PREISPITIVANJE ULOGE MAGNEZIJUMA U ISTRAŽIVANJIMA EPILEPSIJE I ZBRINJAVANJU PACIJENATA SA EPILEPSIJOM

PREGLEDNI RAD

REVIEW ARTICLE

REVISING THE ROLE OF MAGNESIUM IN EPILEPSY RESEARCH AND MANAGEMENT

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SAŽETAK

Magnezijum je mineral bioesencijalan za ekscitabilna tkiva, koji pokazuje višestruka neuroaktivna dejstva. Jon Mg^{2+} stabilizuje ekscitabilne membrane. Epilepsija je jedna od najčešćih hroničnih neuroloških bolesti koju odlikuje spontano ponavljanje neprovociranih epileptičkih napada. Njihovi mehanizmi nastanka nisu potpuno rasvetljeni. Pregled literature o ulozi magnezijuma u bazičnim i kliničkim istraživanjima epilepsije napravljen je da bi se rasvetlio značaj nedostatka magnezijuma u nastanku epileptičke hiperekscitabilnosti mozga, kao i značaj primene preparata magnezijuma u zbrinjavanju pacijenata sa epilepsijom.

Potrebe neurona za magnezijumom su velike. Njegova koncentracija u likvoru je veća nego u serumu. U eksperimentalnim istraživanjima epilepsije perfuzija isečaka hipokampusa veštačkim likvorom sa niskim sadržajem Mg^{2+} predstavlja često korišćen animalni model spontano indukovane epileptiformne aktivnosti. Deficit Mg^{2+} kao elektrolitni disbalans često ostaje klinički neprepoznat, i često se previdi kod bolesnika sa epilepsijom. Nivo Mg^{2+} u likvoru i serumu pacijenata sa epilepsijom niži je nego u zdravih kontrola. Kod njih hipomagnezijemija povećava učestalost epileptičkih napada, a u farmakorezistentnoj bolesti povećava rizik od naprasne, neočekivane smrti. Peroralna suplementacija magnezijumom pomaže u boljoj kontroli napada. Antikonvulzivno dejstvo parenteralnih preparata Mg^{2+} koristi se za suzbijanje napada u pojedinim epileptičkim encefalopatijama kod odraslih i dece (u eklampsiji, uremiji, porfiriji, febrilnim napadima, infantilnim spazmima). Infuzije magnezijuma pomažu i u kontroli epileptičkog statusa.

Subklinički deficit magnezijuma, veoma čest u opštoj populaciji, u epilepsiji može da deluje kao faktor koji doprinosi pojavi epileptičkih napada. Stoga je kod bolesnika sa epilepsijom potrebno proveriti magnezijumski status. Pregled literature pokazuje da magnezijum predstavlja jednostavno antiepileptičko sredstvo čiji terapijski potencijal prevazilazi njegovu aktuelnu kliničku primenu za ovu indikaciju.

Ključne reči: magnezijum, epilepsija, bazična istraživanja epilepsije, klinička istraživanja epilepsije

ABSTRACT

Magnesium is a bioessential mineral with multiple neuroactive effects. Mg^{2+} ion stabilizes excitable membranes. Epilepsy is the third most frequent chronic neurological condition characterized by spontaneous reappearance of unprovoked epileptic seizures, whose underlying mechanisms are not completely understood yet. A literature review on the role of magnesium in basic and clinical epileptology has been made in order to enlighten the importance of magnesium deficiency in the mechanisms of epileptic brain hyperexcitability, as well as the significance of including magnesium into the management of epilepsy patients.

Neuronal magnesium requirements are high. The concentration of magnesium in the cerebrospinal fluid (CSF) is even higher than in the blood. In experimental epilepsy research, perfusing hippocampal slices with artificial CSF containing low concentration of extracellular Mg^{2+} is a frequently used animal model of spontaneously induced epileptiform activity. Magnesium deficiency is the most frequent clinically unrecognized electrolyte disbalance, often overlooked in epilepsy patients. Serum and CSF Mg^{2+} concentrations are lower in patients with epilepsy, as compared to healthy controls. Hypomagnesaemia increases seizure frequency and the risk of sudden unexpected death in pharmacoresistant epilepsy. Oral magnesium supplements help achieve better seizure control. Parenterally administered Mg^{2+} efficiently controls seizures in several epileptic encephalopathies in adults and children (in eclampsia, uremia, porphyria, febrile seizures, infantile spasms), and also helps control status epilepticus.

Subclinical magnesium deficiency, very frequent in general population, acts as a factor contributing to seizure generation in epilepsy. It is recommended to assess magnesium status in epilepsy patients. This literature review reveals the therapeutic potential of magnesium as a simple antiepileptic agent, which exceeds its current clinical use.

Key words: magnesium, epilepsy, basic epilepsy research, clinical epilepsy research

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UVOD

Epilepsija je hronična bolest centralnog nervnog sistema koju odlikuju ponavljanja iznenadnih reverzibilnih epizoda disfunkcije mozga, koje se odvijaju po stereotipnom obrascu. Ovakve epizode su označene kao epileptički napadi, a nastaju spontano kao rezultat naglog i prekomernog generalizovanog ili fokalnog električnog pražnjenja neurona u sivoj masi mozga. Epileptički napadi se mogu prezentovati različitim kliničkim ispoljavanjima. Osim prvog epileptičkog napada koji pacijenti dožive, za dijagnozu epilepsije kao neurološke bolesti, važna je permanentna sklonost mozga ka ponavljanju napada. Iznenadnost, stereotipnost i ponavljanje su tri osnovne karakteristike napada u epilepsiji.

Epilepsija je jedno od najčešćih neuroloških oboljenja, od kojeg boluje u proseku svaka stota osoba u svetu. Epilepsija utiče na kvalitet života i životni vek obolelog. Smrtnost obolelih od epilepsije je značajno povećana u odnosu na opštu populaciju. Smrtni ishodi su najčešće povezani sa osnovnim uzrokom bolesti, posledica su nesrećnih slučajeva i trauma, utapanja, naprasne neočekivane smrti u epilepsiji (engl. *Sudden Unexpected Death in Epilepsy – SUDEP*), i dr.

Prema etiologiji se razlikuju idiopatske, primarne i simptomatske epilepsije. Kod idiopatske epilepsije pacijenti nemaju strukturno, metaboličko ili neko drugo poznato oboljenje ili oštećenje mozga. Primarne epilepsije su uslovljene monogenskim defektima. Simptomatska epilepsija nastaje kao posledica oštećenja mozga poznate etiologije. Epileptički napadi mogu da se jave i kod osoba koje nemaju epilepsiju, kao simptom neke druge bolesti ili oštećenja mozga, kao akutni simptomatski, odnosno provocirani epileptički napadi. Osnovni patofiziološki mehanizmi nastanka napada (iktogeneza) i nastanka epilepsije kao bolesti (epileptogeneza) još uvek nisu dovoljno razjašnjeni, ali je poznato da im najviše doprinose sinaptički i nesinaptički procesi razvoja hiperekscitabilnosti neurona i hipersinhronizacije njihovog električnog pražnjenja [1].

U kliničkoj slici epileptičkih napada se mogu javiti različite motorne, senzitivne, senzorne, vegetativne i psihičke manifestacije, poremećaji ponašanja, poremećaji svesti, i drugo. Glavni tipovi napada u epilepsiji su fokalni i generalizovani napadi. Fokalni napadi se javljaju kada su epileptička pražnjenja ograničena na određeni deo mozga. Epileptički status (Lat. *Status epilepticus – SE*) jeste urgentno stanje u neurologiji i najteže stanje u epileptologiji, koje podrazumeva epileptičku aktivnost produženog trajanja ili ponavljane epileptičke napade između kojih ne dolazi do oporavka svesti [2].

