provedeno u 87 bolesnika upućenih na kliničku i MRI dijagnostiku radikulopatije S1. Sukladnost rezultata EDX s MRI i kliničkim nalazima procijenjena je Pearsonovim χ^2-testom i omjerom izgleda (*odds ratio*, OR). *Rezultati:* Protruzija diska bila je prisutna u 58 %, a ekstruzija diska u 42 % bolesnika. Fizikalni pregled je otkrio odsutnost Ahilova refleksa u 83 % i smanjeni osjet dermatoma S1 u 65 % bolesnika. Osjetljivost EDX u ovom istraživanju bila je oko 92 %. Najviša razina sukladnosti između parametara EDX i nalaza fizikalnog pregleda zabilježena je između odsutnog H-refleksa i sniženog Ahilova refleksa (OR=6,20, p=0,014), ali nije bilo značajnije sukladnosti između H-refleksa i mišićne slabosti ili rezultata testa podizanja ispružene noge (p>0,05). Nije bilo niti povezanosti između tipa hernije diska na MRI i H-refleksa. Utvrđena je korelacija između nenormalnosti H-refleksa i odsutnosti refleksa skočnog zgloba u bolesnika s jednostranom hernijom diska L5-S1 na MRI. *Zaključak:* Rezultati ovoga istraživanja su pokazali kako je u bolesnika s hernijom diska L5-S1 i kompresijom korijena živca S1 ipak korisno provesti EDX u odabranih bolesnika.

Ključne riječi: elektromiografija - ispitivanje živčane provodljivosti, magnetska rezonanca, H-refleks, lumbosakralni, radikulopatija S1



Alcohol misuse in patients with multiple sclerosis

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

ABSTRACT – *Objective:* The aim of the study was to determine the prevalence of alcohol misuse in patients with multiple sclerosis (MS) and to analyze the link between alcohol misuse and patient age, sex, clinical course of MS, disease duration, and degree of disability. *Patients and methods:* The respondents were MS patients older than 18 that underwent inpatient rehabilitation at the Lipik Special Hospital in the period from May 15, 2015 to November 15, 2015. The exclusion criterion was serious cognitive impairment. Data on patient age, sex, degree of disability, clinical course of MS, and time elapsed from MS diagnosis were collected. Diagnosis of alcohol misuse was made by use of the Alcohol Use Disorders Identification Test-Consumption (AUDIT-C) questionnaire. Study patients were divided into two groups according to the presence or absence of alcohol misuse. *Results:* The total number of respondents was 158, of which 15 (9.5%) screened positive for alcohol misuse. In the group of patients with alcohol misuse there was a significantly higher proportion of men (p=0.048). There were no statistically significant between-group differences according to age (p=0.787), disease duration (p=0.506), level of disability (p=0.367), and course of disease (p=0.663). *Conclusion:* According to this study, alcohol misuse was present in 9.5% of MS patients. Because of the numerous health and social consequences of excessive alcohol intake, comprehensive care of MS patients should include counseling on the adverse effects of alcohol.

Key words: multiple sclerosis, alcohol misuse, AUDIT-C questionnaire

INTRODUCTION

According to the World Health Organization (WHO) definition, alcohol misuse is the use of alcohol for a purpose not consistent with legal or medical guidelines (1). The term includes a whole spectrum of drinking above the recommended limits including hazardous alcohol use, harmful alcohol use, and alcohol dependence. Hazardous use is a pattern of alcohol consumption that increases the risk of adverse consequences for the user, while

Lipik Special Hospital for Medical Rehabilitation, Lipik, Croatia

Table 1. *The Alcohol Use Disorders Identification Test – Consumption (AUDIT-C) screening questionnaire (16)*

1. How often do you have a drink containing alcohol? *
Never (0 points), Monthly or less (1 point), Two to four times a month (2 points),
Two to three times a week (3 points), Four or more times a week (4 points)
2. How many drinks containing alcohol do you have on a typical day when you are drinking?
1 or 2 (0 points), 3 or 4 (1 point), 5 or 6 (2 points), 7 to 9 (3 points), 10 or more (4 points)
3. How often do you have six or more drinks on one occasion?
Never (0 points), Less than monthly (1 point), Monthly (2 points), Weekly (3 points), Daily or almost daily (4 points)

