Chapter 9

Antiepileptic Drugs and Risk Factors of Vascular Diseases

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Abstract

Epilepsy is one of the most common neurological diseases, affecting approximately 1% of the population. It is a chronic disease and increased incidence falls in the period up to 1 year and 65 years of age. Most patients require long-term antiepileptic drugs (AEDs) therapy. In addition, approximately 30% of patients with epilepsy do not obtain satisfactory seizure control, which is defined as drug-resistant epilepsy. It is postulated that one of the causes of drug resistance can be polymorphisms of *ABCB1*/*MDR1* gene, tested particularly in tumors. It is believed that the old generation of AEDs, e.g. CBZ, VPA, may change plasma Hcy, asymmetric dimethylarginine (ADMA) levels, disturb lipid levels, C-reactive protein, vitamins, markers of oxidative stress, which are risk factors for vascular and neurodegenerative diseases. Changes in the level of risk factors for vascular disease caused by enzymes inducing AEDs, CBZ, PB, and PHT lead to a small increase in the risk of myocardial infarction. Alteration of Hcy and ADMA levels are also linked to genetic factors, e.g. genetic variants of *MTHFR, MTR, MTHFD1, CBS, DDAH1, eNOS* genes. Individualization of treatment with AEDs and prevention against cardiovascular disease in patients with epilepsy may bring the best therapeutic effects in these patients.

Keywords: AEDs, side effects, epilepsy

1. Introduction

Epilepsy is one of the most common neurological diseases. It is estimated that approximately 50 million people worldwide suffer from epilepsy. The most common treatment of epilepsy is based on long-term use of antiepileptic drugs (AEDs).

AEDs are a very heterogeneous group and exhibit different mechanisms of action. It is divided broadly into two generations: older and newer AEDs. It is believed that the new AEDs are characterized by greater specificity of the mechanism of action, a proper clinical assessment of the first trial and less side effects. New generation (NG) drugs are also rarely caused interactions with other drugs and lesser extent affect mood and cognitive function. On the other hand, the old AEDs should be applied carefully with consideration of drug interactions and potential side effects, e.g., increase homocysteine (Hcy) level [1].

Currently, many studies on hyperhomocysteinemia (HHcy) in epileptic patients treated with AEDs have been performed. The literature indicates that carbamazepine (CBZ) therapy in epileptics leads to an increase of Hcy [2–5]. Treatment with valproic acid (VPA), however, has variable effects; in some cases, Hcy is decreased [6], in others, it is increased [2–4, 7, 8], and in yet others, VPA has no effect on Hcy levels [9–11]. However, lamotrigine (LTG) treatment of epileptic patients has not been shown to lead to an increase in Hcy [6, 12].

It is believed that AEDs increase Hcy level by lowering the level of folate (FA), cofactor remethylation of Hcy to methionine, as a result of impaired the intestinal absorption, increased demand of FA for the hydroxylation processes of AEDs, the activation of hepatic enzymes leading to a final reduction of the FA level or AEDs direct effect on the metabolism of Hcy and renal function [13]. It is believed that only CBZ, phenytoin (PHT), phenobarbital (PB) and primidone reduce the level of FA by an increased activity of liver enzymes [3, 10]. However, VPA does not induce hepatic microsomal enzyme, but may lead to a decrease [2], as well as an increase [3] in the FA level. The VPA may reduce the FA level by inhibiting the enzyme intermediate in biosynthesis of FA and its derivatives. It has been shown that VPA is indeed associated with a lower risk of deficit of FA.

Elevated concentrations of Hcy in epileptic patients treated with AEDs may be associated with a number of clinical complications. It has been shown that increased Hcy level may lead to vascular disease [14], neuropsychiatric [13] and is considered to be a risk factor for seizure and resistance to treatment with AEDs [15].

Literature data have shown that there is a link between HHcy and asymmetric dimethylarginine (ADMA) level in epilepsy [16, 17]. ADMA is considered to be a risk factor for cardiovascular disease [18]. It has been shown that ADMA may mediate atherogenic action of Hcy [14]. ADMA levels in the plasma of patients with atherosclerosis correlate with both endothelial dysfunction and the progression of atherosclerosis [19, 20]. ADMA is a known marker of atherosclerosis [21, 22].

Recent data have also shown that epilepsy patient treated with AEDs may exhibit increased risk of the myocardial infarction, stroke and cardiovascular death [23, 24]. This may be

triggered by influencing the serum Hcy and ADMA concentration [16], the serum lipid levels [25], C-reactive protein (CRP), body weight, as well as other atherosclerotic factors by AEDs [1].

2. Epilepsy and antiepileptic drugs

Epilepsy is not a disease in itself but rather a collection of somatic, vegetative or mental symptoms, which may be the result of a morphological or metabolic change in the brain. The etiology of the disease is varied, and among the most common causes are genetic factors, head trauma, tumors, as well as vascular, degenerative, demyelinating, inflammatory and toxic brain diseases. However, in 60% of the patients the causes of the illness remain still unknown. Traditionally, the patient could have been diagnosed of epilepsy after at least two unprovoked seizures occurring greater than 24 h apart. It has changed recently when the International League Against Epilepsy (ILAE) established the new operational (practical) clinical definition. In some cases these new criteria enable the doctors to speed up the diagnosis and apply the AEDs even after first seizure, when there is a high probability of having another attack [26].

AEDs are among the most common medications used in neurology. Nevertheless, treatment of epilepsy despite over 20 antiseizure drugs is still a challenge, even for an experienced neurologist/epileptologist. Unfortunately, the seizure control in almost 20–40% of the patients remains unsatisfactory. The reasons for refractory epilepsy are not fully clear, however, some literature data have shown that polymorphisms of a few genes, e.g., *ABCB1*/*MDR1* may influence the good or poor therapeutic response [27, 28].