Dijagnoza epilepsije je elektro-klinička, zasnovana na semiologiji napada i nalazu u zapisu elektroence-

INTRODUCTION

Epilepsy is a chronic disease of the central nervous system characterized by repetitive, sudden and reversible episodes of brain dysfunction, which occur in a stereotyped pattern. These episodes are termed as the epileptic seizures, and they arise spontaneously as a result of abrupt and excessive generalized or focal electrical discharge of neurons in the gray matter of the brain. Epileptic seizures can present with different clinical manifestations. Apart from the first epileptic attack that patient experiences, to diagnose epilepsy as a neurological condition, a permanent tendency of the brain to develop repeated seizures must be present. Abruptness, stereotypy and repetition are the three basic features of seizures in epilepsy.

Epilepsy is one of the most common neurological diseases, affecting 1 out of a 100 people worldwide on average. Epilepsy affects the quality of life and the lifespan of the diseased. The mortality of people suffering from epilepsy is significantly increased, as compared to the general population. Fatal outcomes are most often related to the underlying cause of the disease, the consequences of accidents and trauma, drowning, sudden unexpected death in epilepsy (SUDEP), etc.

According to their etiology, epilepsies are classified as being idiopathic, primary or symptomatic. In idiopathic epilepsy, patients have no known structural, metabolic or other brain disease or damage. Primary epilepsies are caused by monogenic defects. Symptomatic epilepsy occurs as a result of brain damage of known etiology. Epileptic seizures can also occur in people who do not have epilepsy, as a symptom of some other brain disease or damage, i.e. as acute symptomatic or provoked epileptic seizures. The basic pathophysiological mechanisms of onset of epileptic seizures (ictogenesis) and the development of epilepsy as a disease (epileptogenesis) are not sufficiently elucidated yet, but it is known that synaptic and non-synaptic processes of the development of neuronal hyperexcitability and the hypersynchronization of their electrical discharge contribute the most [1].

Various motor, sensitive, sensory, vegetative and psychological manifestations, alterations of behavior, disorders of consciousness and other abnormalities may occur as clinical presentation of epileptic seizures. Main types of seizures in epilepsy are focal and generalized seizures. Focal seizures develop when epileptic discharges arise from a specific and limited region of the brain. Status epilepticus (SE) is an emergency condition in neurology and the most severe condition in epileptology, implying epileptic activity of prolonged duration or repeated epileptic seizures between which the patient does not regain consciousness [2].

falograma (EEG). Epilepsiju odlikuju promene u EEG-u koje mogu da se uoče u toku napada (iktalno) i između napada (interiktalno). Prisustvo EEG promena van napada govori u prilog abnormalnoj električnoj aktivnosti mozga i sklonosti da napadi spontano nastaju. Ipak, odsustvo promena u EEG-u, u klinički mirnom periodu, ne isključuje dijagnozu epilepsije.

Terapija epilepsije je individualna – donosi se odluka o lečenju svakog bolesnika ponaosob, zbog različitih uzroka nastanka bolesti, različitih oblika bolesti, razlika u efikasnosti i neželjenim dejstvima lekova, zbog eventualnog prisustva komorbiditeta, i drugih faktora. Primena antiepileptičkih lekova (AEL) ima za cilj uspostavljanje stabilne kontrole napada, odnosno prekidanje započetih napada i suzbijanje njihovog ponavljanja. Prednost ima monoterapija antiepilepticima zbog manje toksičnosti, jednostavnije i redovnije primene, izbegavanja interakcija između lekova i slično. Međutim, veliki je broj bolesnika koji ne reaguju zadovoljavajuće na medikamentozno lečenje epilepsije (farmakorezistentni ili refraktarni oblik bolesti). U ovim slučajevima, epilepsija se može lečiti i metodama elektrostimulacije, hirurškim metodama (npr. operativna resekcija epileptičkog žarišta), i drugim metodama [2].

ZNAČAJ MAGNEZIJUMA ZA PRAVILNO FUNKCIONISANJE NERVNOG SISTEMA

Magnezijum je veoma zastupljen mineral u organizmu sisara. Jon Mg^{2+} zastupljeniji je u intracelularnoj tečnosti (drugi nakon K^+), dok je ekstracelularno to četvrti najzastupljeniji katjon. Njegove intracelularne i ekstracelularne koncentracije su regulisane funkcijom jonskih kanala ćelijske membrane, kao i kontrolnim mehanizmima za njegovo skladištenje u ćelijske ogranele. Održavanje homeostaze magnezijuma je veoma važno za očuvanje opšteg stanja zdravlja [3].

Magnezijum ima mnoge metaboličke funkcije u organizmu (kofaktor brojnih enzima), ali takođe predstavlja i katjon koji je bioesencijalan za sve ekscitabilne ćelije i tkiva. Kao takav, magnezijum je posebno značajan za pravilnu funkciju centralnog nervnog sistema (CNS). U tkivu mozga sisara sadržaj magnezijuma iznosi 6 – 7 mmol/kg (prisutan pretežno u sivoj masi mozga). U fiziološkim uslovima, krvna plazma i likvor, odnosno cerebrospinalna tečnost (CST), razlikuju se međusobno u sadržaju pojedinih jona. Tako je nivo Cl^- viši, nivo K^+ niži, nivoi Na^+ i Ca^{2+} gotovo isti, dok je nivo Mg^{2+} znatno viši u CST-i u odnosu na plazmu. Razlike u koncentracijama jona u plazmi i likvoru postoje zbog aktivnosti horoidnog pleksusa [4]. Jon Mg^{2+} je jedini katjon aktivno sekretovan od strane epitela horoidnog spleta, čija je koncentracija veća u likvoru nego u krvi (ako se izuzme H^+ jon). Transport magnezijuma, odnosno njegovu ak-

The diagnosis of epilepsy is electro-clinical, based on seizure semiology and the findings in recordings of the electroencephalogram (EEG). Epilepsy is characterized by changes in the EEG trace that can be observed during seizures (ictally) and between seizures (interictally). The presence of EEG changes in between seizures suggests abnormal electrical activity of the brain and a tendency of spontaneous seizure occurrence. However, the absence of EEG changes during a clinically asymptomatic period, does not exclude the diagnosis of epilepsy.

The treatment of epilepsy is tailored to the individual patient, i.e. the decision on the therapy is made for each patient separately, due to different causes of the disease, different forms of the disease, differences in the effectiveness and side effects of drugs, possible presence of comorbidities, and other factors. The use of antiepileptic drugs (AEDs) aims to establish stable seizure control, that is to abort ongoing seizures and suppress their future repetition. Monotherapy with antiepileptics is advantageous, as it is less toxic, simple to administer and achieves a more regular patient compliance, whereas it avoids drug interactions, etc. However, there is a large number of patients who do not respond appropriately to pharmacological treatment of epilepsy (pharmacoresistant or refractory form of the disease). In these cases, epilepsy can be treated with electrostimulation methods, epilepsy surgery (e.g. operative resection of the epileptic focus), or other treatment approaches [2].