*A drink containing alcohol is typically a can of beer, a glass of wine, or a shot of hard liquor (e.g., scotch or vodka)

harmful use causes damage to health, which could be physical or mental. Alcohol dependence is defined as a cluster of behavioral, cognitive, and physiologic phenomena that develop after repeated alcohol use and that typically include strong desire to consume alcohol and difficulties in controlling its use, persisting in its use, a higher priority given to alcohol use than other activities and obligations, as well as increased tolerance (1). The term harmful alcohol use is a WHO equivalent for the term alcohol abuse described by the American Psychiatric Association (APA) in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-4), where it is defined as a maladaptive pattern of drinking, leading to clinically significant impairment or distress, as manifested by at least one of the 'abuse' criteria occurring within a 12-month period (2). A 'dependence' diagnosis according to DSM-4 criteria would receive anyone with three or more of the 'dependence' criteria during the same 12-month period (2). Studies consistently showed a high reliability of DSM-4 and WHO alcohol dependence criteria, but lower reliability of alcohol abuse/harmful use criteria (3). The term 'heavy drinking' is referred to drinking that exceeds a certain daily volume of alcohol (three drinks or more a day) or quantity *per* occasion (five drinks or more on an occasion, at least once a week or at least 60 grams or more of pure alcohol on at least one occasion in the past 30 days) (1). Heavy drinking is also included in the spectrum of alcohol misuse (1). In the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), APA no longer uses the terms alcohol abuse and alcohol dependence, but rather refers to 'alcohol use disorders', which are defined as mild, moderate or severe to indicate the level of severity, which is determined by the number of diagnostic criteria met by an individual (4).

Most patients with alcohol misuse are not alcohol dependent, but many of these non-dependent patients account for morbidity and mortality attributed to drinking (5). In addition to compromising physical and mental health, conditions already affected by multiple sclerosis (MS), alcohol misuse may lead to decreased adherence to medical treatment (6). Data on alcohol misuse among MS patients are rather limited. In the studies addressing its prevalence in MS patients, rates between 3% and 40% have been reported (7-15). There are various methods to identify alcohol misuse**,** e.g., formal diagnostic interviews or screening questionnaires (15).

In our study, the Alcohol Use Disorder Identification Test-Consumption (AUDIT-C) questionnaire was used as a measuring instrument (16). It is a brief validated 3-item screening questionnaire for all forms of alcohol misuse (Table 1). The response options for each of the three questions are scored 0-4 points, and the possible scores range 0-12 points. AUDIT-C scores greater than or equal to 4 in men and greater or equal to 3 in women are considered positive for alcohol misuse, based on previous validation studies (16-18). The AUDIT-C questionnaire is derived from the Alcohol Use Disorder Identification Test (AUDIT), a 10-item alcohol screen designed by WHO (19). Another commonly used alcohol intake screening questionnaire, the CAGE questionnaire (20), has equal or inferior screening performance than AUDIT-C (21). The 10-item AUDIT questionnaire is not often in use, probably because of its length (21).

The aim of the study was to determine the prevalence of alcohol misuse in MS patients and to analyze the link between alcohol misuse and patient sex, age, clinical course of MS, disease duration, and degree of disability.

PATIENTS AND METHODS

The study included 158 patients with MS that underwent inpatient rehabilitation at the Lipik Special Hospital for Medical Rehabilitation in the period from May 15, 2015 to November 15, 2015.

Table 2. *Demographic and clinical characteristics of respondents*

Characteristic	Alcohol misuse positive patients	Alcohol misuse negative patients
n (%)	15 (9.5)	143 (90.5)
Age (yrs), ±SD	50.4±14.63	51.2±10.71
Female, n (%)	8 (53.3)	109 (76.2)
Male, n (%)	7 (46.7)	34 (23.8)
EDSS	4	5.5
MS course, n (%) RRMS	6 (40)	74 (51.7)
SPMS	9 (60)	64 (44.8)
PPMS	0 (0)	3 (2.1)
Benign MS	0 (0)	2 (1.4)
Time elapsed from MS diagnosis (yrs), ±SD	15.2±14.92	13.5±9.36

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

Participating in the study were patients older than 18 and diagnosed with MS according to the revised McDonald criteria (22). The exclusion criterion was serious cognitive impairment. Data on patient age, sex, degree of disability, clinical course of MS, and time elapsed from MS diagnosis were collected. The degree of disability for all study subjects was based on the Expanded Disability Status Scale (EDSS) (23), and assessment of cognitive status was performed using the Mini Mental Status Exam (MMSE) (24). Diagnosis of alcohol misuse was made by use of the AUDIT-C questionnaire. Since all validation studies for AUDIT-C had been conducted prior to DSM-5 criteria issuing, terminology according to the WHO and DSM-4 criteria was used on the evaluation and description of alcohol misuse. The respondents were assured that their participation in the study was anonymous and that the data collected would only be used as summary data. The respondents filled out the questionnaire on their own, with interviewer assistance when needed. Patients were divided into two groups according to the presence or absence of alcohol misuse.