The older generation of AEDs consists of CBZ, VPA, PHT, PB, ethosuximide (ESM) and benzodiazepines (BZDs). The new generation (NG) include LTG, topiramate (TPM), gabapentin (GBP), oxcarbazepine (OXCBZ), levetiracetam (LEV), pregabalin (PGB), tiagabine (TGB), vigabatrin (VGB), lacosamide (LCM), and perampanel (PMP). Very important characteristic of AEDs is their ability to induce liver cytochrome P450 (CBZ, PHT, PB) or to block its activity (VPA), which plays an essential role in drug interactions [16, 29]. AEDs act against different targets and have distinguishing pharmacokinetics, efficacy, tolerability and side effects [30]. Although for some AEDs the precise mechanism of action remains still unknown and most of them seem to exhibit more than one mechanism, especially VPA, TPM, and PB, they may be categorized by their principal goal. CBZ, PHE, LTG, OXCBZ, and ZNS act by blocking the activity of voltage-gated sodium channels, while ESM, GBP and PG modulate calcium ones [31]. Increase in gamma-aminobutyric (GABA)ergic transmission by affecting $GABA_A$ receptors, GABA synthesis reuptake or degradation is known for VGB, TGB and BDP. Inhibition of glutamatergic excitation is distinctive for one of the newest drug—PMP [32]. Another mechanism of action is selectively enhancing slow inactivation of voltage-gated sodium channels which has been proved for LCM. Finally, LEV and BRV have an ability to bind to synaptic vesicle SV2A protein [33].

It is known that the use of AEDs, especially for many years induces many adverse effects. The most common side effects of AEDs are sedation, dizziness, ataxia, headache, joint pain, fever, vomiting, eating disorders, clotting disorders, hair loss, gingival hyperplasia, and allergic

reactions [29]. It is believed that the AEDs in pregnant women with epilepsy are the most common causes of fetal defects [34, 35].

3. Polymorphism of the *ABCB1/MDR1* genes and antiepileptic drugs

The *ABCB1/MDR1* gene encodes the P-glycoprotein (P-gp), a transmembrane transporter located at the endothelial cells of the blood-brain barrier (BBB). It is known that overexpression of P-gp by reducing concentration of AEDs in affected brain regions is associated with epilepsy pharmacoresistance. The *ABCB1/MDR1* gene is highly polymorphic therefore it has great variability in the level of P-gp expression and activity among epileptic patients [36]. It is postulated that one of the causes of losing effectiveness of epilepsy treatment may be just polymorphisms of this gene, which has been mostly studied in the context of drug resistant in human cancer cells. There have been described three single nucleotide polymorphisms in the *ABCB1/MDR1* gene C3435T, C1236T and G2677 (A/T) related to epilepsy.

The first, *ABCB1/MDR1* C3435T is located in exon 26. It has been showed that patients with drug-resistant epilepsy were more likely to have the CC than the TT genotype and it is associated with increased expression of the protein that influences the response to AED treatment [37]. These results have not been confirmed by other studies conducted in Indian population [38].

Moreover, the literature data indicate that there is an association between C3435T polymorphism and CBZ doses. The study of Sterjev et al. [39] indicated that patients with the TT genotype require a higher dose of CBZ in comparison with patients with the CT and CC genotypes. No differences in allele frequency and genotype distribution between patient resistance and response on CBZ were observed. Nevertheless, the authors suggest that the genetic variant is not the major responsiveness factor to CBZ treatment. However, in the case of the other hepatic enzyme-inducing AEDs, PB, Basic et al. [40] showed that epileptic patients with CC homozygote had a significantly lower concentration of PB in the cerebrospinal fluid (CSF) than CT heterozygotes and TT homozygotes and they have had also reduced penetration of PB into the brain. Moreover, these patients had a higher seizure frequency than the others.

The other polymorphisms of *ABCB1/MDR1* C1236T and G2677 (A/T) are located in 12 and 21 exons, respectively. It has been showed that both and C3435T polymorphisms have an influence on the AEDs treatment and may be useful in predicting drug-resistant epilepsy [41]. However, the study of Haerian et al. [42] did not demonstrate association between C1236T, C3435T, and G2677 (A/T) and response to VPA treatment in patient with epilepsy. It was found that there were no differences regarding G2677 (A/T) genotype in CSF concentration of PB [40]. It was also showed that there was no correlation with seizure frequency [27].

The literature data did not indicate an important role of *ABCB1/MDR1* gene polymorphisms in epilepsy treatment. There is still not clear influence on P-gp expression and function in response to AED therapy. It seems that more precise knowledge of the frequency of *ABCB1/MDR1* polymorphisms may contribute to a better understanding of disease pathomechanism and its implications for the effective treatment.

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4. Genes important for homocysteine and ADMA metabolism and antiepileptic drug therapy in epilepsy

The polymorphisms in genes *MTHFR*, *MTR*, *MTHFD1*, and *CBS* involved in Hcy metabolism, as shown in **Figure 1**, are not unique to epilepsy and are also involved in heart diseases, neural tube defects, migraine, stroke, Parkinson's and Alzheimer's diseases, schizophrenia, and a few other disorders [43–45].

Hcy

Gene	Locus
MTHFR	1p36.3
MTR	1q43
MTRR	5p15.31
MTHFD1	14q24
CBS	21q22.3

ADMA

Gene	Locus
DDAH1	1p22
eNOS	7q36

Figure 1. Genes associated with homocysteine (Hcy) and asymmetric dimethylarginine (ADMA) metabolism.