THE IMPORTANCE OF MAGNESIUM IN THE PROPER FUNCTIONING OF THE NERVOUS SYSTEM

Magnesium is a mineral found in abundance in mammalian organisms. Mg^{2+} ion is present in higher concentration in the intracellular fluid (second to K^+ ion), than in the extracellular fluid (the fourth most abundant cation). Its intracellular and extracellular concentrations are regulated by the function of cell membrane ion channels, as well as by the control mechanisms regulating its storage in cell organelles. Maintaining magnesium homeostasis is very important for preserving the general state of health [3].

Magnesium has many metabolic functions in the body (a cofactor of numerous enzymes), but it is also a cation bio-essential for all excitable cells and tissues. As such, magnesium is particularly important for the proper functioning of the central nervous system (CNS). In mammalian brain tissue, magnesium content is 6 – 7 mmol/kg (predominantly present in brain gray matter). Under physiological conditions, blood plasma and cerebrospinal fluid (CSF) differ regarding the content of individual ions. Thus, the level of Cl^- is higher, the

tivnu sekreciju, omogućavaju katjonski kanali permeabilni za Mg^{2+} jone – članovi 6 i 7 melastatinske potfamilije kanala za prolazne receptorske potencijale: *TRPM6* i *TRPM7* (engl. *transient receptor potential melastatin*) [5].

Magnezijum ispoljava višestruka neuroaktivna dejstva na molekulskom, ćelijskom i sistemskom nivou. Dejstva magnezijuma na nervni sistem u celini obuhvataju antidepresivno, anksiolitičko, anestetičko, analgetičko, antimigrenozno, antikonvulzivno, antiepileptičko i neuroprotektivno dejstvo [3]. Na nivou ćelijske membrane pojedinačnih neurona, magnezijum ispoljava sveukupno stabilizujuće dejstvo. Elektrofiziološka ispitivanja pokazuju da jon Mg^{2+} učestvuje u regulaciji intrinsičkih svojstava membrane neurona (ekscitabilnost, provodljivost i otpornost) i vrši kompleksnu modulaciju električne aktivnosti neurona putem svojih sinaptičkih i nesinaptičkih dejstava, odnosno efekata na jonske kanale, transportere i pumpe, te receptore u membrani [6]. Magnezijum suprimira hemijsku sinaptičku neurotransmisiju vezivanjem za voltažno zavisne Ca^{2+} kanale presinaptičkih nervnih završetaka, čime suzbija oslobađanje neurotransmitera iz centralnih, kao i perifernih sinapsi (neuro-mišićna spojnica). Pored toga, vanćelijski Mg^{2+} blokira N-metil-D-aspartat (NMDA) jonotropne receptore za glutamat na voltažno zavisan način.

Od nesinaptičkih dejstava, između ostalog je poznato, da sa intracelularne strane membrane, Mg^{2+} jon može da blokira voltažno zavisne Na^+ kanale. Veliki hidratisani joni Mg^{2+} se kompetitivno vezuju za Na^+ kanale u toku njihovog aktiviranog stanja, čime dovode do sporijeg okidanja akcionih potencijala (AP) koji su i manje amplitude [7]. Pojedine studije ukazuju i na aktivirajuće dejstvo jona Mg^{2+} na kalcijumom aktivirane K^+ kanale (K_{Ca}) [8]. Najzad, jon Mg^{2+} neophodan je i za pravilnu funkciju pumpe za Na^+ i K^+ [9]. Svi ovi nalazi potvrđuju značajnu ulogu Mg^{2+} jona u regulaciji ekscitabilnosti neurona, kao i velike potrebe neurona za magnezijumom.

S obzirom da blokira depolarišuće jonske struje kroz voltažno zavisne Na^+ i Ca^{2+} kanale i kanale glutamatergičkih NMDA receptora, kao i da potencira hiperpolarišuće jonske struje K_{Ca} kanala i pumpe za Na^+ i K^+, jon Mg^{2+} ispoljava snažan efekat stabilizacije električnog potencijala i aktivnosti ćelijske membrane. Ovo istovremeno doprinosi važnom neuroprotektivnom dejstvu magnezijuma, budući da se suprotstavlja prekomernoj depolarizaciji ćelije i razvoju patofiziološkog mehanizma ekscitotoksičnosti, koji posreduje u oštećenju i odumiranju neurona u brojnim patofiziološkim stanjima (neurodegenerativnim procesima, ishemijskim lezijama mozga, kraniocerebralnim traumama, epileptičnim pražnjenjima, i dr.). Magnezijum dovodi

level of K^+ is lower, levels of Na^+ and Ca^{2+} are almost the same, whereas the level of Mg^{2+} is significantly higher in the CSF as compared to plasma. Differences in ionic composition of plasma and CSF exist due to choroid plexus activity [4]. Mg^{2+} ion is the only cation actively secreted by the choroid plexus epithelium with a concentration higher in the CSF than in the blood (except for H^+). Magnesium transport i.e. its active secretion occurs through cation channels permeable to Mg^{2+} – the transient receptor potential melastatin channels types 6 and 7 (TRPM6 and TRPM7) [5].

Magnesium exerts multiple neuroactive effects on a molecular, cellular and systemic level. The effects of magnesium on the nervous system as a whole include the antidepressant, anxiolytic, anesthetic, analgesic, antimigraine, anticonvulsant, antiepileptic and neuroprotective effects [3]. Magnesium exerts an overall stabilizing effect on cell membranes of individual neurons. Electrophysiological research shows that Mg^{2+} ion contributes to the regulation of the intrinsic properties of the neuronal cell membrane (excitability, conductivity, and resistance), and performs complex modulation of neuronal electrical activity through its synaptic and non-synaptic effects, i.e. Mg^{2+} effects on ion channels, transporters and pumps, and receptors in the cell membrane [6]. Magnesium suppresses chemical synaptic neurotransmission by binding to voltage dependent Ca^{2+} channels of presynaptic nerve endings, thereby suppressing the release of neurotransmitters from central as well as peripheral synapses (neuromuscular junction). In addition, extracellular Mg^{2+} ions block N-methyl-D-aspartate (NMDA) ionotropic glutamate receptors in a voltage-dependent manner.

Regarding the non-synaptic effects, it is known that intracellular Mg^{2+}, among other things, can block voltage-gated Na^+ channels. Large hydrated Mg^{2+} ions competitively bind to Na^+ channels in their activated state, thus leading to a decrease in action potential (AP) firing rate and AP amplitude [7]. Certain studies also indicate the activating effect of Mg^{2+} ions on calcium-activated K^+ channels (K_{Ca}) [8]. Finally, Mg^{2+} ion is also necessary for the proper functioning of the Na^+/K^+ pump [9]. All of these findings confirm the significant role of Mg^{2+} in the regulation of neuronal excitability, as well as high neuronal requirements for magnesium.

Concerning that Mg^{2+} blocks the depolarizing ion currents through voltage-gated Na^+ and Ca^{2+} channels and channels of glutamatergic NMDA receptors, and potentiates the hyperpolarizing ion currents through K_{Ca} channels and the Na^+/K^+ pump, Mg^{2+} ion exerts a strong effect of overall stabilization of cell membrane electrical potential and activity. This simultaneously contributes to the important neuroprotective effect of

i do povećanog stvaranja vazodilatatornih prostaglandina u mozgu. Takođe je poznato da magnezijum povećava neuroplastičnost i olakšava procese učenja i pamćenja.

