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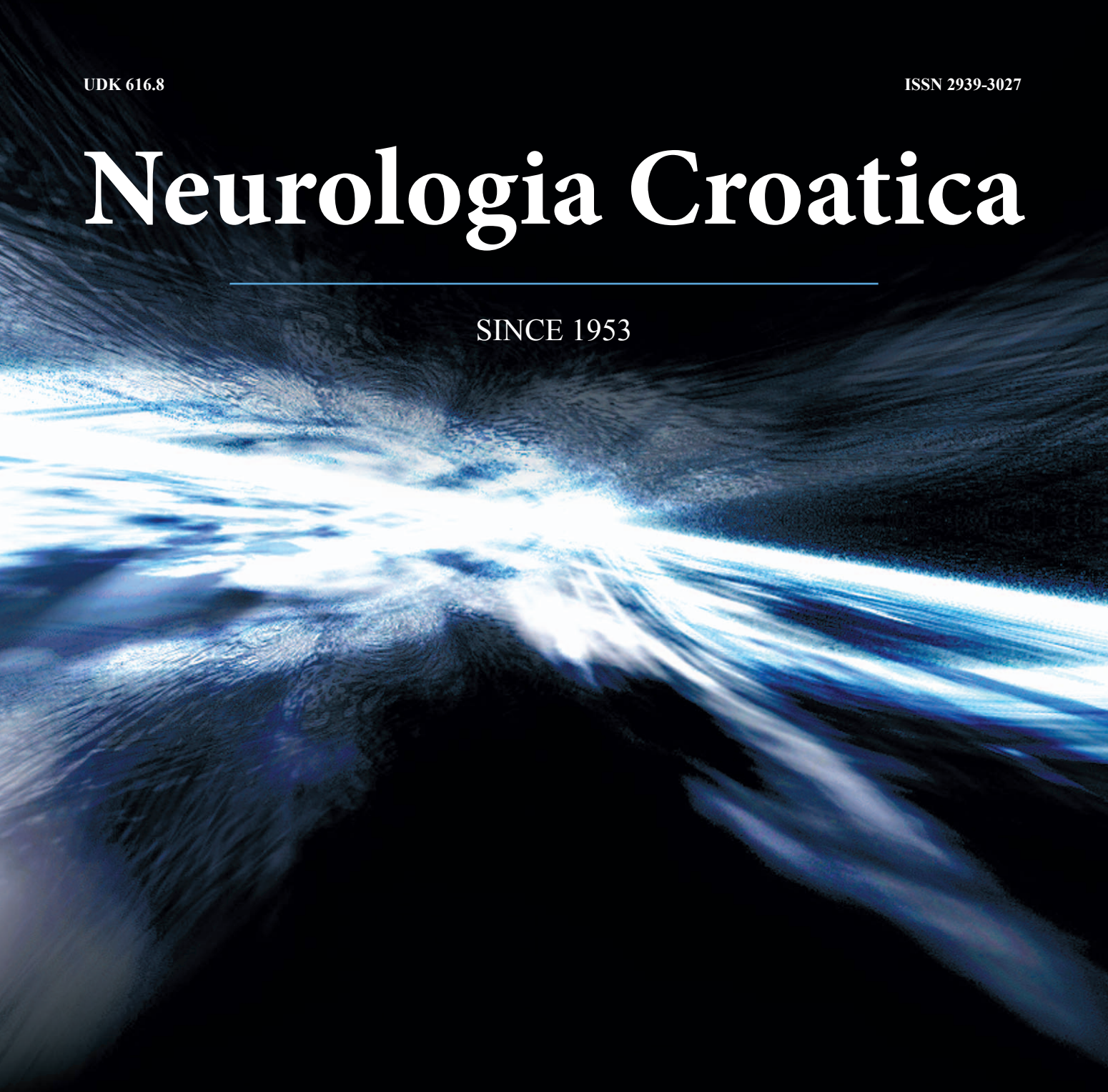

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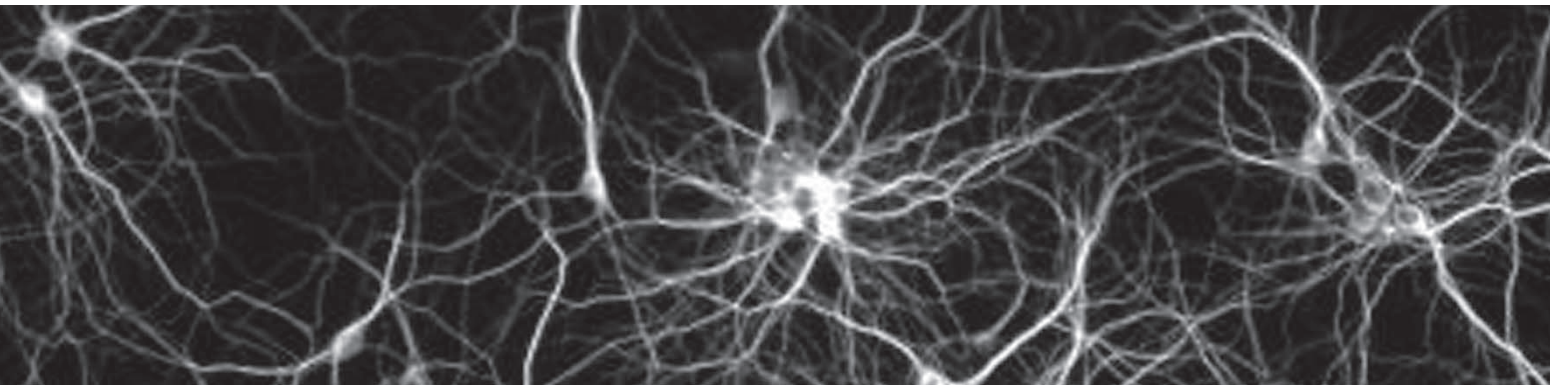


Editorial

Dear Readers and Colleagues,

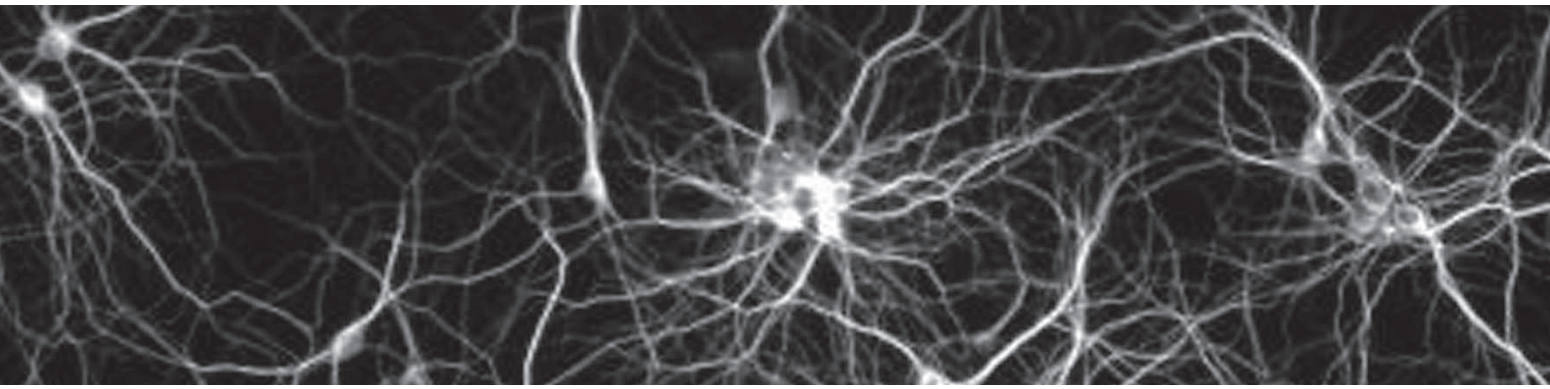
Welcome to the second issue of Neurologia Croatica in 2024, which marks the end of the second year of the journal's online publishing.

