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Review

Atherosclerotic risk among children taking antiepileptic drugs

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Abstract:
Epilepsy is a common chronic neurological disorder that requires long-term or sometimes lifetime therapy. Recent evidence indicates that prolonged use of antiepileptic drugs (AEDs) might modify some vascular risk factors; however, the influence of AED therapy on the development of atherosclerosis has been the subject of controversy. Some epidemiological studies have reported a higher prevalence of ischemic vascular disease among epileptic patients on AEDs, while in other studies the mortality due to atherosclerosis-related cardiovascular disease in treated epileptics has been observed to be lower than in the general population. The etiology of atherosclerosis-related vascular diseases in epileptic patients has not been fully clarified. Since atherosclerotic vascular alterations may start early in life, this review focuses on major atherogenic risk factors among epileptic children, including altered metabolism of homocysteine, disordered lipid profiles, and increased lipoprotein (a) serum levels, as well as thyroid hormone deficiency with special concern for clinical implications.

Key words:
epileptic children, antiepileptic drugs, atherosclerosis, lipids, homocysteine

Abbreviations: AEDs – antiepileptic drugs, ALP – alkaline phosphatase, CBZ – carbamazepine, CVD – cardiovascular disease, EIAEDs – enzyme-inducing antiepileptic drugs, FT4 – free thyroxine, GGT – gamma-glutamyl transferase, Hcy – homocysteine, HDL-c – high-density lipoprotein cholesterol, LDL-c – low-density lipoprotein cholesterol, LME – liver microsomal enzymes, Lp(a) – lipoprotein (a), LTG – lamotrigine, MTHFR – methylenetetrahydrofolate reductase, OXC – oxcarbazepine, p-tHcy – plasma total homocysteine, PB – phenobarbital, ROS – reactive oxygen species, SH – subclinical hypothyroidism, T3 – triiodothyronine, T4 – thyroxine, TC – total cholesterol, TG – triglycerides, TPM – topiramate, TSH – thyrotropin, VLDL-ApoB – very low-density lipoprotein-apolipoprotein B, VPA – valproate

Introduction

Atherosclerosis is the leading cause of death in the developed world, although the true frequency is difficult to accurately determine because it is a predominantly asymptomatic condition [7]. It is a disease of large- and medium-sized arteries, and is characterized by endothelial dysfunction, vascular inflammation, and the presence of buildup (fatty streaks) consisting of lipids, calcium, and cellular debris within the intima of the vessel wall.

Tab. 1. Effect of antiepileptic drugs on serum lipids

Study	Drugs	TC	LDL-c	TG	HDL-c	Details
Eiris et al. [28]	CBZ	▲	▲	–	▲	320 children and adolescents with epilepsy (129 on CBZ, 64 on PB, 127 on VPA)
	PB	▲	▲	–	–	
	VPA	▼	▼	–	–	
Franzoni et al. [38]	CBZ, PB, PHT	▲	ND	–	–	208 children with epilepsy (78 on CBZ, 40 on PB, 17 on PHT, 60 on VPA)
	VPA	▼	ND	–	–	
Eiris et al. [29]	CBZ	▲	▲	–	▲	119 children with epilepsy (58 on CBZ, 22 on PB, 39 on VPA)
	PB	▲	–	–	▲	
	VPA	▼	▼	–	–	
Verrotti et al. [130]	CBZ	▲	▲	▲	▲	114 children with epilepsy (35 on CBZ, 34 on PB, 45 on VPA)
	PB*	▲	▲	▼	–	
	VPA	–	▼	▼	▲	
Sonmez et al. [111]	CBZ	–	–	–	–	64 children with epilepsy (22 on CBZ, 18 on PB, 24 on VPA)
	PB	▲	▲	–	▲	
	VPA	–	–	–	–	
Yilmaz et al. [136]	CBZ	▲	▲	▲	▲	53 children with epilepsy (21 on CBZ, 14 on PB, 18 on VPA)
	PB	▲	–	–	–	
	VPA	–	–	–	–	
Sözüer et al. [112]	CBZ	▲	▲	–	–	39 children with epilepsy (23 on CBZ, 16 on VPA)
	VPA	–	–	–	–	
Demircioğlu et al. [25]	CBZ	▲	▲	–	–	38 children with epilepsy (31 on CBZ, 7 on VPA)