Rutinski se nivo magnezijuma u krvi retko određuje, a i kada se meri – obično se meri samo nivo ukupnog magnezijuma u krvnom serumu (opseg normalnih vrednosti: 0,75 – 0,95 mmol/l). Uzorak treba da bude serum, a ne krvna plazma, jer različiti dodati antikoagulansi (etilendiamin tetraacetat, citrat, oksalat) mogu da vezuju jone Mg^{2+}, usled čega nastaju greške u merenju njihove koncentracije. U cilju određivanja magnezijumskog statusa organizma i ispitivanja pacijenta na hipomagnezijemiju (kao potencijalni uzrok ili doprinoseći faktor za nastanak epileptičkih napada), senzitivniji pokazatelj je merenje koncentracije slobodne, jonizovane frakcije Mg^{2+}, koja predstavlja biološki aktivnu formu jona Mg^{2+}. Normalan opseg vrednosti koncentracije jonizovanog Mg^{2+} u serumu iznosi od 0,50 do 0,70 mmol/l [3].

Hipomagnezijemija je stanje smanjene koncentracije magnezijuma u serumu. Nedostatak magnezijuma kod ljudi može nastati iz nekoliko razloga: nedovoljno unošenje, nedostatak magnezijuma u zemljištu ali i namirnicama biljnog i životinjskog porekla, zatim malapsorpcija i maldigestija, renalni gubici magnezijuma, redistribucija iz vanćelijskog u unutarćelijski prostor, i drugo [10]. Akutna deficijencija može proći nezapaženo, odnosno asimptomatski, ili se manifestuje mučninom, povraćanjem, letargijom i uznemirenošću. Hronični deficit magnezijuma dovodi do težih patofizioloških stanja. Hipomagnezijemija je često neprepoznat elektrolitni disbalans. Njeni znaci se javljaju kada nivo serumskog magnezijuma opadne ispod 0,50 mmol/l. Tada se razvijaju i znaci nervne i neuromišićne iritabilnosti i moždane hiperekscitabilnosti: tetanički grčevi mišića, srčane aritmije, anksioznost, konfuzija, a u teškoj hipomagnezemiji dolazi i do razvoja delirijuma i konvulzija, čak i do pojave epileptičkog statusa [11].

U terapiji hipomagnezijemije se koriste MgO i soli magnezijuma neorganskog i organskog porekla. Različite soli magnezijuma imaju različitu bioiskoristljivost. Tako, na primer, magnezijum pidolat ima veću bioiskoristljivost i penetrantnost na celularnom nivou, i može ubrzo nakon primene da reguliše deficijenciju magnezijuma koja je bila uzročnik glavobolja [12]. Neke od soli magnezijuma čiji se preparati koriste u terapiji su: sulfat, hlorid i karbonat, od neorganskih, i citrat, acetat, laktat, glicinat, aspartat, glukonat, pidolat i treonat, od organskih soli magnezijuma.

Latentna i blaga hipomagnezijemija se mogu lečiti oralnom primenom preparata magnezijuma (npr. magnezijum glukonat). Manifestna i teška hipomagnezi-

magnesium, since it counteracts the excessive membrane depolarization and the development of the pathophysiological mechanism of excitotoxicity, which mediates neuronal damage and death in numerous pathophysiological conditions (neurodegenerative processes, ischemic brain lesions, craniocerebral trauma, epileptic discharges etc). Magnesium also induces increased production of vasodilator prostaglandins in the brain. It is also known that magnesium increases neuroplasticity and facilitates learning and memory.

The level of magnesium in the blood is rarely tested routinely, and even when measured – it is usually the level of total magnesium in the blood serum that is measured (normal range: 0.75 – 0.95 mmol/l). The sample should be the serum, and not blood plasma, because various anticoagulants added (ethylenediamine tetraacetate, citrate, oxalate) can bind Mg^{2+} ions, resulting in errors in the measurement of its concentration. In order to determine magnesium status of the organism and test the patient for hypomagnesemia (as a potential cause or contributing factor for epileptic seizures), a more sensitive indicator should be used, i.e. the concentration of the free, ionized fraction of Mg^{2+} should be measured, as it represents the biologically active form of Mg^{2+} ions. Normal range of the concentration of ionized Mg^{2+} in the serum is between 0.50 and 0.70 mmol/l [3].

Hypomagnesemia is a condition of reduced serum magnesium concentration. Magnesium deficiency in humans can occur for several reasons: insufficient intake, lack of magnesium in the soil, but also in foodstuff of herbal and animal origin, malabsorption and maldigestion, renal loss of magnesium, redistribution from the extracellular to the intracellular space, and other causes [10]. Acute deficiency may undergo unnoticed, i.e. it may be asymptomatic, or it may manifest as nausea, vomiting, lethargy and agitation. Chronic magnesium deficiency leads to more severe pathophysiological conditions. Hypomagnesemia as an electrolyte imbalance is often unrecognized. Its signs appear when serum magnesium levels drop below 0.50 mmol/l. This is when signs of nervous and neuromuscular irritability and brain hyperexcitability develop: tetanic muscle spasms, cardiac arrhythmias, anxiety, confusion, and in severe hypomagnesemia, delirium and convulsions develop, leading even to status epilepticus [11].

In the treatment of hypomagnesemia, MgO and magnesium salts of inorganic and organic origin are used. Different magnesium salts have different bioavailability. Thus, for example, magnesium pidolate has a higher bioavailability and penetrability on a cellular level and can regulate the lack of magnesium causing headaches soon after its administration [12]. Some of the magnesium salts whose preparations are

jemija, pogotovo uz prisutne srčane aritmije i epileptičke napade, zahteva hitnu parenteralnu nadoknadu injekcijama i infuzijama $MgSO_4$, sve do normalizacije srčanog ritma i obustave napada. Pri tom je potreban oprez u slučaju bubrežne slabosti – ako pacijent ima renalno oštećenje, doza magnezijuma se smanjuje.

Magnezijum ima ulogu u prevenciji i terapiji većeg broja neuroloških i neuropsihijatrijskih poremećaja, kao što su anksioznost, depresija, migrenske i tenzione glavobolje, hronična bolna stanja, ali i Alchajmerova (*Alzheimer*) bolest, Parkinsonova bolest, moždani udar i epilepsija [13]. Suplementacija magnezijumom pomaže i u lečenju nesanice, koja predstavlja najčešći poremećaj spavanja [14]. Intracisternalna, intratekalna i epiduralna aplikacija magnezijuma su se pokazale korisnim za produženje efekata anestezije, u cilju postizanja analgezije, kao i u terapiji arterijske hipertenzije. Intranazalna aplikacija magnezijuma je alternativni put unosa leka, onda kada je potrebna njegova distribucija u mozak. Lek se tada transportuje putem vlakana olfaktornog nerva direktno u CNS [4].

MAGNEZIJUM U ISTRAŽIVANJIMA EPILEPSIJE

Epilepsija je hronična bolest nedovoljno poznate etiopatogeneze, kao i veoma različitih kliničkih ispoljavanja. Medikamentno lečenje epilepsije danas dostupnim standardnim antiepileptičkim lekovima povezano je sa brojnim poteškoćama, usled rizika od dozno-zavisne toksičnosti lekova, te potrebe za praćenjem koncentracije leka u plazmi, zbog dugog trajanja terapije, kao i neželjenih interakcija u slučaju potrebe za politerapijom [15]. Antiepileptici mogu da stupaju i u interakcije sa drugim lekovima koje pacijent koristi. Oni takođe mogu da dovedu i do deplecije pojedinih vitamina i minerala, i da na taj način utiču na pojavu napada. Iz tih razloga, kao i zbog velikog ukupnog broja obolelih, mogućih ozbiljnih neželjenih efekata ovih lekova, te velikog broja slučajeva koji su farmakorezistentni na postojeću terapiju (oko 30 % bolesnika sa epilepsijom), i dalje se traga za novim antiepileptičkim lekovima i novim modalitetima lečenja epilepsije, a u cilju postizanja veće efikasnosti i bolje podnošljivosti terapije za epilepsiju. Ovo uključuje i dodatne alternativne i komplementarne pristupe lečenju, koji mogu da doprinesu uspostavljanju bolje kontrole epileptičkih napada.