In this issue we will share an interesting case presentation of the vertebral body infarction as a sign of spinal cord ischemic stroke with our readers. Difficulties related to the entanglement of different conditions and choosing the best course of treatment for each condition without impacting the other are presented in the case report about juvenile absence epilepsy and myasthenia gravis. Through a compelling case report, we will inform our readers about possible renal damage caused by zonisamide treatment. A scoping review will provide better insight into the comorbidities related to epilepsy.

We are grateful to all reviewers who completed their reviews in 2024 because their scientific contribution is highly significant to the success and continuity of Neurologia Croatica.

In the end, I would like to thank all our readers for their support and hope you will enjoy reading this issue.

Mario Habek
Editor-in-chief



Vertebral body infarction as a sign of spinal cord ischemic stroke

Ivan Adamec[1,2], Mario Habek[1,2]

A 51-year-old male with a history of arterial hypertension and anxiety attacks presented to the emergency room with pain in his lower back and numbness and weakness in his left leg. The symptoms started on the same day upon waking up, and the numbness spread from his leg to the genital area during the day. He reported hesitancy and loss of feeling of his urine passing during micturition and had no erection that morning. His medications included bisoprolol/perindopril 5/5 mg daily and escitalopram 10 mg daily. Neurological examination revealed left leg weakness 4/5, with an extensor left plantar response. There was hypoesthesia of his left leg affecting the dorsum of the foot, lateral and back sides of the calf and thigh, and the genital and perianal area. MRI of the thoracic and lumbosacral spinal cord was unremarkable. A follow-up MRI was performed after three weeks and revealed T2-weighted STIR hyperintensity of the Th10 vertebra with post-contrast enhancement, indicating spinal cord ischemia (Fig. 1). There was a small intramedullary hyperintense signal in T2-weighted images at the Th9 level on the left side corresponding to ischemic sequelae. At that time, the patient experienced partial recovery, his sensation was normal, and there was residual weakness in his left foot with normal micturition and erectile function.

Spinal stroke most commonly occurs in the vascular territory of the arteria radicularis magna, or the artery of Adamkiewicz, the largest radiculomedullary artery (1). It most commonly arises from the intercostal artery between segments Th9 to Th12, being the major contributor to the anterior spinal artery in the lower thoracic and upper lumbar region and providing arterial blood for the spinal cord approximately from the Th8 vertebra to the conus medullaris (1). The anterior part of the spinal cord is especially vulnerable to ischemia as the supplying vessels are end arteries and have no anastomoses (1). Occlusion of the anterior spinal artery can lead to the anterior spinal syndrome, which consists of motor weakness, loss of superficial sensation, and sphincter dysfunction. Infarction of the vertebra that may accompany spinal cord ischemia is explained by the shared vascularization of the vertebral body and the spinal cord (2). The common blood supply usually ceases after adolescence; however, degenerative changes in the vertebra may induce neovascularization that reestablishes the shared blood supply (3). In patients with spinal cord ischemic strokes, initial MRI may

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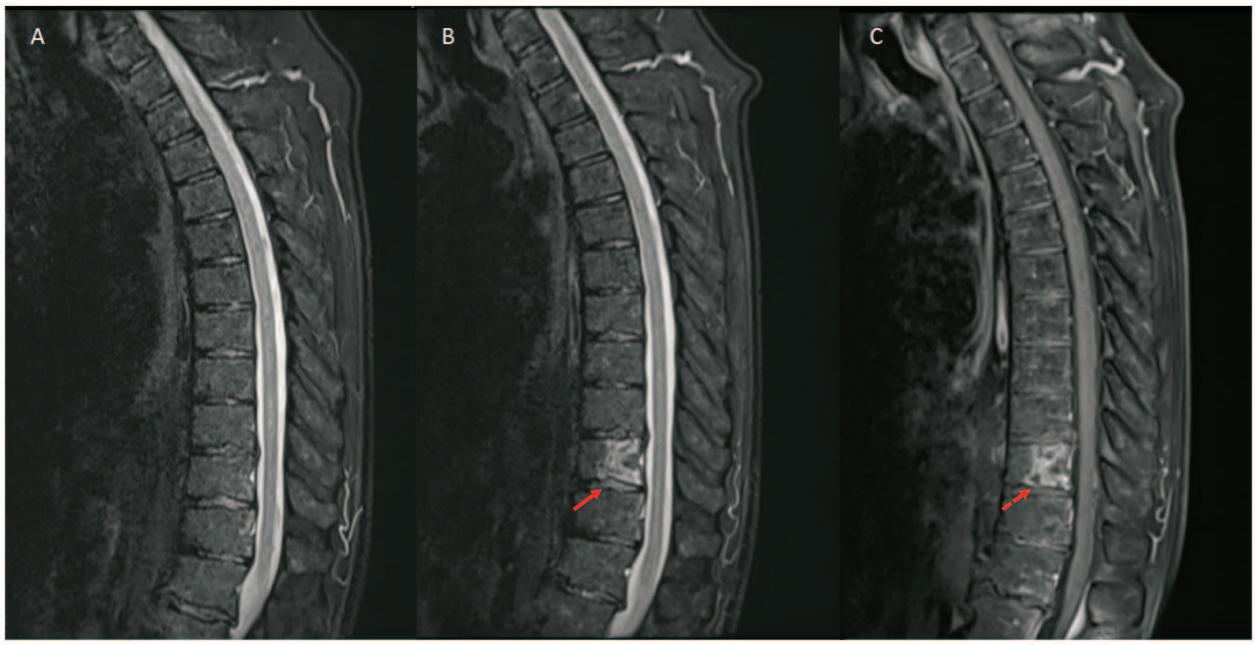

Fig. 1. *MRI of the spinal cord showing initial (a) and follow-up images after three weeks (b, c). A. Sagittal T2 weighted STIR image revealing normal signal of the thoracic vertebra. B. Sagittal T2 weighted STIR image demonstrating hyperintensity of the dorsal part of the Th10 vertebra (red arrow). C. Sagittal T1 weighted post-contrast image demonstrating gadolinium enhancement of the dorsal part of the Th10 vertebra (red dotted arrow). STIR-short-tau inversion recovery.*

not reveal pathological changes. Therefore, infarction of the vertebra, most appropriately demonstrated on STIR sequences, as in the current patient, can represent the only confirmatory sign of spinal cord infarction (4).

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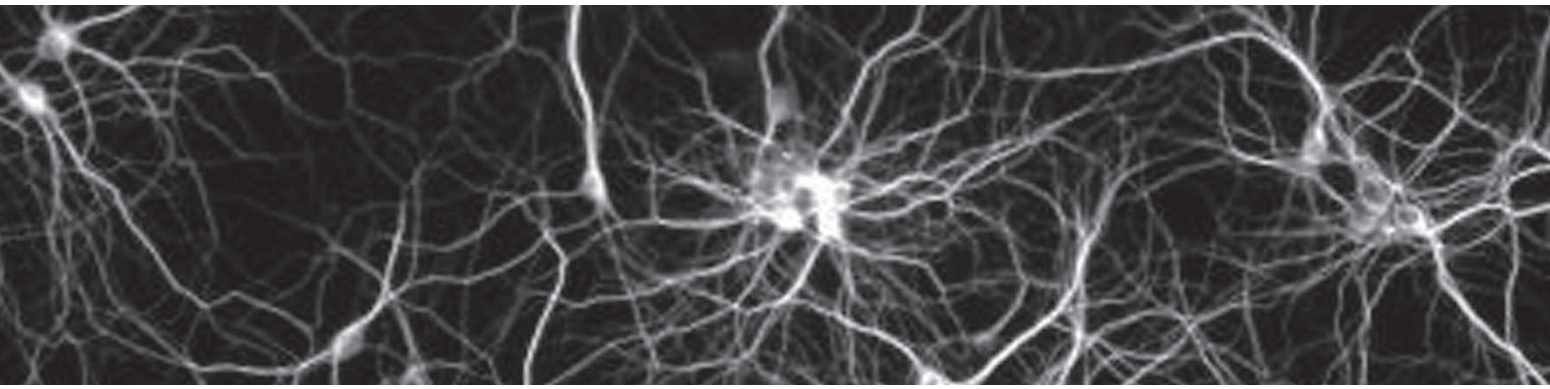