MTHFR gene encodes methylenetetrahydrofolate reductase, MTHFR enzyme. The most common polymorphisms of this gene, C677T and A1298C, are associated with this enzyme deficiency. The *MTHFR* C677T polymorphism leads to the substitution of alanine for valine within the N-terminal catalytic domain of the enzyme. The mean activity of MTHFR enzyme in individuals carrying the CT genotype is 65%, while in TT variant carriers it reaches only 30%, both in comparison to the CC genotype. The *MTHFR* C677T TT is a cause of HHcy [46, 47]. Recent meta-analysis has shown that *MTHFR* C677T polymorphism is a risk factor for epilepsy [45]. The relation between C677T variants and HHcy in patients with epilepsy treated with AEDs was widely studied, but the results are ambiguous. The elevated Hcy level was observed among adult patients with CT and TT genotype [16, 48]. Moreover, it has been shown that children and young adults with TT genotype treated with AEDs have higher Hcy level and lower IQ score compared to those with CC genotype [49]. No contribution in HHcy was found in children treated with CBZ or VPA [50].

The *MTHFR* A1298C polymorphism leads to the substitution of glutamate for alanine within the C-terminal regulatory domain of the MTHFR enzyme. The mean activity of MTHFR protein in subjects with AC genotype is 70%. Furthermore, double heterozygotes of mentioned polymorphism in MTHFR (CT and AC) have an additional loss of activity [43]. Also the frequency of diplotype CT677/AC1298 was higher in epileptic patients than in controls and could be a risk factor for HHcy [51]. The effect of only A1298C polymorphism on Hcy level is minimal [43, 52]. According to meta-analysis the influence of *MTHFR* A1298C polymorphism on epilepsy remains inconsistent [45].

MTR gene encodes methionine synthase, MTR enzyme, while *MTRR* encodes methionine synthase reductase, MTRR enzyme. MTRR protein catalyzes the conversion of inactive form of MTR into active. Both enzymes, MTR and MTRR, are essential for Hcy remethylation to methionine. *MTR* A2756G polymorphism converts aspartic acid to glycine and in *MTRR* A66G methionine replaces isoleucine. It was observed that *MTR* A2756G and *MTRR* A66G polymorphisms are associated with increased Hcy level due to reduction in enzyme activity and may be risk factors for HHcy [53, 54]. On the other hand, other studies deny the influence of G allele of *MTR* A2756G on Hcy level, also in epileptic patients [16, 55]. The G allele of this polymorphism occurred more frequent in epileptics than in controls [16].

MTHFD1 gene encodes three-functional enzyme methylenetetrahydrofolate dehydrogenase/methyltetrahydrofolate cyclohydrolase/formyltetrahydrofolate synthetase, MTHFD1 that regulates the Hcy circulation. *MTHFD1* G1958A polymorphism results in the substitution of an arginine by a glutamine. According to Sniezawska et al. [16], the AA genotype was more frequent in epileptic patients than in controls, but only wild-type genotype was associated with increased Hcy level in AED-treated patients.

CBS gene encodes cystathionine beta-synthase, CBS, an enzyme responsible for Hcy degradation to cystathionine. Missense mutation in *CBS* gene leads to its deficiency and homocystinuria. Reversible cerebral white matter lesions were found in MRI among patients with CBS deficiency [56]. *CBS* T833C polymorphism results in substitution of threonine for isoleucine. Another widely studied polymorphism is 844ins68. The T833C/844ins68 polymorphism is associated with mild HHcy [57]. However, *CBS* T833C polymorphism increases the risk of HHcy in patients treated with AEDs. Moreover, among 20% of patients with TC genotype and increased level of Hcy, the seizures were observed [13].

What is interesting, polymorphisms in Hcy metabolism genes also influence the ADMA level. It was demonstrated that epileptic patients treated with AEDs with gene polymorphisms *MTHFR* (C677T), *MTR* (A2756G), and *MTHFD1* (G1958A) had increased level of ADMA [16].

DDAH1 gene encodes dimethylarginine dimethylaminohydrolase, DDAH enzyme that degrades ADMA, as shown in **Figure 1**. Isoform 1 of DDAH is highly expressed in brain. Lind et al. [58] showed that several polymorphisms in *DDAH1* gene are related to ADMA level, but not to endothelium-dependent vasodilatation. Another group identified 4-nucleotide deletion/insertion variant in the promoter region that leads to reduction of *DDAH1* transcription activity and mRNA level, which increase the ADMA concentration and is a risk factor for thrombosis stroke and coronary heart disease [59]. Polymorphisms in *DDAH1* gene have not been studied in epilepsy yet.

eNOS gene encodes endothelial isoform of nitric oxide synthase, an enzyme that can be inhibited by ADMA. It was observed that polymorphisms in *eNOS* can influence the ADMA level. Studies performed on rats with pilocarpine-induced status epileptics indicated that increased eNOS are related with DDAH1 overexpression via augmented ADMA inhibition [60]. Overexpression of DDAH1 protects against HHcy-induced cerebral vascular dysfunction [61]. The possible role for ADMA-DDAH pathway in neuronal activity modulation was

proposed due to increased ADMA concentration and DDAH1 expression in brain and spinal cord [62].

5. Antiepileptic drugs and other risk factors of vascular diseases

In the literature, there have been many publications indicating an increase in the plasma Hcy level in patients with epilepsy treated with AEDs [16, 63]. It has been showed that elevated level of Hcy above 15 μM (HHcy) in epileptic patients treated with AEDs may be associated with a number of clinical complications. Older publications indicate that HHcy may lead to three times increase the risk of myocardial infarction and twice increase the risk of stenosis of the coronary artery [64] and development of vascular disease [65, 66], neuropsychiatric [13] and considered a risk factor in seizure resistance and resistance to AEDs treatment [15].