Magnezijum, kao jednostavno antiepileptičko sredstvo ima terapijski potencijal veći od njegove trenutne kliničke primene za ovu indikaciju [16]. Kao dodatak postojećem armamentarijumu korišćenih antiepileptičkih agenasa, mogao bi da doprinese poboljšanju prognoze, toka i ishoda bolesti kod bar nekih pacijenata sa epilepsijom. Stoga je najpre potrebno sa-

used in therapy are the following: sulfate, chloride and carbonate (inorganic salts) and citrate, acetate, lactate, glycinate, aspartate, gluconate, pidolate and threonate (organic magnesium salts).

Latent and mild hypomagnesemia can be treated with oral magnesium preparations (e.g. magnesium gluconate). Manifested and severe hypomagnesemia, especially with heart rhythm disorders and epileptic seizures present, requires immediate parenteral compensation with injections and infusions of $MgSO_4$ until heart rhythm normalizes and the seizures cease. In doing so, caution is required in case of kidney failure – if the patient has kidney damage, the dose of magnesium should be reduced.

Magnesium plays a role in the prevention and treatment of a number of neurological and neuropsychiatric disorders, such as anxiety, depression, migraine and tension headaches, chronic pain conditions, but also Alzheimer's disease, Parkinson's disease, stroke and epilepsy [13]. Magnesium supplementation also helps to treat insomnia, the most common sleep disorder [14]. Intracisternal, intrathecal and epidural application of magnesium have proven useful in prolonging the effects of anesthesia, in achieving analgesia, as well as the treatment of arterial hypertension. Intranasal application of magnesium is an alternative route of drug administration when its distribution in the brain is needed. The drug is then transported via the olfactory nerve fibers directly into the CNS [4].

MAGNESIUM IN EPILEPSY RESEARCH

Epilepsy is a chronic disease of insufficiently known etiopathogenesis and of varying clinical manifestations. Medical treatment of epilepsy with standard antiepileptic drugs available today is associated with numerous difficulties, due to the risk of dose-dependent drug toxicity, the need for monitoring drug concentration in the plasma, long duration of the therapy, as well as the unwanted drug interactions in case of need for polytherapy [15]. Antiepileptic drugs can also interact with other drugs that the patient is using. They can also cause depletion of certain vitamins and minerals, and thus affect the occurrence of seizures. For all these reasons, as well as the large total number of epilepsy patients, the possible serious side effects of AEDs, and the large number of pharmacoresistant epilepsy cases (about 30 % of all epilepsy patients), the search for new antiepileptic drugs and new modalities of epilepsy treatment still continues, for the purpose of achieving greater efficiency and better tolerability of epilepsy therapy. This also includes additional alternative and complementary treatment approaches, which can contribute to establishing better control of epileptic seizures.

brati iskustva iz dosadašnje kliničke prakse, kao i naučna saznanja iz objavljenih bazičnih i kliničkih studija o ulozi poremećaja homeostaze magnezijuma u nastanku epilepsije i značaju primene magnezijuma u lečenju epilepsije. U tom smislu nam može pomoći pregled odgovarajuće literature. Ovaj pregledni rad nastojao je da obuhvati pretklinička *in vitro* i *in vivo* istraživanja, urađena sa zajedničkim ciljevima – da se otkrije doprinos koji, nekad i skriveni deficit magnezijuma u organizmu ima u procesima iktogeneze i epileptogeneze, kao i da se utvrde mehanizmi antiepileptičkog i antiepileptogenog dejstva magnezijuma. Najzad, obuhvaćene su i one kliničke studije i prikazi slučajeva koji se bave korišćenjem magnezijuma u terapiji pojedinih tipova epileptičkih napada i epileptičkog stanja.

MAGNEZIJUM U PRETKLINIČKIM ISTRAŽIVANJIMA EPILEPSIJE

U bazičnim neurofiziološkim istraživanjima, ogledi se rade na različitim animalnim modelima bolesti, počev od nivoa organizma u *in vivo* eksperimentima, uključujući i životinjske vrste beskičmenjaka (lat. *invertebrata*) i sisara, preko *in vitro* eksperimenata na izolovanim organima, isečcima mozga, neuronima u kulturi, i slično, pa sve do subćelijskog – molekulskog nivoa izolovanih pojedinačnih jonskih kanala, kao i na kompjuterskim modelima sistema. Brojna fundamentalna istraživanja bazičnih mehanizama u epilepsiji pokazuju da nedostatak Mg^{2+} u organizmu može da bude direktno povezan sa iktogenezom i epileptogenezom [16].

Na membrane centralnih neurona sniženje vanćelijske koncentracije Mg^{2+} deluje da spusti nivo praga nadražljivosti i povećava ekscitabilnost neurona [17]. Smanjenje sadržaja Mg^{2+} u cerebrospinalnoj tečnosti i u intersticijalnoj tečnosti tkiva mozga neuropila koji neurone neposredno okružuje može dovesti do spontanog razvoja epileptiformne aktivnosti.

Mehanizmi epileptogeneze nisu u potpunosti rasvetljeni, tako da je i postojeće znanje o značaju Mg^{2+} jona u epilepsiji – nepotpuno. Ipak, postoje mnoga saznanja o ulozi magnezijuma u eksperimentalnoj epilepsiji. Za ovo postoje brojni primeri u bazičnim studijama epilepsije na modelima *in vitro*. Tako, na primer, nesinaptičko Na^{+}–zavisno epileptiformno pražnjenje, indukovano u Recijusovim neuronima pijavice primenom nikla, biva suprimirano dejstvom Mg^{2+} jona na dozno zavisni način [18,19].

Sniženje koncentracije Mg^{2+} jona u ekstracelularnoj tečnosti izaziva patofiziološku hiperekscitabilnost neurona sisara. Niska vanćelijska koncentracija Mg^{2+} jona, ili potpuno uklanjanje Mg^{2+} jona iz rastvora za perfuziju preparata, indukuje spontani razvoj epileptiformne aktivnosti piramidnih neurona na eksperimentalnim

Magnesium, as a simple antiepileptic agent, has therapeutic potential which surpasses its current clinical application for this indication [16]. As an addition to the existing armamentarium of applied antiepileptic agents, it could contribute to improving the prognosis, course and outcome of the disease in at least some patients with epilepsy. Therefore, it is necessary first of all to gather experiences from clinical practice to date, as well as scientific knowledge from published basic and clinical studies and trials, on the role of disorders of magnesium homeostasis in the onset of epilepsy and the importance of using magnesium in the treatment of epilepsy. A review of relevant literature can be of use for this cause. This review attempts to include preclinical *in vitro* and *in vivo* research, carried out with the common goals to reveal the contribution that sometimes latent magnesium deficiency in the body has in the processes of ictogenesis and epileptogenesis, as well as to determine the mechanisms of antiepileptic and antiepileptogenic magnesium effects. Finally, clinical studies and case reports on the use of magnesium in the therapy of certain types of epileptic seizures and epileptic state have also been included.