Juvenile absence epilepsy and myasthenia gravis: a case report

Marin Begović[1], Biljana Đapić Ivančić[1], Andreja Bujan Kovač[1,2], Ervina Bilić[1,2], Andrea Zemba Čilić[1], Željka Petelin Gadže[1,2]

ABSTRACT – *Objectives:* Juvenile absence epilepsy (JAE) is a genetic generalized epilepsy syndrome that typically starts in adolescence and is characterized by absence seizures and generalized tonic-clonic seizures (GTCS). Myasthenia gravis (MG) is an antibody-mediated autoimmune disease that affects the neuromuscular junction. The management and follow-up of patients affected by both JAE and MG may be challenging due to the potential correlation between increased MG symptoms and epileptic seizures. Antiseizure medications (ASM) that alter Na+ gated channels must be administered with caution in patients affected by both conditions. *Case description:* We present a 43-year-old female patient with JAE who also suffers from generalized seropositive MG. At the age of 23, she had undergone thymectomy as a means of MG treatment. She was treated with pyridostigmine bromide and a low dose of prednisolone with good clinical response and without the need for immunomodulation therapy. The patient has had JAE from the age of 17. For more than 20 years the patient was under ASM comprised of carbamazepine, ethosuximide, and clonazepam seizure free, but in 2023 she had multiple seizures and was admitted to our department. We performed continuous video-EEG monitoring and recorded clinical and electroencephalographic absence seizures. At that point, we introduced levetiracetam to therapy with a positive clinical response. *Results:* Following the successful treatment of both conditions the patient has been seizure free without any relapses of MG symptoms. *Conclusion*: This case report shows that JAE patients with concomitant MG require prudent decision making which considers the best course of treatment for each condition without impacting the other. Further carefully designed studies are needed.

Keywords: juvenile absence epilepsy, myasthenia gravis, antiseizure medications

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INTRODUCTION

Juvenile absence epilepsy (JAE) is a genetic generalized epilepsy syndrome (GGE) that usually starts in adolescence around puberty and is characterized by absence seizures and generalized tonic-clonic seizures (GTCS) (1). In children and adolescents, JAE is responsible for 2.4%–3.1% of cases of newly diagnosed epilepsy (2). Myasthenia gravis (MG) is an antibody-mediated autoimmune disease that affects the neuromuscular junction (3). MG patients, due to the pathophysiology of the disease, require caution when treated with other medications, especially antiseizure medications (ASM) (4). The management and follow-up of patients affected by both JAE and MG may be challenging due to the potential correlation between successful treatment of one of these conditions and concomitant exacerbation of the other one. ASM which affect the neuromuscular junction's Na+ gated channels must be administered with caution.

CASE PRESENTATION

We report the case of a 43-year-old female patient with JAE and generalized seropositive MG. The patient was born following a normal pregnancy without complications, and her early neurodevelopment was unremarkable. There was no family history of epilepsy, nor did she experience febrile seizures during childhood. She was diagnosed with JAE at the age of 17 and subsequently managed by a paediatric neurologist, later transitioning to adult neurology care at another institution.

Electroencephalograms (EEGs) revealed generalized spike-wave discharges (frequency 2–3 Hz, amplitude up to 200 μV) and polyspike-wave discharges (frequency 3–4 Hz, amplitude up to 250 μV) (Fig. 1). At age 22, she developed nasal speech, swallowing difficulties, ptosis of the upper eyelids, and lower limb weakness. Testing for autoantibodies targeting neuromuscular junction proteins was positive for antibodies against the acetylcholine receptor (AChR-MG) and muscle-specific kinase (MuSK-MG), confirming the diagnosis of generalized seropositive MG. She underwent a thymectomy as part of her MG treatment. Her epilepsy was stable under a regimen of carbamazepine (CBZ), ethosuximide (ESM), and clonazepam (CLN). Following the MG diagnosis, in consultation with a neuromuscular specialist, it was decided not to alter her ASM regimen, as it had been effective. MG symptoms were managed with pyridostigmine bromide and alternate-day prednisolone, with good clinical response and no need for immunomodulatory therapy. Although the removal of CBZ in favour of levetiracetam (LEV) was recommended due to the potential adverse effects of CBZ on the neuromuscular junction, the patient was reluctant to change her treatment. She reported that her epilepsy had remained stable for over 20 years, with seizures occurring only during periods of noncompliance with her medication. In 2023, she had multiple seizures and was admitted to our department, where continuous video-EEG monitoring was performed, and the numerous absence seizures were recorded (Fig. 2). During the hospitalization, the patient disclosed her noncompliance to ASM that provoked multiple epileptic seizures she experienced. An analysis of the patient's blood sample revealed that the levels of ASM were below the therapeutic range. Due to the negative effect CBZ may have on the neuromuscular junction, a removal of CBZ and an implementation of LEV, was recommended. During the transition, serum levels of CBZ and LEV were closely monitored, alongside clinical assessments for seizure activity and potential exacerbation of MG symptoms. Following the successful treatment of both neurological conditions, JAE and MG, the patient has been seizure free without any relapses of MG symptoms.

DISCUSSION

Patients who have both JAE and MG have been the subject of a limited number of studies. Considering the mechanism of action of ASM, management and follow-up of patients with these conditions, can be complex. JAE tends to be drug-responsive, but lifelong treatment may be necessary (5). The first line of treatment is with valproic acid (VPA) or ethosuximide (ESM) (6). There are several recorded reports of patients with MG, who presented with aggravation of myasthenic symptoms or even unmasked MG following the administration of ASM such as CBZ (7,8,9). CBZ primarily acts on sodium channels, stabilizing hyperexcitable nerve membranes (10). While this mechanism could theoretically worsen MG by disrupting neuromuscular transmission, individual differences in receptor sensitivity or ion channel function may explain the absence of negative effects in certain patients, including ours. In this case, the decision to continue CBZ therapy was made collaboratively between the patient's epileptologist and neuromuscular specialist, carefully balancing the risks and benefits. Regular monitoring and a proactive approach to man-