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

Indepedent t-test was used to determine if difference existed between the groups of patients and Pearson's correlation coefficient as a measure of the strength of the association between quantitative variables. For all analyses, the level of sigificance was set at $p<0.05$. The distribution of collected data passed the test for normality. Statistical analysis was performed using the SOFA Statistics for Windows.

RESULTS

The study included 158 patients, 117 (74.0%) female and 41 (26.0%) male, mean age 51.1 years, age range 25-80 years. The mean time elapsed from MS diagnosis was 13.6 years (range, 6 months to 62 years). The relapsing-remitting course of the disease (RRMS) was diagnosed in 80 (50.6%), secondary progressive MS (SPMS) in 73 (46.2%), primary progressive MS (PPMS) in 3 (1.9%), and benign MS in 2 (1.3%) patients. The median EDSS was 5.0, range 1.5 to 9.

Out of 158 study patients, 15 (9.5%) screened positive for alcohol misuse, with the median AUDIT-C score of 4 (range 3-8). Patient characteristics according to the presence/absence of alcohol misuse are shown in Table 2. Patients were divided into two groups according to the presence/absence of alcohol misuse (Table 2). In the group of patients with alcohol misuse, there was a significantly higher proportion of men ($p=0.048$). There were no statistically significant between-group differences according to age ($p=0.787$), disease duration ($p=0.506$), level of disability ($p=0.367$), and course of disease ($p=0.663$).

Due to the small number of patients that suffered from PPMS and benign MS course, only patients with RRMS and SPMS were included in the analysis of the relationship of alcohol misuse and MS course.

DISCUSSION

Heterogeneous literature data on the prevalence of alcohol misuse among MS patients could be due to

Table 3. *Probability of alcohol dependence by Alcohol Use Disorders Identification Test – Consumption (AUDIT-C) score (25)*

Men	Women
Score Probability of dependence	Score Probability of dependence
0-2 0.01	0-1 0.01
3-4 0.09	2 0.03
5-6 0.22	3 0.09
7-9 0.45	4-6 0.24
10-12 0.75	7-9 0.42
	10-12 0.88

differences in the methods of data collection, sample size and cultural context (7,15). A number of methods have been used to identify alcohol misuse**,** e.g., formal diagnostic interviews, data from administrative databases, and screening questionnaires (15). Results relating to patients with MS cannot be extrapolated from one country or continent to another, assuming that patients will show similar behavioral patterns (7).

Previous studies have shown that most patients screening positive on the AUDIT-C fall in the hazardous pattern, but are not alcohol dependent (5). Although test results do not allow clear differentiation between alcohol dependence and other forms of alcohol misuse, the probability of alcohol dependence based on AUDIT-C raises with higher test score (25), as shown in Table 3.

According to AUDIT-C score, patients can be placed in one of the risk zones of alcohol dependence (25). The highest AUDIT-C zone in men and women (10-12 points) raised the post-screening probability of alcohol dependence to 75% and 88%, respectively. The next highest zone for men and women (7-9 points) resulted in post-screening probability of 45% in men and 42% in women, whereas the third highest zone increased the post-screening probability to a lesser extent, 22% in men (5-6 points) and 24% in women (4-6 points).

In our study, 9.5% of respondents screened positive for all forms of alcohol misuse, with the median AUDIT-C score of 4 (range 3-8); 3.5 for women (range 3-4) and 4 for men (range 4-8). Out of seven male patients screening positive for alcohol misuse, six patients had AUDIT-C score 4 and one patient AUDIT-C score 8; out of eight female patients screening positive for alcohol misuse, four patients had AUDIT-C score 3 and another four patients AUDIT-C score 4. These findings suggest that most patients that screened positive consumed alcohol in a hazardous or heavy drinking pattern rather than being alcohol dependent. There was no correlation between AUDIT-C score and age (p=0.022, r=- 0.183), disease duration (p=0.846, r=- 0.016) and EDSS score (p=0.015, r=- 0.193), so there was no association of alcohol use with patient age, disease duration and level of disability. A possible explanation for the small proportion of patients in the zone of high risk for alcohol dependence is patients' fear from neurological deficit worsening and effective doctor-patient communication that provided necessary information on the adverse consequences of alcohol intake; when asked to fill in the questionnaire about alcohol usage, many of our patients spontaneously mentioned that they avoided alcohol drinks because of fear from MS worsening or that they followed physician's advice not to drink.

A limitation of the study was the fact that using AUDIT-C or any other questionnaire does not set a definitive diagnosis of alcohol misuse, but provides screening instead. Therefore, positive patients require further assessment.