MAGNESIUM IN PRECLINICAL EPILEPSY RESEARCH

In basic neurophysiological research, experiments are performed on different animal models of disease – starting from the whole organism level in experiments *in vivo*, including invertebrate and mammalian species, over *in vitro* experiments on isolated organs, brain slices, cell cultures etc, down to the subcellular - molecular level of isolated individual ion channels, as well as on computer model systems. Numerous fundamental studies of the basic mechanisms in epilepsy show that the defficiency of Mg^{2+} in the body may be directly linked to ictogenesis and epileptogenesis [16].

A decrease in the extracellular Mg^{2+} concentration acts on the membranes of central neurons to lower the excitation threshold level and increase neuronal excitability [17]. A decrease in Mg^{2+} content in the CSF and the interstitial fluid of the brain tissue (neuropil immediately surrounding the neurons), can lead to the spontaneous development of the epileptiform activity.

The mechanisms of epileptogenesis have not been fully elucidated, which is why the existing knowledge on the importance of Mg^{2+} in epilepsy is also incomplete. However, there is a significant body of knowledge regarding the role of magnesium in experimental epilepsy. There are numerous examples of this in basic studies of epilepsy on *in vitro* models. For example, Mg^{2+} reversibly suppresses in a dose-dependent manner the non-synaptic Na^{+}-dependent epileptiform

modelima intaktnog hipokampusa miša i isečaka hipokampusa pacova [20].

Nedostatak magnezijuma takođe ima epileptogeno dejstvo kod oglednih životinja *in vivo*. Fokalna eksperimentalna epileptička aktivnost akutno izazvana topikalnom primenom penicilina na korteks ogledne životinje biva suprimirana intravenoznim (*i.v.*) davanjem Mg^{2+}. Pri tom je stepen supresije izazvanog interiktalnog EEG pražnjenja direktno srazmeran postignutoj koncentraciji Mg^{2+} jona u serumu životinje. Magnezijum ostvaruje centralno antikonvulzivno dejstvo po dospevanju do epileptičkog fokusa prolaskom kroz oštećenu i propustljivu krvno-moždanu barijeru [21].

Deficit magnezijuma u ishrani ovaca direktno izaziva pad nivoa Mg^{2+} u plazmi i nivoa Mg^{2+} u likvoru, kao i nastanak konvulzija koje se prekidaju intravenoznim davanjem Mg^{2+} [22]. Slično tome, dijetna restrikcija magnezijumau ishrani snižava konvulzivni prag mozga pacova za izazivanje napada pentilen-tetrazolom, što se koriguje peroralnom nadoknadom magnezijuma [23].

Peroralno davanje MgO u niskim dozama pokazuje protektivni efekat protiv razvoja epileptičkih napada, izazvanih kod pacova primenom maksimalnog elektrošoka, dok suplementacija magnezijum oksidom u visokim dozama pojačava dejstvo standardnih AEL-a fenitoina i karbamazepina na ovom eksperimentalnom modelu [24].

MAGNEZIJUM U KLINIČKIM ISTRAŽIVANJIMA EPILEPSIJE

Iako su poremećaji magnezijumskog statusa sa nastankom deficita Mg^{2+} često udruženi sa pojavom epileptičkih napada, u kliničkoj praksi se kod bolesnika sa epilepsijom nivo Mg^{2+} jona u krvi, na žalost, i danas retko određuje i prati. Dok deficit magnezijuma deluje prokonvulzivno, njegova nadoknada pokazuje efikasno centralno antikonvulzivno dejstvo. Davanje infuzija soli Mg^{2+} je ranije imalo veću primenu u kliničkoj epileptologiji. Nakon kasnijeg razvoja i uvođenja novih AEL-a, magnezijum sulfat se održao do danas samo u lečenju pojedinih specifičnih tipova epileptičkih napada – $MgSO_4$ je ostao antikonvulziv izbora uglavnom samo za konvulzije kod određenih hipertenzivnih i metaboličkih epileptičkih encefalopatija.

Ipak, u novije vreme sve je veći broj kliničkih studija koje ponovo skreću pažnju na klinički značajan, a nedovoljno iskorišćen potencijal antiepileptičkog dejstva preparata magnezijuma za parenteralnu i peroralnu primenu. Mehanizmi antiepileptičkog dejstva magnezijuma su nedovoljno razjašnjeni, ali je verovatno da im doprinose ona sinaptička i nesinaptička dejstva kojima jon Mg^{2+} i fiziološki ostvaruje stabilizujuće dejstvo na električni potencijal i električnu aktivnost membrane neurona (u

discharge induced in leech Retzius neurons by the application of nickel [18,19].

A decrease in the concentration of Mg^{2+} in the extracellular fluid causes pathophysiological hyperexcitability of mammalian neurons. Low extracellular Mg^{2+} concentration or complete removal of Mg^{2+} from the perfusion solution (zero Mg^{2+} artificial CSF) induces spontaneous development of epileptiform activity of pyramidal neurons in experimental models of intact mouse hippocampus and rat hippocampal slices [20].

Magnesium deficiency also has an epileptogenic effect in experimental animals *in vivo*. Focal experimental epileptic activity acutely induced by topical application of penicillin to the cortex of an experimental animal is suppressed by intravenous (*i.v.*) administration of Mg^{2+}, the degree of suppression of the induced interictal EEG discharge being directly proportional to the achieved Mg^{2+} concentration in the serum of the animal. Magnesium achieves a central anticonvulsive effect upon reaching the epileptic focus by passing the damaged and permeable blood-brain barrier [21].

Magnesium deficiency in the diet of sheep directly causes a drop in both plasma and CSF Mg^{2+} levels, as well as the onset of convulsions, which can be suppressed by *i.v.* administration of Mg^{2+} [22]. Likewise, a dietary magnesium restriction lowers the rat brain convulsive threshold for pentylene-tetrazole induced seizures, the effect being corrected by oral magnesium supplementation [23].

Oral administration of MgO in low doses shows a protective effect against the development of epileptic seizures induced in rats by applying maximal electroshock, while supplementation with MgO in high doses enhances the effect of standard AEDs phenytoin and carbamazepine on this experimental model [24].

MAGNESIUM IN CLINICAL EPILEPSY RESEARCH

Although disorders of magnesium status resulting in Mg^{2+} deficiency are often associated with epileptic seizures, in clinical practice today unfortunately the level of Mg^{2+} in the blood is still rarely tested and monitored in patients with epilepsy. While magnesium deficiency has a proconvulsant effect, magnesium compensation shows an efficient central anticonvulsant effect. Administering infusions of Mg^{2+} salts was previously used more widely in clinical epileptology. However, since the development and introduction of new AEDs, magnesium sulfate continued to be applied only in the treatment of certain specific types of epileptic seizures – $MgSO_4$ has mainly remained the anticonvulsant of choice only for the convulsions in certain hypertensive and metabolic epileptic encephalopathies.

neepileptičnim uslovima), kao i mogućnost njegovog prelaska, po terapijskom davanju, iz krvi u CNS, u patofiziološkim uslovima oštećenja i povećanja propustljivosti krvno-moždane barijere u ovim bolestima.