Currently, it is believed that the impact of the AED risk of vascular disease depends on the type of drug used in patients with epilepsy. AEDs can be divided into two groups: hepatic enzyme-inducing AEDs (CBZ, PB, PHT) leading to an increase in cholesterol, low-density lipoprotein (LDL), total cholesterol, triglycerides, C-reactive protein (CRP), and Hcy level and hepatic enzyme-inhibiting AEDs (VPA) whose impact on the level of Hcy is not clear [16, 24, 67]. It is believed that the action of liver cytochrome P450-inducing AEDs leads to metabolic changes of macromolecular compounds, in particular lipids [68]. On the other hand, the liver cytochrome P450 inhibition of AEDs is not associated with metabolic changes but exhibits a proatherogenic effect by the impact on insulin resistance, body weight gain, and elevated oxidative stress [69]. At the same time, the share of inducing- and inhibiting AEDs in the pathogenesis of ischemic stroke and myocardial infarction is diverse.

Although, the study on a cohort of 252,407 patients aged above 18 years of age using inducing and inhibiting liver enzyme AEDs has shown that inducing AEDs do not lead to an increased risk of ischemic stroke and cause a small increase in myocardial infarction. While inhibiting AEDs also do not lead to an increased risk of ischemic stroke and lead to a reduction in the risk of myocardial infarction [24]. Moreover, according to Renoux et al. [24], only prolonged use of inducing AEDs led to an increase in the risk of myocardial infarction.

So far there is no effective therapy leading to a reduction in the level of Hcy and/or ADMA and other risk factors for vascular lesions, e.g., lipids and proteins following the AEDs used in epilepsy treatment. These issues require further study.

6. Summary

AEDs especially the older generation, including CBZ, PB, and PHT may lead to increased plasma Hcy concentrations and changes in the level of plasma ADMA in patients with epilepsy, as shown in **Figure 2**. It is believed that CBZ, PB, and PHT lead to elevated levels of plasma Hcy and/or ADMA by inducing liver enzyme. On the other hand, VPA does not lead to activation of liver enzymes, and its effect on plasma levels of Hcy and/or ADMA is varied.

Longer duration of the use of AEDs associated with impaired intestinal absorption of FA (CBZ, PB, and PHT) leads to an increase in incidents of myocardial infarction involving elevated levels of Hcy and/or ADMA or by other mechanisms of vascular lesions. However, VPA does not lead to an increase in incidents of ischemic stroke and leads to a decrease of myocardial infarction. It seems that the toxic effect of AEDs not only involves production of neurotoxic Hcy but also involves induction of apoptosis.

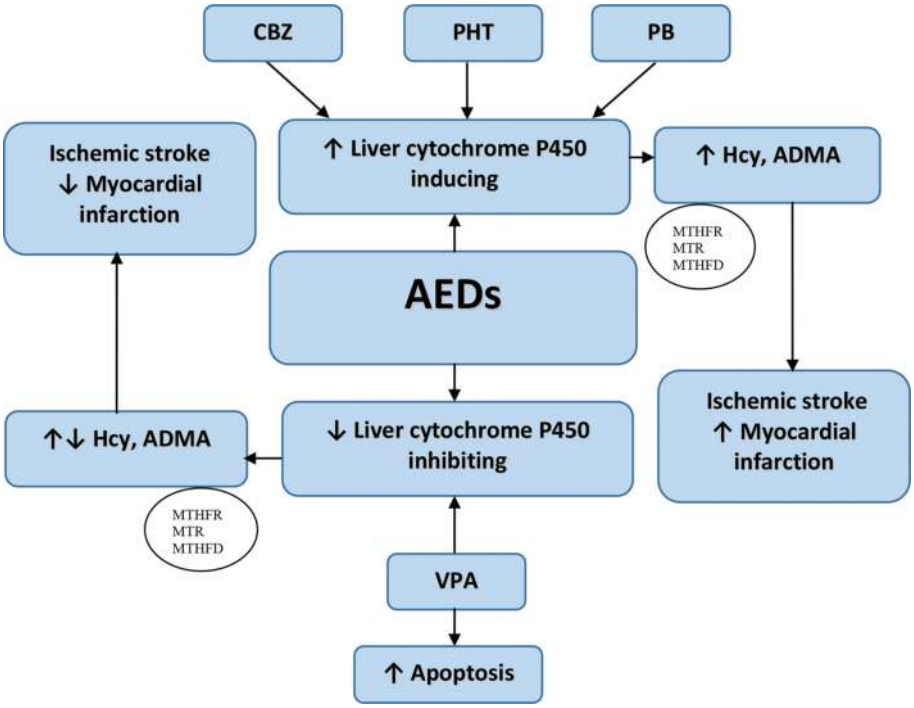

Figure 2. Antiepileptic drugs (AEDs) and risk factors of vascular diseases in epilepsy. Enzymes associated with Hcy-homocysteine metabolism, MTHFR, MTR, MTHFD1. ADMA, asymmetric dimethylarginine; CBZ, carbamazepine; VPA, valproic acid; PHT, phenytoin; PB, phenobarbital; ↑, increase; ↓, decrease level.

Supplementation with B-group vitamins and FA, and arginine may improve the effectiveness of AED therapy in patients with epilepsy.

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References

[1] Lagan-Jedrzejczyk U, Lianeri M, Kozubski W, Dorszewska J. Homocysteine and apoptotic factors in epileptic patients treated with antiepileptic drugs. In: Kilmer McCully, editor. Homocysteine: structure, biosynthesis and health implications. NOVA Sciences Publishers, Inc., NY, USA; 2014, p. 83–111.