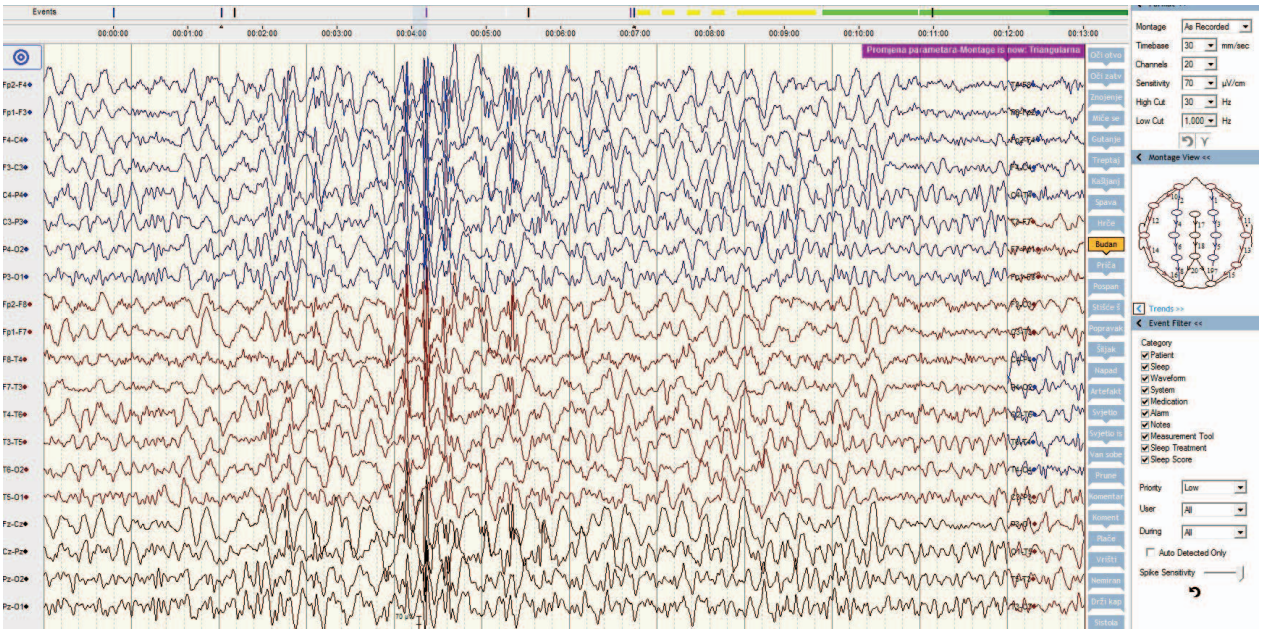

Fig. 1. *EEG of the patient showing generalized spike-wave (frequency 2-3 Hz, amplitude up to 200 uV) and polyspike-wave (frequency 3-4 Hz, amplitude up to 250 uV) discharges.*

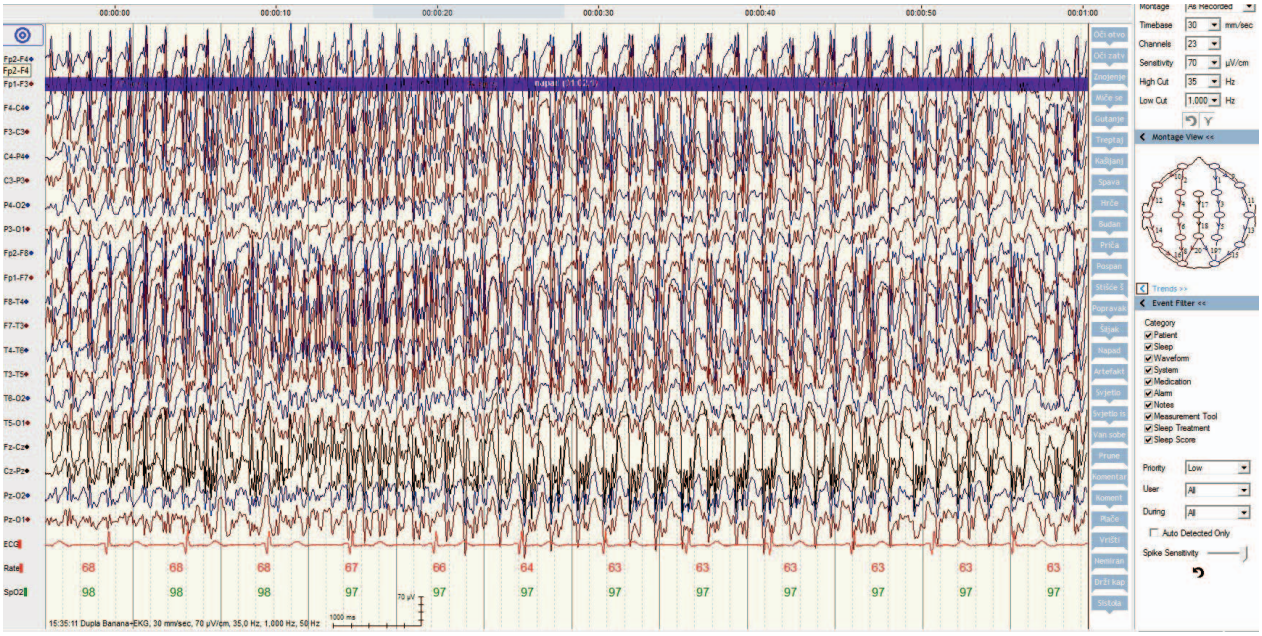

Fig. 2. *Showing absence seizure on a continuous video-EEG monitoring with typical generalized 3-5.5 Hz spike – wave discharges.*

aging MG symptoms likely contributed to the absence of complications. It has also been demonstrated that ASM, such as ESM, phenobarbital (PB), and phenytoin (PHT), have an impact on neuromuscular transmission in *in vitro* models (11). The patient in our case report is a rare example of a patient who, due to a good clinical response, had CBZ in antiepileptic therapy for many years following the diagnosis of MG, without worsening of MG symptoms. The patient's MG remained well-controlled following thymectomy, which likely contributed to disease stability (12). Thymectomy is known to reduce autoantibody production, particularly against acetylcholine receptors (AChR), potentially mitigating CBZ's adverse effects on neuromuscular transmission. Despite being seropositive, for both AChR-MG and MuSK-MG, the patient's MG symptoms were manageable without immunomodulatory therapy. This relatively mild MG phenotype may have reduced her susceptibility to CBZ-induced exacerbations.

We also wish to point out that clinical worsening of JAE, which can sometimes be caused by CBZ, did not happen in our patient. It is noteworthy that while CBZ was eventually replaced with levetiracetam (LEV) following a relapse linked to noncompliance, this shift demonstrated that alternative therapies could maintain control of both conditions without risking exacerbation. LEV is often introduced gradually to minimize side effects, particularly neuropsychiatric symptoms (13). Given the patient's history of stable epilepsy control on CBZ, careful overlap during the transition was necessary to avoid breakthrough seizures. The favourable response to LEV supports its use as a safer option for managing epilepsy in patients with coexisting MG. LEV is generally well-tolerated, though long-term use may be associated with mood disturbances or behavioural changes in some individuals (13). Regular follow-ups would be essential to monitor for such effects. More than 80% of JAE patients using the recommended ASM have well controlled epilepsy, with seizures occurring only due to the noncompliance to ASM. Our patient is an example of such case.

CONCLUSION

This case highlights the necessity of prudent decision-making when managing patients with JAE and coexisting MG, given the potential adverse effects of ASM on MG symptoms. It is essential to select a treatment strategy that effectively addresses both conditions without compromising the management of either. Choosing an ASM with a favourable pharmacokinetic profile, low risk of drug interactions, and proven efficacy in controlling seizures is critical in such cases. As demonstrated in our case presentation, further well-designed longitudinal studies are needed to evaluate the impact of CBZ and other ASM on MG symptoms. Such research would provide valuable insights to guide clinical practice and optimize outcomes for patients with these coexisting conditions.