▲– increase, ▼ – decrease, – – changes were not statistically significant, ND – not determined, * normalization of all parameters after the end of therapy. CBZ – carbamazepine, PB – phenobarbital, PHT – phenytoin, VPA – valproic acid, TC – total cholesterol, LDL-c – low-density lipoprotein cholesterol, TG – triglycerides, HDL-c – high-density lipoprotein cholesterol

Some epidemiological studies have indicated that the prevalence and death rates from atherosclerosis-related cardiovascular disease (CVD) are slightly elevated in adult epileptic patients taking antiepileptic drugs (AEDs) [1, 31, 41]. However, other studies have come to the contrasting conclusion that mortality due to ischemic heart disease appears to be lower in treated epileptics than in the general population [69, 90]. Epidemiological studies in adults with epilepsy have found that the risk for ischemic heart disease is increased by 34%, and the risk for fetal CVD is increased by 68% [31, 41]. In a cohort of 9000 patients, once hospitalized for epilepsy, a cause-specific mortality assessment found a standardized mortality ratio of 2.5 for ischemic heart disease and 3.5 for stroke [92]. However, in a study of 30–50 year old males, no difference was found in the total coronary risk profile between those with epilepsy and controls [91]. Thus, the influence of AED therapy on the development of atherosclerosis has been the subject of controversy, although recent evidence indicates that prolonged antiepileptic treatment might modify some vascular risk factors [31].

It has been well documented that atherosclerotic vascular alterations may start early in life and progress with age [122]. The first signs of hyperlipidemia can be detected in childhood [117], and fatty streaks,

which are the earliest pathologic lesions of the atherogenic process, can be observed in the aorta and coronary arteries of individuals by the age of 20 [7].

Thus, recent studies have focused on the incidence of vascular risk factors and a higher risk of atherosclerosis development among children with epilepsy; however, this link has not yet been firmly established and remains controversial [25, 59, 98, 122, 131].

Epilepsy is a relatively frequent chronic disorder in childhood and often requires lifelong therapy. It is widely suggested that either epilepsy itself or the prolonged administration of some AEDs is associated with the undesirable metabolic side effects implicated in dysfunction of the vessel wall. This dysfunction can promote atherogenesis and ultimately result in occlusive vascular diseases such as stroke, myocardial infarction, and peripheral arterial disease [1, 21, 45, 47, 78]. The study conducted by de Chadarevian et al. [23] demonstrated the presence of atherosclerotic changes at autopsy of an 11-year-old child who died following a status epilepticus who had been treated with carbamazepine (CBZ) for long-standing epilepsy. The child had hypercholesterolemia and an over 40% reduction in the vessel lumen diameter due to marked intimal proliferation and accumulation of foam cells in the coronary arteries [23].

This review focuses on atherogenic metabolic alterations among epileptic children, including altered metabolism of homocysteine (Hcy), disordered lipid profiles, and increased lipoprotein (a) serum level, as well as thyroid hormone deficiency with special concern for clinical implications.

Lipid profile

Elevated total cholesterol (TC), i.e., hypercholesterolemia, as well as increased low-density lipoprotein cholesterol (LDL-c) and triglyceride (TG) levels are well-known atherogenic risk factors, whereas a protective role has been established for high-density lipoprotein cholesterol (HDL-c) [44].

Several studies have reported that epileptic children demonstrate alterations in their lipid profile, apolipoprotein metabolism, and atherogenic ratios during long-term treatment with AEDs, particularly with enzyme-inducing antiepileptic drugs (EIAEDs) including CBZ and phenobarbital (PB) [25, 29, 38, 111, 130] (Tab. 1). However, the published data are conflicting, and little is known about the precise nature and underlying mechanisms of such changes.

CBZ is among the drugs of choice in the treatment of epilepsy in pediatric patients [25]. Prolonged treatment with CBZ has been shown to shift serum lipid levels to resemble an atherogenic profile with increased TC [25, 28, 29, 50, 112, 130, 136], LDL-c [25, 28, 29, 112, 130, 136], and TG levels [130, 136]. On the other hand, the majority of studies have reported an increase in serum levels of protective HDL-c in CBZ-treated children with epilepsy [28, 29, 50, 98, 130, 136], or have failed to demonstrate any change in HDL-c during treatment [25, 38, 111, 112].