[2] Karabiber H, Sonmezgoz E, Ozerol E, Yakinci C, Otlu B, Yologlu S. Effects of valproate and carbamazepine on serum levels of homocysteine, vitamin B12, and folic acid. Brain and Development; 2003, 25:113–115. DOI: 10.1016/S0387-7604(02)00163-8.

[3] Attilakos A, Papakonstantinou E, Schulpis K, Voudris K, Katsarou E, Mastroyianni S, Garoufi A. Early effect of sodium valproate and carbamazepine monotherapy on homocysteine metabolism in children with epilepsy. Epilepsy Research; 2006, 71:229–232. DOI: 10.1016/j.eplepsyres.2006.06.015.

[4] Hamed SA, Hamed EA, Hamdy R, Nabeshima T. Vascular risk factors and oxidative stress as independent predictors of asymptomatic atherosclerosis in adult patients with epilepsy. Epilepsy Research; 2007, 74:183–192. DOI: 10.1016/j.eplepsyres.2007.03.010.

[5] Badiou S, Breton H, Peyriere H, Charasson V, Crespel A, Gelisse P, Cristol JP, Hillaire-Buys D. Comparison of carbamazepine and oxcarbazepine effects on aminothiol levels. European Journal of Clinical Pharmacology; 2008, 64:83–87. DOI: 10.1007/s00228-007-0388-z.

[6] Gidal B, Tamura T, Hammer A, Vuong A. Blood homocysteine, folate and vitamin B-12 concentrations in patients with epilepsy receiving lamotrigine or sodium valproate for initial monotherapy. Epilepsy Research; 2005, 64:161–166. DOI: 10.1016/j.eplepsyres.2005.03.005.

[7] Boger RH, Bode-Boger SM, Sydow K, Heistad DD, Lentz SR. Plasma concentration of asymmetric dimethylarginine, an endogenous inhibitor of nitric oxide synthase is elevated in monkey with hyperhomocysteinemia or hypercholesterolemia. Arterio-

sclerosis, Thrombosis, and Vascular Biology; 2000, 20:1557–1564. DOI: 10.1161/01.ATV.20.6.1557.

[8] Verrotti A, Pascarella R, Trotta D, Giuva T, Morgese G, Chiarelli F. Hyperhomocysteinemia in children treated with sodium valproate and carbamazepine. Epilepsy Research; 2000, 41:253–257. DOI: 10.1016/S0920-1211(00)00150-9.

[9] Yoo JH, Hong SB. A common mutation in the methylenetetrahydrofolate reductase gene is a determinant of hyperhomocysteinemia in epileptic patients receiving anticonvulsants. Metabolism; 1999, 48:1047–1051. DOI: 10.1016/S0026-0495(99)90204-4.

[10] Apeland T, Mansoor MA, Strandjord RE. Antiepileptic drugs as independent predictors of plasma total homocysteine levels. Epilepsy Research; 2001, 47:27–35. DOI: 10.1016/S0920-1211(01)00288-1.

[11] Unal O, Deda G, Teber S, Ertem M, Akar N. Thrombophilic risk factors in epileptic children treated with valproic acid. Pediatric Neurology; 2009, 40:102–106. DOI: 10.1016/j.pediatrneurol.2008.10.005.

[12] Sener U, Zorlu Y, Karaguzel O, Ozdamar O, Coker I, Topbas M. Effects of common antiepileptic drug monotherapy on serum levels of homocysteine, vitamin B12, folic acid and vitamin B6. Seizure; 2006, 15:79–85. DOI: 10.1016/j.seizure.2005.11.002.

[13] Siniscalchi A, Mancuso F, Gallelli L, Ibbadu G, Mercuri NB, De Sarro G. Increase in plasma homocysteine levels induced by drug treatments in neurologic patients. Pharmacological Research; 2005, 52: 367–375. DOI: 10.1016/j.phrs.2005.05.013.

[14] Yoo JH, Lee SC. Elevated levels of plasma homocyst(e)ine and symmetric dimethylarginine in elderly patients with stroke. Atherosclerosis; 2001, 158:425–430. DOI: 10.1016/S0021-9150(01)00444-0.

[15] Kubova H, Folbergrova J, Mares P. Seizures induced by homocysteine in rats during ontogenesis. Epilepsia; 1995, 36:750–756. DOI: 10.1111/j.1528-1157.1995.tb01611.x.

[16] Sniezawska A, Dorszewska J, Rozycka A, Przedpelska-Ober E, Lianeri M, Jagodzinski PP, Kozubski W. MTHFR, MTR, and MTHFD1 gene polymorphisms compared to homocysteine and asymmetric dimethylarginine concentrations and their metabolites in epileptic patients treated with antiepileptic drugs. Seizure; 2011, 20:533–540. DOI: 10.1016/j.seizure.2011.04.001.

[17] Ozdemir O, Yakut A, Dinleyici EC, Aydogdu SD, Yarar C, Colak O. Serum asymmetric dimethylarginine (ADMA), homocysteine, vitamin B(12), folate levels, and lipid profiles in epileptic children treated with valproic acid. European Journal of Pediatrics; 2011, 170:873–877. DOI: 10.1007/s00431-010-1366-5.

[18] Kielstein JT, Bode-Boger SM, Frolich JC, Ritz E, Haller H, Fliser D. Asymmetric dimethylarginine, blood pressure, and renal perfusion in elderly subjects. Circulation; 2003, 107:1891–1895. DOI: 10.1161/01.CIR.0000060496.23144.A7.

[19] Chan JR, Boger RH, Bode-Boger SM, Tangphao O, Tsao PS, Blaschke TF, Cooke JP. Asymmetric dimethylarginine increases mononuclear cell adhesiveness in hypercholesterolemic humans. Arteriosclerosis, Thrombosis, and Vascular Biology; 2000, 20:1040–1046. DOI: 10.1161/01.CIR.0000060496.23144.A7.