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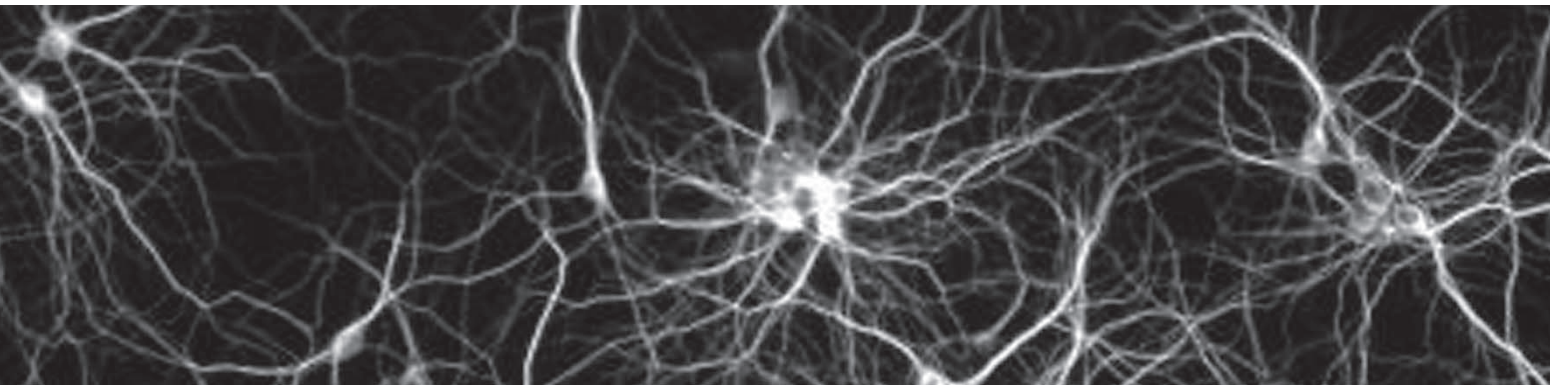

Acute renal insufficiency caused by zonisamide treatment

Zurap Raifi[1], Berislav Ruška[1], Gordana Sičaja[1], Ana Sruk[1]

ABSTRACT – *Objective*: To inform about possible renal damage caused by zonisamide treatment. *Case description*: We present a case of a 69-year-old female with newly diagnosed focal epilepsy, in whom the therapy with zonisamide caused acute renal insufficiency. *Results*: After initiation of zonisamide in therapy, the patient developed signs of renal failure, which resolved after zonisamide therapy cessation. *Conclusion*: One should be aware of possible renal damage as a side effect of zonisamide.

Keywords: antiseizure medication, renal insufficiency, zonisamide

INTRODUCTION

Zonisamide is a sulfonamide drug that can be used to treat various types of (epileptic) seizures, although it is most commonly used for the treatment of focal epilepsy (1). The most common side effects of zonisamide include cognitive and psychiatric impairments, as well as weight loss (2). Here we present a rare case of acute renal insufficiency caused by treatment with zonisamide in a patient with focal epilepsy.

CASE REPORT

In 2019, a female patient, who was at the time 69 years old, reported to the neurologist with a history of episodes that resembled focal seizures with sensory onset and impaired awareness. The patient described that in such episodes she initially feels tingling in a small finger of her left hand, which then spreads to other fingers and the lateral side of the left forearm. Soon after, she becomes puzzled, oblivious, and responds inadequately. Usually, after around 15 to 20 minutes, such episodes resolve spontaneously. Two such episodes happened in 2017 and one in 2018. The patient suffered from hypertension, type 2 diabetes, hyperlipidemia, and osteopenia years prior. On the workup, electroencephalography (EEG) showed no epileptiform activity, carotid ultrasound showed no hemodynamic abnormalities, and her brain magnetic resonance imaging (MRI) showed

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extensive chronic cerebrovascular changes with cortical atrophy. Initially, the patient was not keen to start antiseizure medication (ASM) since she had already been taking eight other drugs for her other medical conditions. However, around a year later, in the first half of 2020, she had another seizure similar to the ones previously described, so it had been decided to start treatment with zonisamide. We gradually increased the dose by 100 mg every two weeks, ultimately reaching a daily dose of 300 mg. Soon after reaching the target dose, she began to experience symptoms such as nausea with occasional vomiting, infrequent loose stools, weight loss, and oliguria. Her blood test showed elevated levels of serum creatinine (457 μmol/L, ref. value 49-90 μmol/L) and urea (15.7 mmol/L, ref. value 2,8-8,3 mmol/L), which indicated acute renal insufficiency. She was hospitalized at the nephrology department, and fluid replacement therapy was started. Kidney ultrasound showed no abnormalities. Drug toxicity was suspected, so zonisamide dose had been slowly reduced. A series of laboratory findings thereafter showed a gradual recovery of kidney function. Nephrologists concluded that zonisamide was the cause of acute renal insufficiency, and deemed the kidney biopsy unnecessary. Zonisamide had been replaced with lamotrigine, and the patient had been discharged from the hospital. In the follow-up control examinations, the patient was feeling well, and her epilepsy was well controlled with lamotrigine. Laboratory findings during control intervals showed satisfactory renal recovery with residual chronic renal impairment, which has not progressed further.

DISCUSSION

In this paper, we present a case of acute renal insufficiency caused by zonisamide. Although nephrolithiasis as a possible adverse event of zonisamide has been previously debated (2), renal failure as another possible side effect is not commonly known. We found only two previous reports of zonisamide related zonisamide-related renal injury by searching the literature. The first was described in a 29-year-old Japanese male (3). However, in that case, kidneys were one of many organs that were damaged indirectly due to the drug-induced hypersensitivity syndrome phenomenon. The second report was in a 33-year-old American male, where renal failure was directly associated with zonisamide (4). In our case, renal failure was also firmly time-related to zonisamide treatment, while all of the other possible causes were excluded by the treating nephrologist. If we consider that together with the aforementioned case, we can confidently conclude that there is a direct correlation between the two. The pathophysiological mechanism that could explain this phenomenon is speculative. However, it might be associated with the drug's sulfonamide structure and its effect of inhibition of carbonic anhydrase. As mentioned earlier, the formation of kidney stones has already been described as an adverse effect of chronic use of zonisamide, but it has long been known as an adverse effect of chronic use of sulfonamides in general (2,5). Moreover, the effect of sulfonamide urine crystal precipitation could be aggravated by the effect of zonisamide's carbonic anhydrase inhibition, leading to alkalinisation of urine. Even though this adverse effect happens during chronic drug use, it has been described in other sulfonamides that sulfonamide crystals in some cases, especially in acute exposure, can precipitate intratubular and cause an intratubular obstruction, which leads to retrograde urine flow, and therefore, anuric kidney injury (5,6). Previously described cases of acute renal failure caused by acetazolamide, which shares the same sulfonamide structure, and the effect of carbonic anhydrase inhibition with zonisamide, support this theory (6). After all, it is important to mention that our patient was probably more prone to kidney injury due to a long history of hypertension and diabetes. This case report, together with one previously described, supports the fact that zonisamide can cause renal impairment and that clinicians should be aware of it when introducing this antiseizure drug into therapy. It is important, however, to keep in mind the limitations of single case reports and their lack of generalizability, therefore further research is necessary to confirm this observed adverse effect and its clinical importance.

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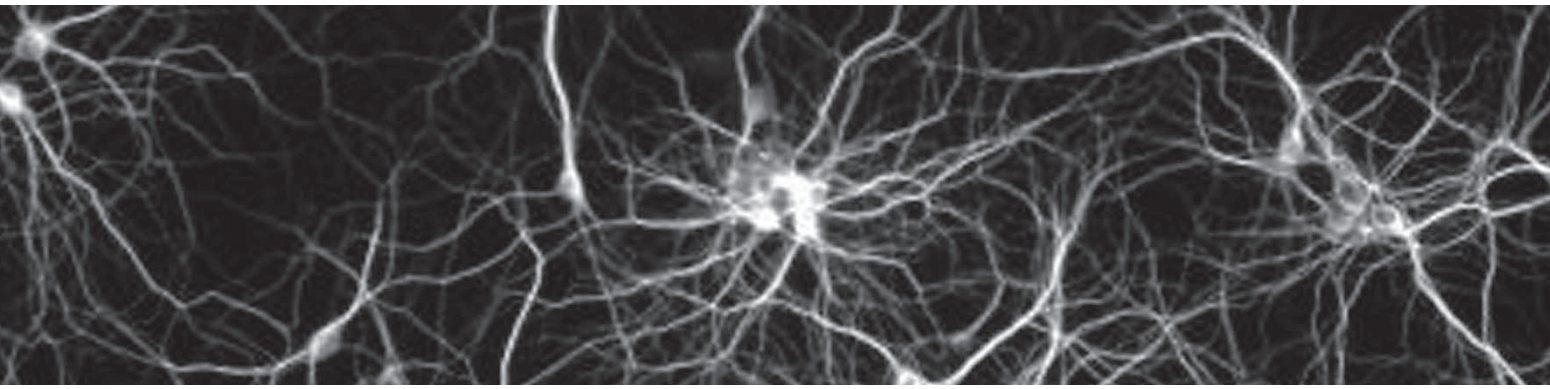