Značajno sniženje nivoa magnezijuma pronađeno je u serumu kod osoba sa dijagnozom idiopatske epilepsije. Deficit magnezijuma je prepoznat, između ostalog, i kod odraslih sa generalizovanim konvulzivnim napadima, kao i dece sa febrilnim konvulzijama, u poređenju sa zdravom populacijom [25,26]. Najveći deficit magnezijuma je ustanovljen u epileptičkom statusu i u teškim oblicima epilepsije [27]. U bolesnika sa farmakorezistentnom epilepsijom hipomagnezijemija povećava učestalost napada, a time i rizik od pojave *SUDEP*-a [28].

Kada je primena magnezijuma u terapiji epilepsije u pitanju, u kliničkim studijama i preglednim radovima se u terapijskim protokolima navodi i magnezijum kao sredstvo u lečenju pojedinih tipova epileptičkih napada. Ima studija koje pokazuju da se konvulzivni napadi bolje kontrolišu uz adekvatnu suplementaciju magnezijumom [27]. Pokazano je da dnevna primena 450 mg magnezijuma kod pacijenata sa konvulzijama smanjuje potrebu za primenom AEL-a [29]. Oralna suplementacija magnezijumom u epilepsiji pomaže i u smanjenju učestalosti napada kod bolesnika sa epilepsijom [30].

TERAPIJSKE PRIMENE MAGNEZIJUMA U EPILEPSIJI

Nakon otkrića antiepileptičkih lekova, $MgSO_4$ je ostao antikonvulziv izbora za manji broj indikacija u oblasti epilepsije kod odraslih. Magnezijum se daje za hitno zbrinjavanje eklampsije i teške preeklampsije, hipertenzivnog sindroma koji se javlja tokom trudnoće, porođaja ili babinja, i odlikuje se razvojem generalizovanih konvulzija majke. Patogeneza eklamptičkih konvulzija i dalje je nedovoljno ispitana. Eklampsija predstavlja urgentno stanje u porodiljstvu, životno ugrožavajuće za majku i plod.

Primena magnezijuma se veoma dobro pokazala u lečenju generalizovanih konvulzivnih napada u eklampsiji. Magnezijum ima prednost u lečenju za ovu indikaciju nad ostalim antiepilepticima, zbog svoje visoke efikasnosti i dobrog bezbednosnog profila za majku i dete. Stoga *i.v.* infuzija $MgSO_4$ i danas predstavlja lek prvog izbora za prevenciju i kontrolu eklamptičkih konvulzija, koji značajno smanjuje maternalnu smrtnost u eklampsiji [31].

Antikonvulzivno dejstvo parenteralno datog $MgSO_4$ takođe ima kliničku primenu u prevenciji i prekidanju ponovnih konvulzivnih napada u uremiji, porfiriji, hipomagnezijemiji i u eklamptičkom statusu [32,33].

However, an increasing number of clinical studies has recently once again drawn attention to the clinically significant, but underutilized potential of antiepileptic effect of magnesium preparations for parenteral and oral administration. The mechanisms of the antiepileptic action of magnesium are as yet insufficiently elucidated, but they are likely to be mediated by those synaptic and non-synaptic effects through which Mg^{2+} ion physiologically exerts a stabilizing effect on the electrical potential and electrical activity of the neuronal cell membrane (under non-epileptic conditions), as well as by the possibility of Mg^{2+} penetration, upon therapeutic administration, from the blood to the CNS tissue, under pathophysiological conditions of damage to and an increase in the permeability of the blood-brain barrier in these diseases.

A significant decrease in Mg^{2+} concentration was found in the serum of people diagnosed with idiopathic epilepsy. Magnesium deficiency has been recognized among others, in adult patients with generalized convulsive attacks and in children with febrile convulsions, compared to healthy population [25,26]. The greatest deficit of magnesium was found in status epilepticus and in severe forms of epilepsy [27]. In patients with drug-resistant epilepsy, hypomagnesemia increases the frequency of seizures, and thus the risk of SUDEP [28].

Regarding the use of magnesium in the treatment of epilepsy in clinical studies and review papers, in therapeutic protocols there are mentions of magnesium as means of treating certain types of epileptic seizures. There are studies showing that convulsive seizures are controlled better with an adequate magnesium supplementation [27]. Daily administration of 450 mg of magnesium in patients with convulsions has been shown to reduce the need for AEDs [29]. Oral magnesium supplementation in epilepsy also helps to reduce the frequency of seizures in patients with epilepsy [30].

THERAPEUTIC APPLICATION OF MAGNESIUM IN EPILEPSY

Since the discovery of antiepileptic drugs, $MgSO_4$ has remained the anticonvulsant of choice for a very limited number of indications in the field of epilepsy in adults. Magnesium is given for the emergency management of eclampsia and severe preeclampsia, a hypertensive syndrome that occurs during pregnancy, labor or postpartal confinement, characterized by the development of generalized convulsions of the mother. The pathogenesis of eclamptic convulsions is still incompletely investigated. Eclampsia is an urgent condition in obstetrics, life-threatening for both mother and child.

Magnezijum ima svoje mesto u kliničkoj primeni i u pedijatrijskoj epileptologiji, pre svega u lečenju infantilnih epileptičkih encefalopatija. Veći broj kliničkih studija nalazi da je nivo serumskog magnezijuma kod dece sa febrilnim napadima niži u odnosu na kontrolu, i da se parenteralni $MgSO_4$ može koristiti u njihovom lečenju [26, 33].

Vestov (*West*) sindrom je oblik epilepsije ranog dečjeg uzrasta, koju odlikuje elektro-klinički trijas: infantilni spazmi, psihomotorna retardacija i nalaz hipsaritmije u EEG-u. Kod dece sa epileptičkim spazmima i Vestovim sindromom lečenje adrenokortikotropnim hormonom (engl. *adrenocorticotropic hormone – ACTH*) u kombinaciji sa *i.v.* magnezijum sulfatom daje bolje rezultate od hormonske monoterapije, naročito u pogledu normalizacije EEG zapisa kod deteta [35].

Status epilepticus (*SE*) jedno je od najčešćih urgentnih stanja neurokritičnih pacijenata. Ubrzo nakon što je Lazar (*Lazard*) objavio prvi, i to uspešni pokušaj lečenja eklampsije, koji je sproveo 1925. godine intravenoznim davanjem $MgSO_4$ [36], Storhajm (*Storchheim*) je objavio svoje nalaze u vezi sa praćenjem i poređenjem ishoda lečenja epileptičkog statusa standardnom terapijom i lečenja *i.v.* magnezijum sulfatom. Pokazalo se da terapija magnezijumom omogućava stabilizaciju stanja pacijenata posle terapije i njihovo dobro preživljavanje [37]. Noviji podaci iz literature navode da se infuzije soli magnezijuma mogu davati pacijentima u *SE*-u sa ili bez hipomagnezijemije, u eklamptičnom i neeklamptičnom epileptičkom statusu [11].

Ukoliko *SE* pokazuje produženo trajanje (> 60 min), usled rezistencije na uobičajenu terapiju benzodiazepinima i nesedirajućim antiepilepticima, označava se kao refraktarni *status epilepticus* (*RSE*). Magnezijum je koristan i u lečenju refraktarne epilepsije [27,38] i refraktarnog epileptičkog stanja [39,40]. Smatra se da se infuzije $MgSO_4$ mogu koristiti i za pedijatrijski *RSE* [41]. U jednog broja bolesnika se *RSE* održava čak i duže od 24 h uprkos terapiji opštim anesteticima – tzv. super-refraktarni *status epilepticus* (*SRSE*). Ova tri entiteta: *SE*, *RSE* i *SRSE* prate visok morbiditet i mortalitet. Trenutno ne postoji jedinstveni terapijski algoritam za kontrolu *SRSE*-a. Među mnogo dostupnih terapijskih pristupa različite efikasnosti, davanje infuzija $MgSO_4$ se može razmotriti za kontrolu *SRSE*-a, premda je malo literature dostupno o tome [42].