[20] Cooke JP, Oka RK. Atherogenesis and the arginine hypothesis. Current Atherosclerosis Reports; 2001, 3:252–259.

[21] Kielstein JT, Bode-Boger SM, Frolich JC, Haller H, Boger RH. Relationship of asymmetric dimethylarginine to dialysis treatment and atherosclerosis disease. Kidney International; 2001, 78:9–13. DOI: 10.1046/j.1523-1755.2001.59780009.x.

[22] Miyazaki H, Matsuoka H, Cooke JP, Usui M, Ueda S, Okuda S, Imaizumi T. Endogenous nitric oxide synthase inhibitor: a novel marker of atherosclerosis. Circulation; 1999, 99:1141–1146. DOI: 10.1161/01.CIR.99.9.1141.

[23] Olesen JB, Abildstrøm SZ, Erdal J, Gislason GH, Weeke P, Andersson C, Torp-Pedersen C, Hansen PR. Effects of epilepsy and selected antiepileptic drugs on risk of myocardial infarction, stroke, and death in patients with or without previous stroke: a nationwide cohort study. Pharmacoepidemiology and Drug Safety; 2011, 20:964–971. DOI: 10.1002/pds.2186.

[24] Renoux C, Dell'Aniello S, Saarela O, Filion KB, Boivin JF. Antiepileptic drugs and the risk of ischaemic stroke and myocardial infarction: a population-based cohort study. BMJ Open; 2015, 5:e008365. DOI: 10.1136/bmjopen-2015-008365.

[25] Vyas MV, Davidson BA, Escalaya L, Costella J, Saposnik G, Burneo JG. Antiepileptic drug use for treatment of epilepsy and dyslipidemia: systematic review. Epilepsy Research; 2015, 113:44–67. DOI: 10.1016/j.eplepsyres.2015.03.002.

[26] Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A, Cross JH, Elger CE, Engel J Jr, Forsgren L, French JA, Glynn M, Hesdorffer DC, Lee BI, Mathern GW, Moshé SL, Perucca E, Scheffer IE, Tomson T, Watanabe M, Wiebe S. ILAE official report: a practical clinical definition of epilepsy. Epilepsia; 2014, 55:475–482. DOI: 10.1111/epi.12550.

[27] Lagan-Jedrzejczyk U, Oczkowska A, Florczak A, Florczak-Wyspianska J, Karczewski J, Swiejkowska A, Wiktorowicz K, Przedpelska-Ober E, Kozubski W, Dorszewska J. ABCB1/MDR1 gene polymorphisms and the level of apoptotic factors in epilepsy patients treated with antiepileptic drugs. European Journal of Neurology. 2015, 22:Suppl 1, 341.

[28] Striano P, Vari MS, Mazzocchetti C, Verrotti A, Zara F. Management of genetic epilepsies: from empirical treatment to precision medicine. Pharmacological Research; 2016, 11:426–429. DOI: 10.1016/j.phrs.2016.04.006.

[29] Florczak A, Florczak J, Dorszewska J. Antiepileptic drugs and apoptosis. Farmakoterapia w Psychiatrii Neurologii; 2010, 26:145–152 (in Polish).

[30] Santulli L, Coppola A, Balestrini S, Striano S. The challenges of treating epilepsy with 25 antiepileptic drugs. Pharmacological Research; 2016, 107:211–219. DOI: 10.1016/j.phrs.2016.03.016.

[31] Foldvary-Schaefer N, Fong JS, Morrison S, Wang L, Bena J. Lacosamide tolerability in adult patients with partial-onset seizures: impact of planned reduction and mechanism of action of concomitant antiepileptic drugs. Epilepsy Behavior; 2016, 57:155–160. DOI: 10.1016/j.yebeh.2016.02.007.

[32] Pack AM. Perampanel: another choice for patients with idiopathic generalized epilepsy who have tonic-clonic seizures. Epilepsy Currents; 2016, 16:27–28. DOI: 10.5698/1535-7597-16.1.27.

[33] Lynch BA, Lambeng N, Nocka K, Kensel-Hammes P, Bajjalieh SM, Matagne A, Fuks B. The synaptic vesicle protein SV2A is the binding site for the antiepileptic drug levetiracetam. Proceedings of the National Academy of Science of United States of America. 2004, 101:9861–9866. DOI: 10.1073/pnas.0308208101.

[34] Strickler SM, Dansky LV, Miller MA, Seni MH, Andermann E, Spielberg SP. Genetic predisposition to phenytoin-induced birth defects. Lancet; 1985, 2:746–749. DOI: 10.1016/S0140-6736(85)90629-4.

[35] Holmes LB, Harvey EA, Coull BA, Huntington KB, Khoshbin S, Hayes AM, Ryan LM. The teratogenicity of anticonvulsant drugs. New England Journal of Medicine; 2001, 344:1132–1138. DOI: 10.1056/NEJM200104123441504.

[36] Gidal BE. P-glycoprotein expression and pharmacoresistant epilepsy: cause or consequence? Epilepsy Currents; 2014, 14:136–138. DOI: 10.5698/1535-7597-14.3.136.

[37] Siddiqui A, Kerb R, Weale ME, Brinkmann U, Smith A, Goldstein DB, Wood NW, Sisodiya SM. Association of multidrug resistance in epilepsy with a polymorphism in the drug-transporter gene ABCB1. New England Journal of Medicine; 2003, 348:1442–1448. DOI: 10.1056/NEJMoa021986.