Epilepsy and comorbidities

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INTRODUCTION

Epilepsy is one of the most common neurological diseases (1,2). It is a chronic brain disorder characterized by an enduring predisposition to generate epileptic seizures. Recurring seizures leave neurobiological, cognitive, psychological and social consequences which affect patients' quality of life (2,3). Comprehensive medical term comorbidity refers to distinct conditions, diseases and syndromes that occur alongside the main condition. Comorbidities are defined as medical conditions that simultaneously coexist with a primary diagnosis (4). It is estimated that more than half of young adults suffer from at least one chronic health condition (4) and the number increases with age (6). Numerous somatic, psychiatric and cognitive diseases are more often present in patients with epilepsy than in the general population (7). Approximately 50% of adults with epilepsy have at least one comorbidity (4). Their importance in the clinical approach towards patients is emphasized by the fact that they are an essential part of the current classification according to International League Against Epilepsy (ILAE) (8).

THE SIGNIFICANCE OF COMORBIDITIES IN PATIENTS WITH EPILEPSY

The results have shown that the most common comorbidities in people with epilepsy are anxiety and major depressive disorder. Despite the significant frequency, depression and anxiety are still poorly recognized by physicians. In adults, hypertension (18.2%), stroke (14.5%), heart disease (11%), diabetes (10.2%) and arthritis (9.2%) are among frequent comorbidities as well (9). Comorbidities have a significant impact on selecting appropriate treatment option. Treatment can be more complex because it requires an approach that extends beyond controlling seizures alone (10). However, co-

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morbidities can enable earlier detection of epilepsy. For example, if a patient suffers from neoplastic brain disease, epilepsy may be detected earlier due to regular monitoring and clinical examinations. It is necessary to timely diagnose and properly treat comorbidities because they can be predisposing factors to unfavorable seizure outcomes. Treating comorbidities enables better control of epileptic seizures. It works the other way around, too. Treating epileptic seizures has a beneficial effect on comorbid conditions. Further research of comorbidities will contribute to a better understanding of epilepsy itself (4). Genetic factors can also modify the mutual interaction between epilepsy and comorbidities (4). Charlson and Elixhauser comorbidity indices are well-established for prediction of hospitalization costs, hospital length of stay and impact of comorbidities on hospital mortality. Each comorbidity is weighted and assigned a score, and based on their sum, individual prognosis is predicted. (4,11,12). Epilepsy-specific comorbidity index (ESI) is also used in clinical practice. Prognostic points are assigned to numerous conditions: disorders of the pulmonary circulation, hypertension, arrhythmias, congestive heart failure, peripheral vascular disease, kidney disease, solid tumors without metastases, paraplegia and hemiplegia, aspiration pneumonia, dementia, brain tumors, anoxic brain injury, moderate and severe liver disease and metastatic cancer. A higher number of points achieved is associated with higher mortality (4,13,14). The most common causes of death among patients with epilepsy are comorbidities such as neoplastic, cardiovascular or cerebrovascular disease (4,15).

EPILEPSY AND NEURODEVELOPMENTAL DISORDERS

Among children and young people with epilepsy, there is a higher prevalence of neurodevelopmental disorders which include autistic spectrum related disorders (ASDs), intellectual disabilities and attention deficit hyperactivity disorder (ADHD). Despite the high prevalence and negative effect on the clinical course of epilepsy, patients often don't receive adequate therapy due to delayed diagnosis or misdiagnosis. These patients experience side effects of antiepileptic drugs (AEDs) more frequently and are prone to developing drug-resistant epilepsy (16). The risk of developing epilepsy among patients with autism is 2.7-44.4%, which is seven times higher risk than the rest of the population. The coexistence of these conditions is particularly present among people with intellectual disabilities, and it is more common in women, elderly, people with lower socioeconomic status (17). Two theories explain the higher incidence of ASDs in patients with epilepsy. Epileptic seizures can affect the synaptic plasticity responsible for learning and behavior. The excitatory/inhibitory imbalance noted during seizures can produce permanent physiological and functional damage during neurodevelopment. It can cause abnormal synaptic reorganization and cortical neurons dysfunction. Another theory assumes that an underlying neurological disorder predisposes individuals to the development of both epilepsy and ASDs (17). Genetic disorders in which coexistence of these conditions is more common include Rett syndrome, fragile X syndrome and complex tuberous sclerosis complex (18). Some of the specific epileptic syndromes in which it is more frequent are infantile spasms and Dravet syndrome (17).

EPILEPSY AND VASCULAR DISEASES

Cerebrovascular diseases are the most common underlying cause of epilepsy in elderly (19). They cause 30-50% of new-onset epilepsies (20). There is an expected growth of the epilepsy prevalence due to the increasing percentage of elderly people in the population. Cerebrovascular diseases associated with epilepsy are ischemic stroke, cerebral hemorrhage, post-reperfusion state (after thrombolysis or thrombectomy) and small blood vessel diseases due to arteriolosclerosis (19). Predictors of the epilepsy development after stroke are younger age, cortical involvement, extent and severity of post-stroke lesions and a hemorrhagic component (19). Genetic factors have an important role in the epilepsy pathogenesis. For example, CD40-1C/T polymorphism is associated with an increased tendency of post-stroke seizures (20). Early epileptic seizures occur within the first seven days of a stroke, while seizures that occur after this period are considered late (19). Epilepsy after an ischemic stroke usually occurs in an area with insufficient oxygenation which is not completely necrotic. Hemorrhages due to blood-brain barrier disruption after an ischemic insult are extremely important as well (20). Seizures are more frequent after primary intracerebral or subarachnoid hemorrhage than after cerebral ischemic infarction (21). Epilepsy is usually caused by cortical venous hemorrhage (20). The frontal and temporal lobes are

characteristic sites of epileptogenesis, which explains increased incidence of seizures after complete infarction of the anterior cerebral circulation (21). Epilepsy is usually caused by cortical venous hemorrhage (20). The frontal and temporal lobes are characteristic sites of epileptogenesis, which explains increased incidence of seizures after complete infarction of the anterior cerebral circulation (21). Risk factors for cerebrovascular diseases are also associated with the development of epilepsy. Among them, high blood pressure, high cholesterol, coronary and peripheral arterial disease have the largest effect (22). Epileptic patients have an increased risk of acute myocardial infarction and sudden cardiac death (SCD) (23). In 2020, the clinical entity „epileptic heart" was introduced into the literature. It is described as the damage to the heart and coronary vasculature caused by the cardiotoxic effect of catecholamines and repeated hypoxia (24, 25). Sudden cardiac death constitutes a 4.5-fold greater risk for premature death in patients with epilepsy compared to sudden unexpected death in epilepsy (SUDEP), which by definition excludes all known causes of mortality, including cardiac comorbidities (25). Antiepileptic drugs have adverse effects on the electrophysiology of the cardiac myocytes and circulating lipids (23). Inducers of cytochrome P450 can adversely affect the lipid profile, while sodium channel blockers may be potentially arrhythmogenic. Moreover, there is a possibility of the interaction between the AEDs and anticoagulant/ antiplatelet therapy. Therefore, it is necessary to appropriately prescribe medications and their dosage. This particularly refers to the potent inducers of liver enzymes, such as carbamazepine, phenobarbitone, phenytoin and primidone, which can reduce the levels of concomitantly administered drugs in therapy. Due to the increasing use of new oral anticoagulant drugs, the use of zonisamide, lamotrigine and lacosamide is recommended. They have no clinically relevant interactions with the mentioned group of medications (24,25).