The influence of PB on lipid profile has also been extensively investigated in epileptic children, with a number of studies showing increased TC [24, 28, 29, 38, 98, 130, 136], LDL-c [28, 111, 128, 130], and HDL-c values [29, 50, 111], as well as lower TG levels [130]. In a comparative study, Sonmez et al. [111] demonstrated significant increases in TC, LDL-c, and HDL-c levels in pediatric patients treated with PB, whereas the changes in these parameters in children treated with CBZ were not statistically significant. In contrast, Castro-Gago et al. [14] reported high plasma levels of LDL-c in 20% of subjects receiving PB and in 25% of patients receiving CBZ (as opposed to 9% of control subjects). However, these changes in lipid metabolism seem to be transient, and they reverse in children put on a low-fat diet and after the end of the therapy [14, 29, 130].

The influence of CBZ and PB on serum lipids among epileptic children seems to be related to the liver microsomal enzyme (LME)-inducing properties of these drugs [14, 25]. CBZ, PB, and other EIAEDs are principally metabolized by the hepatic cytochrome P450 enzyme system. This system also catalyzes the transformation of cholesterol into biliary acids. Thus, during long-term treatment, EIAEDs might compete with cholesterol in the utilization of the P450 enzyme system, leading to a reduced transformation rate of cholesterol into bile acids with increased TC serum levels [14, 25, 38]. A direct link between the serum anticonvulsant level and the extent of LME activation has been demonstrated [80, 81]. The inductive effect of CBZ on the P450 enzyme system is thought to be reflected by the increase in the serum levels of hepatic enzymes, such as gamma-glutamyl transferase (GGT) and alkaline phosphatase (ALP) [10, 25, 111]. Demircioğlu et al. [25] documented in-

creased levels of both GGT and ALP in epileptic children during CBZ treatment, with a peak in the second month of therapy, and a positive correlation with TC and LDL serum levels. However, other LMEs involved in lipid metabolism may also be possible targets for EIAEDs. Recently, overexpression of the microsomal triglyceride transfer protein has been found to increase the liver secretion of VLDL-ApoB (very low-density lipoprotein – apolipoprotein B) and VLDL-triglycerides, but whether CBZ might affect these processes remains to be established [10].

The other AED commonly used for managing childhood epilepsy is valproate (VPA) [25]. In a number of studies, decreased values of TC [24, 28, 29, 38], LDL-c [28, 29, 128, 130], and TG [120, 130] have been reported in children treated with VPA. On the other hand, some investigators have found that VPA therapy did not affect the LDL-c level, while levels were significantly increased in patients treated with CBZ [25, 112, 136]. In terms of HDL-c levels, either higher [24, 50, 128, 130] or similar values [25, 38, 98, 111, 112] have been observed among VPA-treated pediatric patients and control groups. Moreover, it has been found that both TC/HDL-c and LDL-c/HDL-c ratios remained unchanged, or were only slightly decreased in pediatric patients on VPA [14, 25, 28, 29], while in patients on CBZ, these ratios increased [25, 112]. These ratios of cholesterol fractions are thought to be better predictors for the development of atherosclerosis. Decreased values of TC/HDL-c and LDL-c/HDL-c are powerful protective factors against atherosclerosis, while elevated ratios increase the risk [25, 45]. The mechanism for the VPA effect on the serum lipid profile remains uncertain, since VPA does not induce LME activation [14, 25]. A possible explanation for the altered lipid metabolism seen during VPA therapy was reported by Horie and Suga [58], who observed enhanced hepatic peroxisomal β-oxidation leading to a decrease in LDL-c and apolipoprotein B in rats treated with VPA. Another plausible mechanism is that weight gain induced by VPA might give rise to insulin resistance, leading eventually to hyperinsulinemia and dislipidemia [62, 88].

Recently, it has been reported that newer AEDs have a minor impact on vascular risk factors, but only a few studies of their effect on the lipid profile have been performed so far [64, 70, 109]. Switching from CBZ to oxcarbazepine (OXC) has been reported to have a favorable effect on the serum lipid profile in adults [64], and Franzoni et al. [39] have recently demonstrated that OXC does not alter the serum lipid profile in children when administrated as the first AED. Similarly, in epileptic children treated with topiramate (TPM), the reduction in TC and TG levels between baseline and after 12 months of treatment was not significant [37].