There are only few studies that analyzed the link between alcohol misuse and disease related or demographic characteristics of respondents. In our study, alcohol misuse was more common in men, whereas we found no statistically significant differences according to age, disease duration, level of disability, and course of disease between the patients with and without alcohol misuse.

In the study by Beier *et al.* (14), alcohol misuse was more common in men, while in the studies by Turner *et al.* (9) and Fragoso *et al.* (7) the prevalence was similar in both sexes. As other factors that may influence sex difference in the prevalence of alcohol misuse were not analyzed in any of the studies, the reason for different findings in MS patients remain unknown.

In the study by Fragoso *et al.* (7), there was no statistically significant age difference between the patients with and without alcohol misuse, as in our study. Opposite to these findings, a few previous studies found that alcohol misuse was more prevalent in a younger age group (8,10,14). Lower level of disability was found in the group of patients with alcohol misuse in all studies that compared alcohol intake and disability level between two groups of patients (7-10).

In the study by Bombardier *et al.* (8), alcohol misuse was more common in patients with shorter disease duration. None of the studies analyzed the factors that may influence the relationship of alcohol misuse in MS patients according to particular

age groups, level of incapacity (medium, moderate and severe), disease duration, and disease course.

Unlike the previous studies, in which respondents were selected from MS societies and hospital databases, or respondents were attending outpatient consultation, our respondents were MS patients referred for inpatient rehabilitation. Different selection of respondents could have an impact on the results, since our sample excluded some of patients with short disease duration associated with low functional deficit, younger age, and relapsing-remitting course of the disease because these patients are rarely treated as inpatients.

CONCLUSION

According to this study, alcohol misuse was present in 9.5% of MS patients. Because of the numerous health and social consequences of excessive alcohol intake, comprehensive care of MS patients should include counseling on the adverse effects of alcohol.

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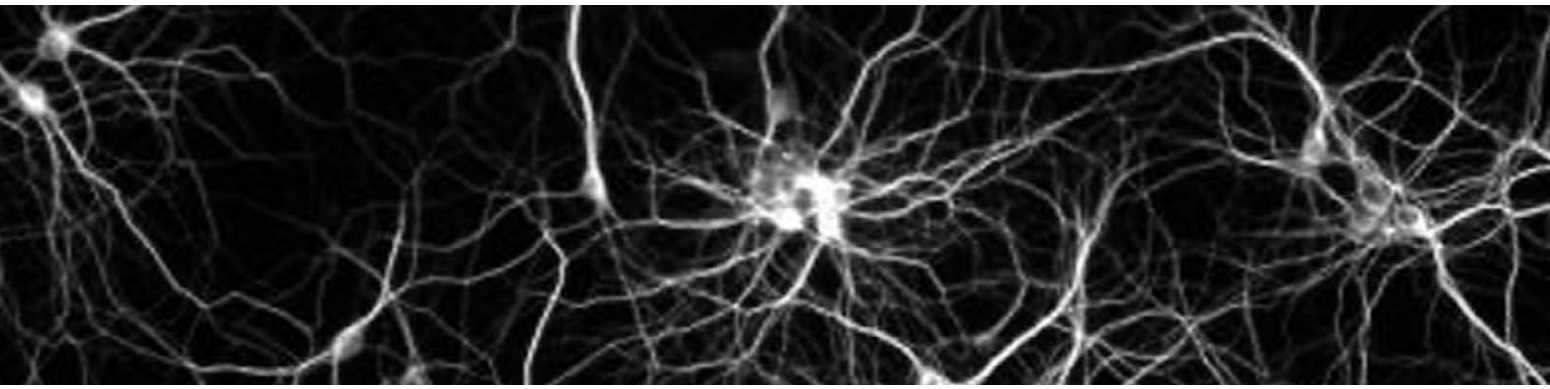
Address for correspondence: Merisanda Časar Rovazdi, MD, Lipik Special Hospital for Medical Rehabilitation, Marije Terezije 13, HR-34551 Lipik, Croatia; E-mail: merisanda.casar@bolnica-lipik.hr