EPILEPSY AND NEURODEGENERATIVE DISEASES

Primary neurodegenerative diseases cause 10-20% of epilepsy in the elderly. The number is assumed to be even higher because clinical manifestations of epilepsy are often unrecognized and misdiagnosed (20). Half of epilepsy cases in the elderly is of unknown cause. It is estimated that neurodegenerative diseases are the second most common cause of epilepsy after a stroke. Some theories presume that certain percentage of epilepsies of unknown cause is actually consequence of presymptomatic neurodegenerative diseases (26).

EPILEPSY AND MIGRAINE

Headache has long been associated with epilepsy. Postictal epileptic headache is more common than preictal and ictal (27,28). The hypothesis of a possible mutual pathogenetic background is based on the neurons hyperexcitability and ion channels abnormalities. Imbalance between excitatory molecules such as glutamate and inhibitory like gamma-aminobutyric acid (GABA) has been proven both in epilepsy and migraine (28). It is assumed that the migraine aura phenomenon is caused by a transient wave of mass neuronal depolarizations, also known as cortical spreading depression. It leads to oligemia (hypoperfusion), after which, during the headache phase, hyperperfusion occurs (29). In the differential diagnosis of migraine aura, especially the visual one, it is necessary to think about epileptic seizure because they have overlapping symptoms (27). In familial hemiplegic migraine (FHM), a rare autosomal dominant form of migraine with aura, these two conditions can coexist (27). Numerous AEDs are effective in the migraine treatment. The ones used for prophylaxis are topiramate and valproate. It has been proven their harmful effect during pregnancy (27).

EPILEPSY AND MULTIPLE SCLEROSIS

The prevalence of epilepsy among patients with multiple sclerosis (MS) is between 0.5% and 10.8%, and epileptic seizures are 3 to 6 times more common than in the general population (30). Epilepsy is usually diagnosed ten years after establishing MS diagnose (31). The cause of epileptic seizures is insufficiently explained. However, it is assumed that cortical and juxtacortical inflammation, demyelination and atrophy play an important role in pathogenesis (32). Status epilepticus is more frequent, but resistance to AEDs is less common (32). Early introduction of immunomodulatory/immunosuppressive therapy decreases prevalence of epilepsy in patients with multiple sclerosis (31). Research on the frequency of certain types of epileptic seizures that occur in multiple sclerosis show different results. Some have indicated that focal to bilateral tonic-clonic seizures are the most common, while others have revealed generalized tonic-clonic seizures being most prevalent. It is difficult to determine the epilepsy prognosis (32). Active

epilepsy carries the risk of MS progression from relapsing-remitting multiple sclerosis into secondary progressive multiple sclerosis (33). Epileptic seizures can be the first clinical presentation of multiple sclerosis because demyelinated plaques in the brain act as epileptic foci (34). Depending on the relationship between epileptic seizures and MS activity, patients are divided into three groups (34):

a) those whose seizures are associated with MS relapse
b) those whose seizures are not associated with MS relapse
c) those with frequent seizures associated with cognitive deterioration.

EPILEPSY AND AUTOIMMUNE DISEASES

ILAE included autoimmunity in the classification of epilepsy based on six etiological factors (35). Since 2017, according to ILAE recommendations, it is considered if the seizures result from an underlying autoimmune disorder (36). Antibodies directed against antigens on neuronal cell surface are the most important in epileptogenesis. There are also antibodies directed against intracellular antigens such as anti-glutamic acid decarboxylase antibodies. These can be found in 80% of patients with diabetes type 1 (37). Systemic lupus erythematosus (SLE) and diabetes mellitus type 1 have the highest risk of developing epilepsy (38). It is important to be careful about the interaction of immunosuppressants and antiepileptic therapy (38). Immunomodulators are increasingly included in the treatment of refractory epilepsy (35). Autoimmune epilepsy is often drug-resistant (36).

EPILEPSY AND BRAIN TUMORS

Sometimes, epilepsy can be the only symptom of a brain tumor (39). Epilepsy associated with brain tumors accounts for 12% of acquired epilepsies and 4-10% of total epilepsy number (40). Among all tumor types, seizures are most common with glioneuronal tumors (70–80%), especially in patients with frontotemporal or insular lesions (41). Seizures are also common in patients with glioma, with the highest rates of epilepsy (60–75%) observed in individuals with low-grade gliomas located in superficial cortical or insular regions. Approximately 20–50% of patients with meningioma and 20–35% of those with brain metastases also suffer from seizures (41). There is a specific group of tumors associated with epilepsy called "long-term epilepsy associated tumors" (LEAT). Their characteristics include a slow growth rate, early-onset drug-resistant epilepsy, neocortical localization and temporal lobe predominance. The most common LEATs are dysembryoplastic neuroepithelial tumors and gangliogliomas (39). Tumor-related seizures are symptomatic by nature. Semiologic characteristics depend on localization of tumors. Focal seizures with impaired awareness are more common in temporal tumors and focal to bilateral tonic-clonic seizures are more common in extratemporal tumors (42). Cortical tumors are associated with a higher risk of causing seizures. Additionally, frontal, temporal and parietal tumors are associated with a higher risk of causing epilepsy than occipital tumors. Infratentorial tumors are rarely associated with epilepsy (42). Epilepsy associated with tumors has a poorer response to antiepileptic therapy, which is confirmed by the fact that it is pharmacoresistant in 30% of the cases. The clinical outcome is better if surgical resection is performed. Surgical treatment should be considered as early as possible, regardless of pharmacoresistance. This would avoid long-term consequences of epileptic seizures, side effects of antiepileptic drugs and tumor progression (39). After surgical treatment, approximately 60-90% of patients is seizure free (41).

EPILEPSY AND PSYCHIATRY DISEASES

Back in the 1880's, Gowers noticed the increased frequency of behavioral symptoms and mental health issues among people suffering from epilepsy. The importance of recognizing conditions in the domain of the psychiatric disorders has become increasingly significant during the recent years. Underlying causes of the dysregulation and the consequent seizure generation may also affect the mechanisms responsible for mood and behavior control (43). According to the results of clinical studies involving patients with epilepsy and psychiatric comorbidities, the prevalence of any psychiatric disorder was observed in up to 43.3% in the general population of patients with epilepsy, in 51% of patients with idiopathic generalized epilepsy, and in 43.1% of patients with temporal lobe epilepsy. The most common psychiatric disorders associated with epilepsy include mood disorders – affective disorders (up to 40%), anxiety disorders (up to 30.8%), personality disorders (up to 11% in juvenile myoclonic epilepsy) and psychotic disorders (in about 2-9% of patients with epilepsy) (44). Mood disorders are the leading psychiatric comor-

bidity in epilepsy, followed by anxiety disorders. Although mood disorders most often occur after the epilepsy onset, some studies have proven that it can precede the development of the epilepsy. Psychosis of epilepsy is a rare comorbidity in patients with epilepsy, but one of the most prominent psychotic disorder due to another medical condition. A meta-analysis of 57 studies of people with psychosis and related disorders showed a prevalence of 5.6 to 7% in patients with temporal lobe epilepsy (44, 45). It can be classified according to its temporal relation to seizures as preictal, ictal, paraictal, interictal and postictal, with the latter being the most common, occuring in 60% of patients (44, 46). The prevalence of psychosis is highest in patients with focal epilepsy, especially those with medial temporal lobe involvement. This comorbidity presents a challenge in treatment and requires an individualized and multidisciplinary approach to improve the patient's quality of life (44).