[38] Vahab SA, Sen S, Ravindran N, Mony S, Mathew A, Vijayan N, Nayak G, Bhaskaranand N, Banerjee M, Satyamoorthy K. Analysis of genotype and haplotype effects of ABCB1 (MDR1) polymorphisms in the risk of medically refractory epilepsy in an Indian population. Drug Metabolism and Pharmacokinetics; 2009, 24: 255–260. DOI: 10.2133/dmpk.24.255.

[39] Sterjev Z, Trencevska GK, Cvetkovska E, Petrov I, Kuzmanovski I, Ribarska JT, Nestorovska AK, Matevska N, Naumovska Z, Jolevska-Trajkovic S, Dimovski A, Suturkova L. Mint. The association of C3435T single-nucleotide polymorphism, Pgp-glycoprotein gene expression levels and carbamazepine maintenance dose in patients with epilepsy. Neuropsychiatr Disease and Treatment; 2012, 8:191–196. DOI: 10.2147/NDT.S28285.

[40] Basic S, Hajnsek S, Bozina N, Filipcic I, Sporis D, Mislov D, Posavec A. The influence of C3435T polymorphism of ABCB1 gene on penetration of phenobarbital across the

blood–brain barrier in patients with generalized epilepsy. Seizure; 2008, 17:524–530. DOI: 10.1016/j.seizure.2008.01.003.

[41] Qiang LU, Liwen WU, Liri JIN, Qi XU, Yan SHEN. Association analysis of a polymorphism of MDR1 Gene and refractory temporal lobe epilepsy in a Chinese population. Neurology Asia; 2007, 12:94–95.

[42] Haerian BS, Lim KS, Tan HJ, Mohamed EH, Tan CT, Raymond AA, Wong CP, Wong SW, Omar H, Roslan H, Mohamed Z. Association between ABCB1 polymorphism and response to sodium valproate treatment in Malaysian epilepsy patients. Epileptic Disorder; 2011, 13:65–75. DOI: 10.1684/epd.2011.0419.

[43] Weisberg I, Tran P, Christensen B, Sibani S, Rozen R. A second genetic polymorphism in methylenetetrahydrofolate reductase (MTHFR) associated with decreased enzyme activity. Molecular Genetics and Metabolism; 1998, 64:169–172.

[44] Casas JP, Bautista LE, Smeeth L, Sharma P, Hingorani AD. Homocysteine and stroke: evidence on a causal link from Mendelian randomisation. Lancet; 2005, 365:224–232. DOI: 10.1016/S0140-6736(05)17742-3.

[45] Wu YL, Yang HY, Ding XX, Zhao X, Chen J, Bi P, Sun YH. Association between methylenetetrahydrofolate reductase C677T polymorphism and epilepsy susceptibility: a meta-analysis. Seizure; 2014, 23:411–416. DOI: 10.1016/j.seizure.2014.01.018.

[46] Liu A, Menon S, Colson NJ, Quinlan S, Cox H, Peterson M, Tiang T, Haupt LM, Lea RA, Griffiths LR. Analysis of the MHTFR C677T variant with migraine phenotypes. BMC Research Notes; 2010, 3:213–218. DOI: 10.1186/1756-0500-3-213.

[47] Schürks MM, Rist PM, Kurth T. MTHFR 677C>T and ACE D/I polymorphisms in migraine: a systematic review and meta-analysis. Headache; 2010, 50:588–599. DOI: 10.1111/j.1526-4610.2009.01570.x.

[48] Belcastro V, Striano P, Gorgone G, Costa C, Ciampa C, Caccamo D, Pisani LR, Oteri G, Marciani MG, Aguglia U, Striano S, Ientile R, Calabresi P, Pisani F. Hyperhomocysteinemia in epileptic patients on new antiepileptic drugs. Epilepsia 2010;51:274–279. DOI: 10.1111/j.1528-1167.2009.02303.x.

[49] Di Rosa G, Lenzo P, Parisi E, Neri M, Guerrera S, Nicotera A, Alibrandi A, Germanò E, Caccamo D, Spanò M, Tortorella G. Role of plasma homocysteine levels and MTHFR polymorphisms on IQ scores in children and young adults with epilepsy treated with antiepileptic drugs. Epilepsy Behavior; 2013, 29:548–551. DOI: 10.1016/j.yebeh.2013.09.034.

[50] Vurucu S, Demirkaya E, Kul M, Unay B, Gul D, Akin R, Gokçay E. Evaluation of the relationship between C677T variants of methylenetetrahydrofolate reductase gene and hyperhomocysteinemia in children receiving antiepileptic drug therapy. Progress in Neuro-Psychopharmacology & Biological Psychiatry; 2008, 32:844–848. DOI: 10.1016/j.pnpbp.2007.12.018.

[51] Caccamo D, Condello S, Gorgone G, Crisafulli G, Belcastro V, Gennaro S, Striano P, Pisani F, Ientile R. Screening for C677T and A1298C MTHFR polymorphisms in patients with epilepsy and risk of hyperhomocysteinemia. Neuromolecular Medicine; 2004, 6: 117–126.

[52] Meisel C, Cascorbi I, Gerloff T, Stangl V, Laule M, Müller JM, Wernecke KD, Baumann G, Roots I, Stangl K. Identification of six methylenetetrahydrofolate reductase (MTHFR) genotypes resulting from common polymorphisms: impact on plasma homocysteine levels and development of coronary artery disease. Atherosclerosis; 2001, 154:651–658. DOI: 10.1016/S0021-9150(00)00679-1.