Zlouporaba alkohola u oboljelih od multiple skleroze

SAŽETAK – *Cilja rada:* Cilj rada je bio odrediti učestalost zlouporabe alkohola kod oboljelih od multiple skleroze (MS) i analizirati povezanost zlouporabe alkohola sa spolom i dobi bolesnika, kliničkim oblikom MS, trajanjem bolesti i stupnjem onesposobljenosti. *Ispitanici i metode:* Ispitanici su bili oboljeli od MS stariji od 18 godina koji su u razdoblju od 15. svibnja 2015. do 15. studenoga 2015. provodili stacionarnu rehabilitaciju u Specijalnoj bolnici Lipik. Isključni kriterij bilo je teže kognitivno oštećenje. Prikupljeni su podatci o spolu i dobi ispitanika, stupnju onesposobljenosti, kliničkom obliku MS i vremenu proteklom od postavljanja dijagnoze MS. Dijagnoza zlouporabe alkohola postavljena je pomoću upitnika AUDIT-C (*Alcohol Use Disorders Identification Test – Consumption*). Ispitanici su podijeljeni u dvije skupine ovisno o prisutnosti ili odsutnosti zlouporabe alkohola. *Rezultati:* Ukupan broj ispitanika bio je 158, od kojih je 15 (9,5%) bilo pozitivno na probiru za zlouporabu alkohola. Utvrđena je statistički značajno veća zastupljenost muškaraca (p=0,048) u skupini ispitanika koja je zloupotrebljavala alkohol. Nije nađena statistički značajna razlika između dviju skupina u odnosu na životnu dob (p=0,787), trajanje bolesti (p=0,506), stupanj onesposobljenosti (p=0,367) i klinički tijek bolesti (p=0,663). *Zaključak:* Prema ovoj je studiji zlouporaba alkohola bila prisutna u 9,5% oboljelih od MS. Zbog brojnih zdravstvenih i socijalnih posljedica prekomjernog uzimanja alkohola, briga o pacijentima oboljelim od MS trebala bi obuhvatiti i savjetovanje o štetnim učincima alkohola.

Ključne riječi: multipla skleroza, zlouporaba alkohola, upitnik AUDIT-C



Carbamazepine-induced hypersensitivity reactions: case report

Borislav Vuković[1], Ivana Vuković[2], Dobrinka Petković[3], Andrea Šimić Klarić[4]

ABSTRACT – *Background:* Antiepileptic drugs can cause adverse cutaneous drug reactions. Most of the adverse cutaneous reactions have a favorable course, but there are serious cutaneous drug reactions such as Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms. *Case report:* This paper presents a case of a 63-year-old male patient with ventriculoperitoneal shunt implanted six years before due to hydrocephalus, and treated at Department of Neurology in April 2014 for intracerebral hematoma in the left temporobasal region, which caused the first generalized tonic-clonic epileptic seizure. Carbamazepine was introduced in a daily oral dose of 400 mg. Five weeks after therapy initiation, he presented with generalized maculopapular exanthema and facial edema. Leukocytosis and monocytosis were verified on the second day of rash onset. He felt weakness on day 10 of rash onset, and high transaminase levels were recorded, increasing steadily for the next 10 days. Complete regression of rash occurred one month after carbamazepine discontinuation and corticosteroid therapy administration; his laboratory findings normalized after four months. *Conclusion:* Persistence of generalized maculopapular rash, facial edema, hematologic abnormalities, and toxic lesion of the liver suggest a hypersensitivity reaction to carbamazepine.

Key words: hypersensitivity reactions, carbamazepine, epilepsy

INTRODUCTION

Medications can cause adverse cutaneous reactions. According to research in the population of India, the major causative drug groups were antimicrobials, nonsteroidal anti-inflammatory drugs (NSAIDs) and antiepileptic drugs (1). Most of the adverse cutaneous reactions have a favorable course, but there are serious cutaneous drug reac-

[1] Požega General County Hospital, Department of Neurology, Požega, Croatia
[2] Rijeka University Hospital Center, Department of Pediatrics, Rijeka, Croatia
[3] Požega General County Hospital, Department of Infectious Diseases, Požega, Croatia
[4] Požega General County Hospital, Department of Pediatrics, Požega, Croatia