ZAKLJUČAK

Nivo jona Mg^{2+} u serumu i likvoru ima veliki značaj za normalnu funkciju nervnog sistema, u zdravlju i u bolesti. Zbog svoje regulatorne uloge u funkciji neurona i CNS-a, kao i uloge disbalansa magnezijumskog statusa u nastanku određenih neuroloških, neuropsihijatrijskih

The use of magnesium has proven to be very beneficial in the treatment of generalized convulsive attacks in eclampsia. For this indication magnesium has a therapeutic advantage over other antiepileptics due to its high efficacy and a strong safety profile for the mother and the child. Therefore, *i.v.* infusion of $MgSO_4$ remains even today the drug of first choice for the prevention and control of eclamptic convulsions, as it significantly reduces maternal mortality in eclampsia [31]. The anticonvulsant effect of parenterally administered $MgSO_4$ also has its clinical application for the prevention and termination of recurrent convulsive seizures in uremia, porphyria, hypomagnesemia and in eclamptic status [32,33].

Magnesium has its place in clinical application in pediatric epileptology as well, primarily in the treatment of infantile epileptic encephalopathies. A number of clinical studies have found that serum magnesium levels in children with febrile seizures (convulsions) are lower as compared to controls, and that parenterally administered $MgSO_4$ can be used in their treatment [26,33].

West syndrome is a form of early childhood epilepsy characterized by the electro-clinical triad: infantile spasms, psychomotor retardation and hypsarrhythmia in the EEG trace. In children with epileptic spasms and West syndrome, treatment with adrenocorticotropic hormone (ACTH) in combination with *i.v.* magnesium sulfate gives better results than the hormone monotherapy alone, especially regarding the normalization of the EEG recording of the child [35].

Status epilepticus (SE) is one of the most common emergency conditions in neurocritical patients. Shortly after Lazard had published success of the first attempt to treat eclampsia giving *i.v.* magnesium sulfate, which he conducted in 1925 [36], Storchheim published his findings concerning the follow-up and comparison of the outcomes of status epilepticus treatment with standard therapy and with *i.v.* $MgSO_4$. Magnesium treatment was shown to facilitate the stabilization of the patients' condition after the given therapy, as well as their favorable survival [37]. Recent data from the literature indicate that magnesium salt infusions can be given to patients in SE with or without hypomagnesemia, in eclamptic and non-eclamptic status epilepticus [11].

Prolonged SE (lasting longer than 60 min), showing resistance to the standard therapy with benzodiazepines and non-sedating antiepileptics, is designated as the refractory status epilepticus (RSE). Magnesium is also useful in the treatment of refractory epilepsy [27,38] and refractory status epilepticus [39,40]. Intravenous $MgSO_4$ infusions are also considered to be useful for pediatric RSE [41]. In some patients RSE persists

i neuromišićnih poremećaja i oboljenja, magnezijum ima svoje mesto kao predmet proučavanja u širokoj oblasti neuronauka.

Pregled literature o značaju magnezijuma u bazičnim i kliničkim studijama u epileptologiji pomaže u razumevanju uloge koju poremećaji homeostaze magnezijuma imaju u patofiziološkim mehanizmima odgovornim za nastanak epilepsije. S obzirom da je deficit magnezijuma u organizmu veoma čest u opštoj populaciji, mogao bi biti češći od pretpostavljenog i među bolesnicima sa epilepsijom. Imajući sve ovo u vidu, potrebno je da rutinske laboratorijske pretrage kod ovih bolesnika obuhvate, između ostalog, i proveru magnezijumskog statusa, posebno nivoa jonizovane frakcije Mg^{2+} u serumu bolesnika.

Magnezijum pokazuje višestruka neuroaktivna dejstva, kao i značajan efekat stabilizacije patofiziološke hiperekscitabilnosti neurona, kakva postoji u epileptičkim pražnjenjima. Ipak, potrebna su dodatna istraživanja koja bi se specifično fokusirala na procenu efikasnosti primene preparata magnezijuma kod bolesnika sa epilepsijom, a posebno na procenu korisnosti oralne suplementacije magnezijumom kao dopunske terapije za bolju kontrolu epileptičkih napada u slučaju razvoja refraktarnosti na postojeće lekove.

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SPISAK SKRAĆENICA

SUDEP – engl. *sudden unexpected death in epilepsy*
SE – lat. *Status epilepticus*
EEG – elektroencefalogram
AEL – antiepileptički lekovi
CNS – centralni nervni sistem
CST – cerebrospinalna tečnost
TRPM – engl. *transient receptor potential melastatin*
NMDA – N-metil-D-aspartat
AP – akcioni potencijal
K_{Ca} – kalcijumom aktivirani K^+ kanali
i.v. – intravenski
ACTH – adrenokortikotropni hormon (engl. *adrenocorticotropic hormone*)
RSE – refraktarni *status epilepticus*
SRSE – super-refraktarni *status epilepticus*

Sukob interesa: Nije prijavljen.

even longer than 24 hours despite the therapy with general anesthetics. This is the super-refractory status epilepticus (SRSE). These three entities: SE, RSE and SRSE are associated with high morbidity and mortality. Currently, there is no single therapeutic algorithm for the control of SRSE. Among the many available therapeutic approaches of varying efficacy, administration of $MgSO_4$ intravenous infusions can be considered for the control of SRSE, although there is scarce literature dealing with this particular issue [42].

CONCLUSION

The level of Mg^{2+} in the serum and the cerebrospinal fluid is very important for proper functioning of the nervous system, both in health and disease. Due to its regulatory role in the function of neurons and the CNS, as well as the role of magnesium status disbalances in the development of certain neurological, neuropsychiatric and neuromuscular disorders and diseases, magnesium has its place as a research focus in the broad field of neurosciences.

Literature review dealing with the importance of magnesium in basic and clinical studies in epileptology helps us understand the role that the disorders of magnesium homeostasis have in the pathophysiological mechanisms responsible for the development of epilepsy. Given that magnesium deficiency is very common in general population, it could be more common than believed among patients with epilepsy as well. Bearing all this in mind, it is necessary that routine laboratory tests in these patients should include, among other analyses, checking magnesium status of the patient, especially the level of the ionized fraction of Mg^{2+} in the serum.

Magnesium shows multiple neuroactive effects, as well as a significant effect of stabilizing the pathophysiological hyperexcitability of neurons, present in epileptic discharges. However, additional research are needed to focus specifically on the evaluation of the effectiveness of the use of magnesium preparations in patients with epilepsy, and especially on the evaluation of the usefulness of oral magnesium supplementation, as an additional therapy for better control of epileptic seizures in case of the development of refractoriness to existing drugs.

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LIST OF ABBREVIATIONS/ACRONYMS

SUDEP – sudden unexpected death in epilepsy
SE – status epilepticus
EEG – electroencephalogram
AED – antiepileptic drug
CNS – central nervous system
CSF – cerebrospinal fluid
TRPM – transient receptor potential melastatin
NMDA – N-methyl-D-aspartate
AP – action potential
K_{Ca} – calcium activated K^+ channel
i.v. – intravenous
ACTH – adrenocorticotropic hormone
RSE – refractory status epilepticus
SRSE – super-refractory status epilepticus

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