[53] Laraqui A, Allami A, Carrié A, Coiffard AS, Benkouka F, Benjouad A, Bendriss A, Kadiri N, Bennouar N, Benomar A, Guedira A, Raisonnier A, Fellati S, Srairi JE, Benomar M. Influence of methionine synthase (A2756G) and methionine synthase reductase (A66G) polymorphisms on plasma homocysteine levels and relation to risk of coronary artery disease. Acta Cardiologica; 2006, 61:51–61. DOI: 10.2143/AC.61.1.2005140.

[54] Kluijtmans LA, Young IS, Boreham CA, Murray L, McMaster D, McNulty H, Strain JJ, McPartlin J, Scott JM, Whitehead AS. Genetic and nutritional factors contributing to hyperhomocysteinemia in young adults. Blood; 2003, 101:2483–2488.

[55] Klerk M, Lievers KJ, Kluijtmans LA, Blom HJ, den Heijer M, Schouten EG, Kok FJ, Verhoef P. The 2756A>G variant in the gene encoding methionine synthase: its relation with plasma homocysteine levels and risk of coronary heart disease in a Dutch case–control study. Thrombosis Research; 2003, 110:87–91. DOI: 10.1016/S0049-3848(03)00341-4.

[56] Sasai H, Shimozawa N, Asano T, Kawamoto N, Yamamoto T, Kimura T, Kawamoto M, Matsui E, Fukao T. Successive MRI findings of reversible cerebral white matter lesions in a patient with cystathionine β-synthase deficiency. Tohoku Journal of Experimental Medicine; 2015, 237:323–327. DOI: 10.1620/tjem.237.323.

[57] Gaustadnes M, Ingerslev J, Rütiger N. Prevalence of congenital homocystinuria in Denmark. New England Journal of Medicine; 1999, 340:1513. DOI: 10.1056/NEJM199905133401915.

[58] Lind L, Ingelsson E, Kumar J, Syvänen AC, Axelsson T, Teerlink T. Genetic variation in the dimethylarginine dimethylaminohydrolase 1 gene (DDAH1) is related to asymmetric dimethylarginine (ADMA) levels, but not to endothelium-dependent vasodilation. Vascular Medicine; 2013, 18:192–199. DOI: 10.1177/1358863X13496488.

[59] Ding H, Wu B, Wang H, Lu Z, Yan J, Wang X, Shaffer JR, Hui R, Wang DW. A novel loss-of-function DDAH1 promoter polymorphism is associated with increased susceptibility to thrombosis stroke and coronary heart disease. Circulation Research; 2010, 106:1145–1152. DOI: 10.1161/CIRCRESAHA.109.215616.

[60] Hirotsu C, Matos G, Tufik S, Andersen ML. Changes in gene expression in the frontal cortex of rats with pilocarpine-induced status epilepticus after sleep deprivation. Epilepsy Behavior; 2013, 27:378–384. DOI: 10.1016/j.yebeh.2013.02.024.

[61] Rodionov RN, Dayoub H, Lynch CM, Wilson KM, Stevens JW, Murry DJ, Kimoto M, Arning E, Bottiglieri T, Cooke JP, Baumbach GL, Faraci FM, Lentz SR. Overexpression of dimethylarginine dimethylaminohydrolase protects against cerebral vascular effects of hyperhomocysteinemia. Circulation Research; 2010, 106:551–558. DOI: 10.1161/CIRCRESAHA.109.200360.

[62] Greco R, Ferrigno A, Demartini C, Zanaboni A, Mangione AS, Blandini F, Nappi G, Vairetti M, Tassorelli C. Evaluation of ADMA-DDAH-NOS axis in specific brain areas following nitroglycerin administration: study in an animal model of migraine. Journal of Headache Pain; 2015, 16:560. DOI: 10.1186/s10194-015-0560-2.

[63] Bochyńska A, Lipczyńska-Łojkowska W, Gugała-Iwaniuk M, Lechowicz W, Restel M, Graban A, Lipska B, Ryglewicz D. The effect of vitamin B supplementation on homocysteine metabolism and clinical state of patients with chronic epilepsy treated with carbamazepine and valproic acid. Seizure; 2012, 21:276–281. DOI: 10.1016/j.seizure.2012.01.013.

[64] Selhub J, Jacques PF, Bostom AG, D'Agostino RB, Wilson PW, Belanger AJ, O'Leary DH, Wolf PA, Schaefer EJ, Rosenberg IH. Association between plasma homocysteine concentrations and extracranial carotid-artery stenosis. New England Journal of Medicine; 1995, 332:286–291. DOI: 10.1056/NEJM199502023320502.

[65] Verrotti A, Domizio S, Angelozzi B, Sabatino G, Morgese G, Chiarelli F. Changes in serum lipids and lipoproteins in epileptic children treated with anticonvulsants. Journal of Paediatrics and Child Health; 1997, 33:242–245. DOI: 10.1111/j.1440-1754.1997.tb01588.x.

[66] Tan TY, Lu CH, Chuang HY, Lin TK, Liou CW, Chang WN, Chuang YC. Long-term antiepileptic drug therapy contributes to the acceleration of atherosclerosis. Epilepsia; 2009, 50:1579–1586. DOI: 10.1111/j.1528-1167.2009.02024.x.

[67] Katsiki N, Mikhailidis DP, Nair DR. The effects of antiepileptic drugs on vascular risk factors: a narrative review. Seizure; 2014, 23:677–684. DOI: 10.1016/j.seizure.2014.05.011.

[68] Mintzer S. Metabolic consequences of antiepileptic drugs. Current Opinion in Neurology; 2010, 23:164–169. DOI: 10.1097/WCO.0b013e32833735e7.

[69] Verrotti A, Scardapane A, Franzoni E, Manco R, Chiarelli F. Increased oxidative stress in epileptic children treated with valproic acid. Epilepsy Research; 2008, 78:171–177. DOI: 10.1016/j.eplepsyres.2007.11.005.