tions such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalized exanthematous pustulosis (AGEP) (2). The presence of an aromatic ring in antiepileptic structure is associated with a significantly increased risk of skin reactions. Skin reactions are three times more frequent with aromatic antiepileptic drugs than with nonaromatic antiepileptic drugs (3). Some antiepileptics such as carbamazepine, eslicarbazepine, phenytoin and lamotrigine can cause severe skin reactions, and carbamazepine causes most of them (3-6). Carbamazepine is an antiepileptic from the carboxamide group with marked anticonvulsive and psychotropic activity. Carbamazepine is presumed to inhibit voltage-gated sodium channels. Decreased release of glutamate and stabilization of neuron membrane is the basis of antiepileptic activity. Decreased dopaminergic and noradrenergic conduction of impulses affects manic manifestations. Due to the mentioned qualities, carbamazepine is used in the treatment of epilepsy, chronic painful syndromes and psychiatric disorders (bipolar affective disorder, resistant depression, borderline syndrome). Patients mostly tolerate therapy very well, but there are many side effects with a variable rate of occurrence, e.g., blood disorders, liver and kidney disorders, central disorders, and rash. Rare side effects are agranulocytosis, aplastic anemia, pseudolymphoma, systemic lupus erythematosus, SJS, TEN, DRESS, and toxic hepatitis. Carbamazepine shows interindividual and interethnic variability in clinical efficacy and adverse drug reactions (5,7,8). Carbamazepine can cause different forms of hypersensitive skin reactions in up to 10% of patients (7). DRESS is an infrequent but life-threatening reaction of hypersensitivity associated with antiepileptic drug intake, mostly carbamazepine and phenytoin. The clinical manifestations are rash, hematologic abnormalities, high body temperature, and affection of visceral organs, mostly liver (9). Symptoms typically occur 2-6 weeks after treatment initiation. High fever (usually >38 °C) and rash generally are the first signs, followed by other systemic symptoms including cervical, axillary and inguinal lymphadenopathy, acute liver and kidney failure, pulmonary and cardiac infiltrates, and hematologic abnormalities with eosinophilia and atypical lymphocytes (10). The incidence of DRESS in general population is 0.4/1,000,000 inhabitants (6). The incidence has been estimated to be between 1/1000 and 1/10,000 in the population exposed to anticonvulsants. The pathophysiology is unknown, combining immune and genetic factors (11).

The liver has numerous functions, including metabolism of many substances and medications. Medications can lead to hepatic impairment. Drug-induced hepatitis is found in 1%-3% of patients and 30% of all fulminant hepatitis cases are caused by medications. Drug-induced hepatitis can be successfully recovered, persist as a chronic disease, or lead to acute liver insufficiency and death (12).

CASE REPORT

We present a 63-year-old male patient with ventriculoperitoneal shunt implanted six years before due to hydrocephalus, probably of inflammatory etiology. In April 2014, he was treated at Department of Neurology for intracerebral hematoma in the left temporobasal region, with first generalized tonic-clonic epileptic seizure as its consequence. Carbamazepine was used for treatment in a daily dose of 400 mg. He also took the antihypertensive ramipril. During hospital stay, all laboratory findings where within the reference ranges. Neuroradiology diagnostics (multi-slice computed tomography (MSCT) of the brain) showed acute intracerebral hematoma of 22 mm in diameter, localized in the left temporobasal region, with surrounding edema, and enlargement of the third and lateral ventricles, which suggested compensated hydrocephalus with implanted catheter according to Pudentz. MSCT angiography of the head and neck vessels was normal. Electroencephalography (EEG) showed irritating dysrhythmic frontotemporoparietal changes, which tended to be better expressed over the left side, with paroxysmal tendencies. He presented with generalized itchy maculopapular exanthema and facial edema in the fifth week of carbamazepine therapy (Fig. 1).

We verified leukocytosis and monocytosis on the second day of rash appearance. The patient felt weakness on day 10 of rash onset, and we found a twofold increase of transaminase levels that increased steadily for the next 10 days, when the aspartate aminotransferase level was 10 times higher, alanine aminotransferase level 30 times higher, gamma-glutamyltransferase level 6 times higher and bilirubin level two times higher than normal; the level of alkaline phosphatase was also elevated. Carbamazepine therapy was discontinued immediately upon rash appearance and parenteral administration of methylprednisolone 1.5 mg/kg/day and antihistamine was introduced. We did not introduce a new antiepileptic drug, and the patient used only diazepam in the oral dose of 5 mg for a

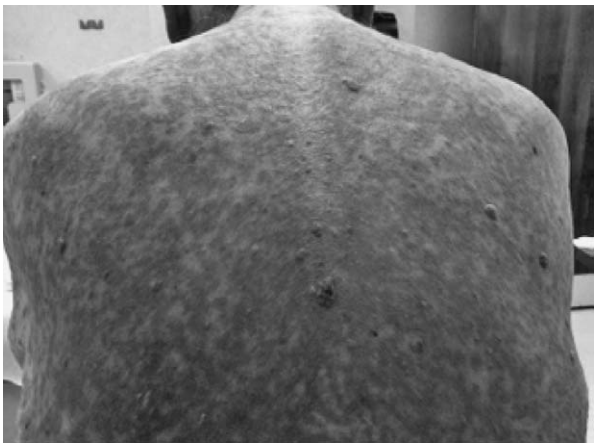


Fig. 1. *Generalized maculopapular exanthema.*

couple of days. No new epileptic seizures were observed. The rash was appearing daily throughout the next month. Complete rash regression was recorded at one month carbamazepine therapy discontinuation and corticosteroid therapy administration. Monocyte count was normal at two months and all laboratory findings were within the reference range at four months.

