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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 (OXCZ), 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, OXCZ, 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.

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 | | ADMA | |
|---------------|---------|--------------|-------|
| Gene | Locus | Gene | Locus |
| <i>MTHFR</i> | 1p36.3 | <i>DDAH1</i> | 1p22 |
| <i>MTR</i> | 1q43 | <i>eNOS</i> | 7q36 |
| <i>MTRR</i> | 5p15.31 | | |
| <i>MTHFD1</i> | 14q24 | | |
| <i>CBS</i> | 21q22.3 | | |

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.

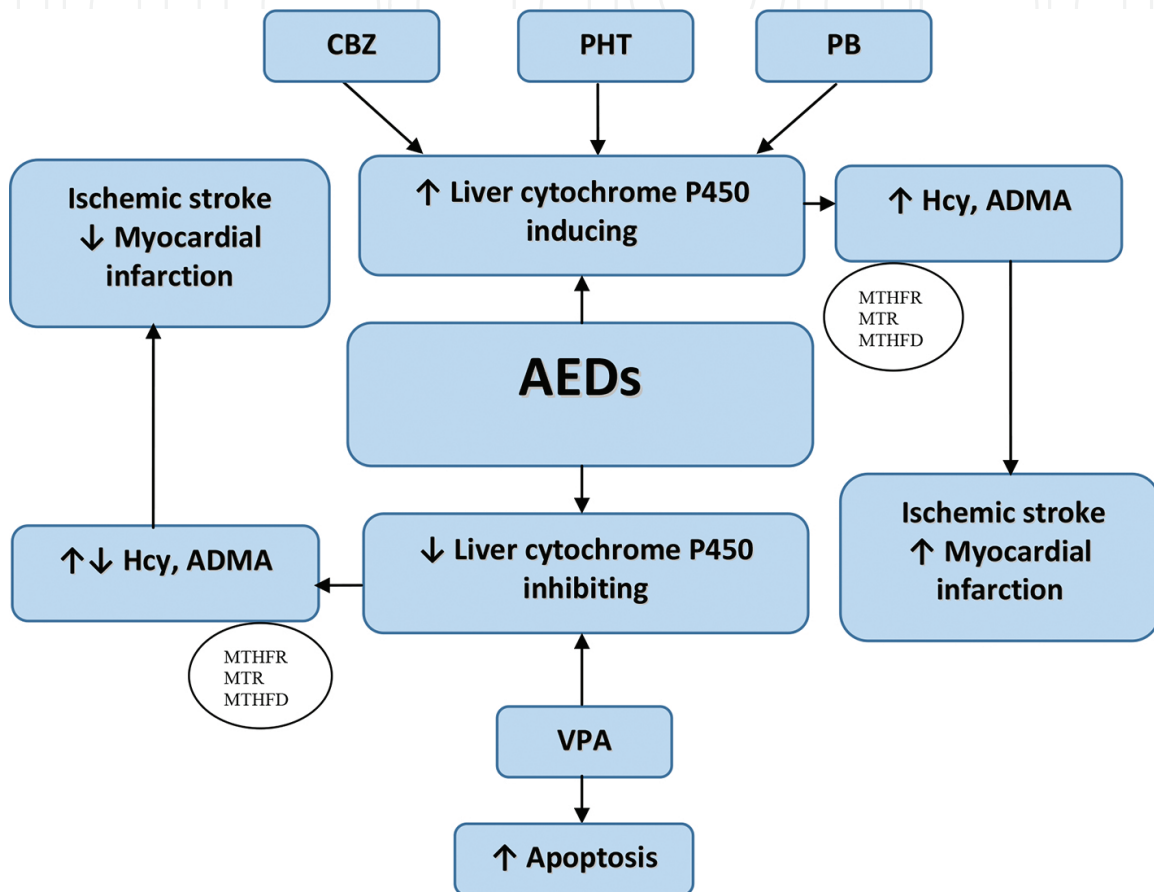


Figure 2. Antiepileptic drugs (AEDs) and risk factors of vascular diseases in epilepsy. Enzymes associated with Hcy-homocysteine metabolism, MTHFR, MTR, MTHFD1. ADMA, asymmetric dimethylarginine; CBZ, carbamazepine; VPA, valproic acid; PHT, phenytoin; PB, phenobarbital; ↑, increase; ↓, decrease level.

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

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