EPILEPSY AND SLEEP DISORDERS

Sleep disturbances in people suffering from epilepsy can be caused by nocturnal seizures, sedation as a side effect of AEDs, inadequate sleep hygiene, insufficient amount of sleep and sleep disorders as comorbidities (47). The most common comorbidity in people with refractory epilepsy is obstructive sleep apnea (47). Treatment with nasal continuous positive airway pressure (CPAP) reduces hypoxia and sleep fragmentation, which consequently leads to better seizure control (48). SUDEP is a sleep-related fatal complication of epilepsy. It most often occurs in people between the age of 15 and 40. Risk factors are male sex, refractory epilepsy and polytherapy. The exact mechanism is yet unknown, but there are some evidences that generalized tonic-clonic seizures playing an important role in pathogenesis (47). There are also some indications that SUDEP is caused by postictal apnea (49). Epileptic seizures can worsen sleep architecture. However, mentioned comorbidities can cause seizure exacerbation as well. Antiepileptics can also worsen sleep architecture (50). Patients treated with lamotrigine have an increased risk of insomnia, while phenobarbitone is associated with excessive daytime sleepiness. A side effect of some antiepileptic drugs, such as valproate, is obesity (51). On the other hand, zonisamide has proven itself effective in the treatment of obese patients with epilepsy. It helps in losing weight and consequently lowers the risk of obstructive sleep apnea development (52).

CONCLUSION

Comorbidities include numerous somatic and psychiatric conditions. Although comorbidities are frequent in patients with epilepsy, there are still uncertainties in the significance of these conditions. Common risk factors and pathophysiological mechanisms of the disease are oftentimes present. Comorbidities not only affect the quality patients' life, but also the clinical course of epilepsy itself. Generally, they are associated with a less favorable clinical outcome and consequently worse quality of life. They directly increase healthcare expenditures due to more frequent hospitalizations and challenges in establishing an optimal treatment strategy. The importance of adequate screening methods and preventive measures lies in the opportunity to early detect simultaneously present diseases that may not be clinically manifest in the beginning. Enhanced comprehension of the mutual effect of these conditions could contribute to improving the effectiveness of the therapeutic approach.

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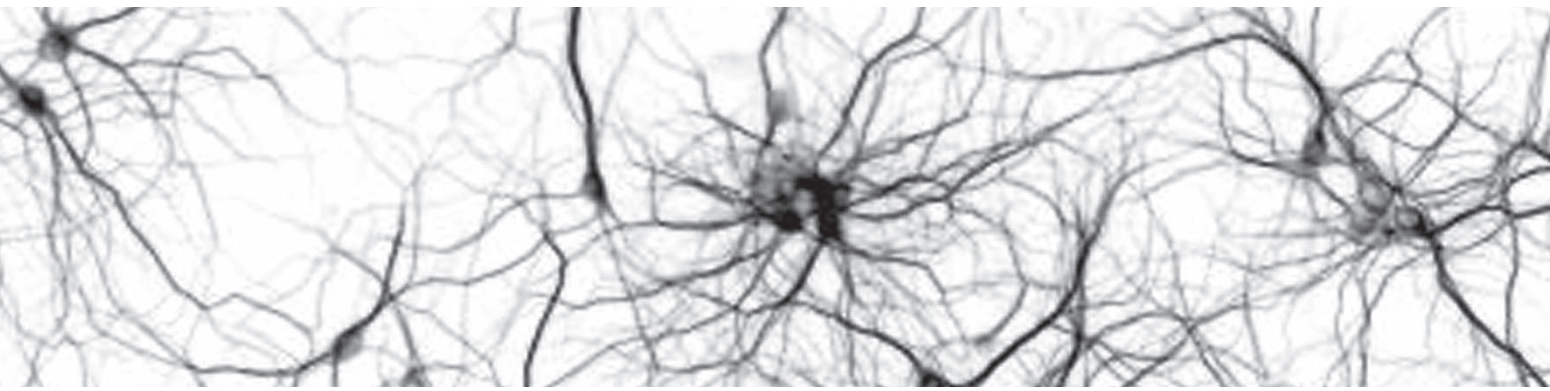

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Instructions to authors

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Neurologia Croatica brings articles covering clinical neurology, basic neuroscience, and other related fields.

Neurologia Croatica publishes the following types of articles:

Original contributions: Maximum length is 3000 words, excluding tables, figure legends, and references. Total word count should be provided with each manuscript including abstract, all text, tables, figure legends, and references.

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

Case reports: Case reports need to have important and novel learning points and report on unusual syndromes or diseases; a simple narrative or challenging patient(s) is insufficient. Maximum length is 1500 words, excluding tables, figure legends, and references.

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In addition, announcements of professional and scientific meetings will be published.

Authors are responsible for the authenticity of data and for methodologic acceptability.

Submission of a manuscript implies that it is submitted exclusively to this journal and its contents have not been published previously except in abstract form.

A statement confirming the copyright transfer to Neurologia Croatica signed by the first author is necessary for publication.

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All articles are subject to review; referees are selected by the Editorial Board. Author(s) may suggest three potential referees (include names, full address, phone & fax numbers and e-mail) in the covering letter.

MANUSCRIPT PREPARATION

The form and contents of the manuscript should be carefully checked.

All manuscripts should be written in English, with additional abstract and key words in Croatian. Manuscripts with illustrations attached and Author Guarantee Statement, prepared according to the instructions below, should be sent by mail as hard copy in triplicate, two of these without the names of authors and institutions, and by e-mail to the Editor-in-Chief's address/e-address. Authors should keep copies of the original manuscript and other related material, since the materials received will not be returned to the authors.

The editor retains the right to shorten the material accepted for publication if necessary.

The complete manuscript, including text, figures, tables and references, should be typed on one side of the paper only, double-spaced, with 3-cm left margin and right margin not justified. Each paragraph should be indented by five spaces.

Author should mark in the margin where figures and tables are to be inserted.

Each section should start on a new page (i.e. title page, abstract, figures, tables, legends and references).

The title page should comprise:

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

Abstract should be no longer than 250 words. Original contributions should have structured abstracts with the following headings: objectives, methods, results and

conclusions. Abstract for Neurological reviews should not be structured. Case reports should have structured abstract with the following headings: objectives, case description, results, conclusion. Images in neurology and letters to the editor do not require an abstract. It should only present the main results and avoid general formulations and well-known facts.

Three to ten key words should be supplied in alphabetical order immediately following the abstract.

Please search for the key words at the web page http://www.ncbi.nlm.nih.gov/pubmed/, link MeSH Database.

Text should be divided, when appropriate, into sections: Introducion, Material and Methods, Results, Discussion, and Conclusion.

Scientific papers, including the list of references, should not exceed 12 pages (32 lines with 60 characters each per page), and brief communications 3 pages.

Tables should be typed on separate sheets, not to be submitted as photographs. Illustrations should be provided unmounted, in the form and condition suitable for reproduction. Freehand drawings, raw laboratory material, e.g., strip charts, roentgenograms, etc., should be photographed in B/W. Photographs should not be larger than 20x25 cm. If the attachements are in color (tables, photographs, etc.), the author should pay for the expenses of printing that page in agreement with Denona Printing House.

For every photograph of a recognizable patient written permission is required.

The author(s) should be aware that the size of illustrative material may be reduced if needed.

Tables and figures should be numbered in Arabic numerals in the order they are mentioned in the text. Legends for each of them should be typed separately, each legend on a separate sheet. The number of figures should not exceed 6.

List of references should include only those works that are cited in the text and that have been accepted for publication or already published.

The list should be arranged according to the order of appearance in the text and then numbered.

Several works of the same first author should be listed chronologically by the year of publication. Index Medicus abbreviations of journal names should be used.

REFERENCES

Journals

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

Mubrin Z, Kos M. Assessment of dementia. Flow chart approach to clinical diagnosis.

Neurol Croat 1992;41:141-156.

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

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

Books

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

Chapter in a book

Geschwind N. The borderland of neurology and psychiatry: some common misconceptions.

In: Bensom DF, Blumer D, eds. Psychiatric aspects of neurologic disease. New York: Grune and Stratton, 1975:1-9.

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

Reprints of the published article should be ordered before publication.

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