DISCUSSION

The skin is commonly affected within adverse reactions caused by medications. Most cutaneous reactions have a favorable course (2). Severe cutaneous adverse drug reactions such as SJS, TEN, DRESS and AGEP require fast diagnosis and therapy because lethal outcome is possible (4,5,9). Corticosteroids are administered in the treatment of skin reactions and systemic symptoms (3,6,9). Immunoglobulins or combination of corticosteroids, infliximab and high-dose intravenous immunoglobulins are used in the treatment of TEN (13). DRESS is an infrequent but acute and life-threatening reaction of hypersensitivity connected with taking antiepileptics, mostly carbamazepine and phenytoin. Clinical manifestations are rash, hematologic abnormalities, high body temperature, and affection of visceral organs, mostly liver (4,9). DRESS is an idiosyncratic reaction caused by medications, which appears at the beginning of therapy. Systemic corticosteroids are the current mainstay of treatment and they can reduce symptoms of delayed hypersensitivity reactions. A recommended starting dose is 1.0-1.5 mg/kg/day of prednisone or an equivalent drug. This dosage should be slowly tapered over 6-8 weeks to avoid a flare-up of symptoms (14). Disappearance of systemic manifestations is slow, over 1-6 months (6). Although there is still no universal consensus about the definition of DRESS, two diagnostic criteria are mainly adopted, the RegiSCAR study group (15), and the Japanese consensus group that emphasizes the existence of human herpes virus-6 reactivation (16).

Among antiepileptics, carbamazepine and phenytoin most often cause SJS/TEN and DRESS in Asian population. Liver is the organ most commonly affected with DRESS syndrome (5). In a study of cutaneous adverse drug reactions conducted in India from January 1995 till April 2013, lethal outcome for all skin changes caused by drugs was 1.71% and for SJS/TEN 16.39% (1). In Asian population, mortality for DRESS syndrome caused by antiepileptics was 7.7% and for SJS/TEN caused by antiepileptics 6.1%, while the most common outcome was liver lesion (5). Morimoto *et al*. describe a patient that presented with fatigue, high body temperature, cervical lymphadenopathy, generalized rash, face edema and perioral vesicles, leukocytosis and liver dysfunction during carbamazepine therapy for trigeminal neuralgia, with high antibodies of human herpes virus at the time of eruption (17). The incidence of skin changes as a reaction to medications in Indian population was 9.22/1000 patients. Maculopapular rash occurred in 32.39%, fixed drug eruption in 20.13%, urticaria in 17.49%, and SJS/TEN in 6.84% of patients. The most common cause of skin changes were antimicrobials (45.46%), nonsteroidal anti-inflammatory drugs (NSAIDs) (20.87%) and antiepileptics (14.57%). Commonly implicated drugs were sulfonamides (13.32%), beta lactams (8.96%), and carbamazepine (6.65%) (1).

Recent studies have revealed significant connection between human leukocyte antigens (HLA) and predisposition for adverse drug reaction as skin changes and liver lesion (7,8,18). Taking carbamazepine in persons with HLA-B* 15:02 is combined with the occurrence of SJS and TEN in South-East Asian patients only, whilst HLA-A*31:01 is associated with all phenotypes of hypersensitivity in multiple ethnicities (18). The HLA-B*15:02 allele has been shown to be strongly correlated with carbamazepine-induced SJS/TEN in South-East Asian population but not in European population. HLA-A*31:01 is associated with all phenotypes of hypersensitivity in multiple ethnicities (18,19). The presence of the HLA-A*31:01 allele was combined with carbamazepine-induced hypersensitivity reactions among persons originating from north Europe (19,20). The prevalence of HLA-A*31:01 allele in the population of north Europe is 2%-5%. The presence of HLA-A*31:01 al-

lele increases the risk of hypersensitive reaction by 5.0%-26.0%, whereas its absence reduces risk by 5.0%-l 3.8% (19).

Carbamazepine is the most frequently reported drug for DRESS syndrome among anticonvulsants, and liver is the most frequently affected organ (11). Hepatitis caused by medication can be successfully recovered, can persist as a chronic disease, or can lead to acute liver insufficiency and death. Diagnosis of medication-induced liver injury is based on history data on drug intake, clinical findings, laboratory results, and histopathologic diagnosis.

Our patient presented with generalized maculopapular rash, facial edema, leukocytosis, monocytosis, and toxic liver lesions five weeks after carbamazepine therapy initiation. Skin changes disappeared after one month of corticosteroid therapy, and laboratory findings normalized after four months. High body temperature and enlarged lymph nodes were not recorded in our patient.

CONCLUSION

Rash occurrence in patients taking antiepileptic drugs requires further follow up. In case of severe cutaneous drug reactions, it is necessary to stop antiepileptic therapy immediately and start with the administration of parenteral corticosteroid therapy. Systemic corticosteroids can reduce symptoms of delayed hypersensitivity reactions.

In our patient, persistence of generalized maculopapular rash, facial edema, hematologic abnormalities, and toxic lesion of the liver suggested a hypersensitivity reaction to carbamazepine.

Pharmacogenetic testing is recommended to detect patients at high risk of carbamazepine-induced hypersensitivity reactions.

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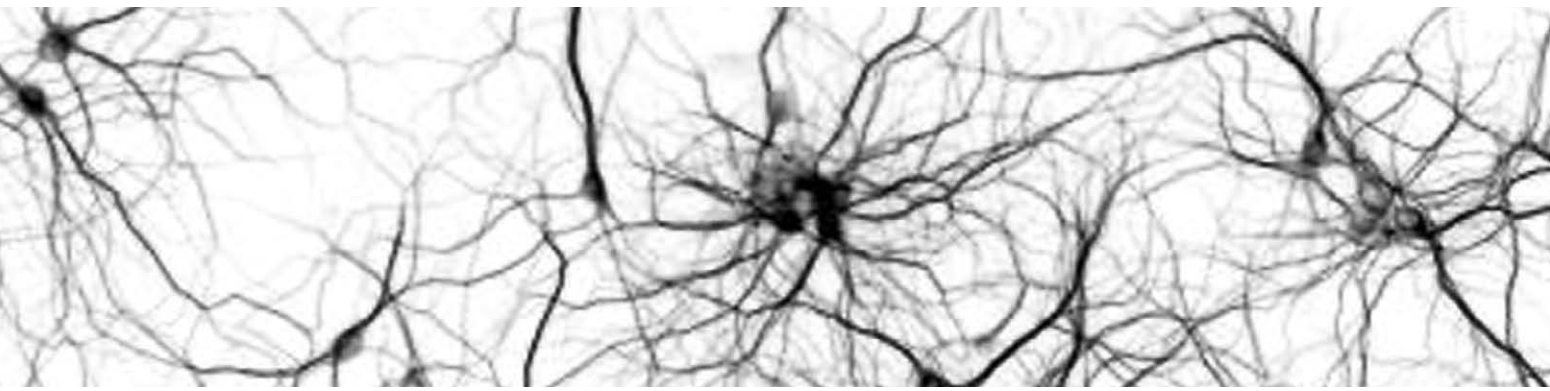
Address for correspondence: Borislav Vuković, MD, Požega General County Hospital, Department of Neurology, Osječka 107, HR-34000 Požega, Croatia; E-mail: vukovic.neuro@gmail.com

Karbamazepinom izvazvane reakcije preosjetljivosti: prikaz slučaja

SAŽETAK – *Uvod:* Antiepileptici mogu izazvati neželjene kožne reakcije. Većina kožnih promjena ima povoljan klinički tijek, međutim, postoje i teške kožne reakcije kao što su Stevens-Johnsonov sindrom, toksična epidermalna nekroliza, reakcija na lijekove s eozinofilijom i sistemskim simptomima. *Prikaz slučaja:* Prikazuje se slučaj 63-godišnjeg bolesnika kojemu je šest godina ranije postavljena ventrikuloperitonejska drenaža zbog hidrocefalusa, a u travnju 2014. godine je liječen na odjelu neurologije zbog intracerebralnog hematoma lijevo temporobazalno s posljedičnim prvim generaliziranim toničko-kloničkim epileptičkim napadajem. Uvedena je peroralna terapija karbamazepinom u dnevnoj dozi od 400 mg. U petom tjednu od primjene lijeka pojavio se generalizirani makulopapulozni osip praćen svrbežom i oteklinom lica, a drugog dana od pojave osipa zabilježena je leukocitoza i monocitoza. Desetog dana od nastanka osipa je uz osjećaj slabosti i malaksalosti zabilježeno povišenje vrijednosti transaminaza s porastom vrijednosti u sljedećih deset dana. Mjesec dana nakon ukidanja terapije karbamazepinom i nakon provedene kortikosteroidne terapije došlo je do potpune regresije osipa, a nakon četiri mjeseca uslijedila je potpuna normalizacija laboratorijskih nalaza. *Zaključak:* Pojava generaliziranog makulopapuloznog osipa, otoka lica, hematoloških abnormalnosti, toksične lezije jetre ukazuje na reakciju preosjetljivosti na karbamazepin.

Ključne riječi: reakcija preosjetljivosti, karbamazepin, epilepsija



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