On the basis of the reviewed studies, it may be concluded that children treated with CBZ or PB seem to be at a higher atherogenic risk than healthy controls. The evaluation of this risk in children receiving VPA is controversial since reports are conflicting.

Children with either high TC and LDL-c levels or low values of HDL-c should be put on a dietary regimen like the current dietary recommendation for the treatment of hyperlipidemia. Since modifications in the lipid profile induced by AEDs seem to be transient and reversible, monitoring may be limited to the duration of therapy [14].

Lipoprotein (a)

Lipoprotein (a) [Lp(a)], discovered by Berg in 1963 [8], is a particle of protein and lipid composition that closely resembles low-density lipoproteins, but its plasma levels and metabolism are distinctive [5]. Recently, Lp(a) has been shown to be another independent risk factor for the development of atherosclerosis [44, 101]. Thus, elevated Lp(a) levels greater than 30 mg/dl might increase the risk of early occlusive vascular disease in children on antiepileptic drugs [122]. Nevertheless, there are a few studies concerning the effect of AEDs on plasma Lp(a) levels in epileptic children, and the results are rather controversial [5, 14, 111, 122, 128, 133]. The study by Tümer et al. [122] has shown significantly higher plasma Lp(a) levels in epileptic children undergoing chronic monotherapy with CBZ, PB, or VPA in comparison to the control group. Moreover, in the patient group, 28.8% of children on drugs and none of the control subjects were found to have Lp(a) levels exceeding 30 mg/dl, which is considered the threshold value for early atherosclerosis [122]. In addition, these authors have found no significant difference in Lp(a) levels between the monotherapy and combined drug treatment [122]. Similarly, Sonmez et al. [111] have found that plasma Lp(a) levels were significantly increased after

3, 6, and 12 months of treatment with either CBZ, PB, or VPA. The percentages of children with plasma Lp(a) levels exceeding 30 mg/dl were 63%, 44%, and 33% in the CBZ-, PB-, and VPA-treated groups, respectively. Voudris et al. [133] have demonstrated a significant increase in the serum concentration of Lp(a) after 6, 12, and 24 months of CBZ and VPA monotherapy. On the other hand, in the study by Castro-Gago et al. [14], there were no significant differences in mean Lp(a) levels between the control group and the groups of epileptic children treated with either CBZ or PB, whereas the VPA-treated group showed low levels of Lp(a). This result is in agreement with a report by Verrotti et al. [128].

Several possible mechanisms have been considered to explain the increase in Lp(a) serum concentration. First, because Lp(a) is transported in plasma with the LDL, the elevated Lp(a) levels might result from an increased LDL secretion rate that is observed in patients on AEDs [11]. Second, the kidney has been shown to be involved in regulating the catabolism of Lp(a). Substantial amounts of this atherogenic lipoprotein seem to be removed by the kidney [73], and CBZ is known to affect renal excretory function [110]. Third, increased Lp(a) may result from subclinical hypothyroidism (SH), as thyroxine reduces its plasma level [57]. However, the most likely mechanism for the changes in Lp(a) status is the enzyme-inducing properties of AEDs, such as CBZ and PB [8], since the serum level of Lp(a) is predominantly modulated through changes in its production rate in the liver [54].

Based on the reviewed literature, plasma lipoprotein (a) levels should be measured before starting antiepileptic therapy, and those patients with an elevated pretreatment level or those who are at higher atherosclerotic risk (i.e., children with diabetes mellitus or family history of cardiovascular disease) should be monitored carefully throughout the therapy [111, 122].

Overt and subclinical hormone deficiency

Recently, it has been suggested that thyroid function disturbance might be one of the mechanisms that causes the altered lipid profile seen in epileptic children [46, 47], since thyroid hormones are implicated in the regulation of lipoprotein metabolism, and their dysfunction is associated with significant changes in the concentration, size, and composition of plasma HDL-c and LDL-c [10, 13, 60].

Overt hypothyroidism is a disease that is clearly associated with accelerated atherosclerosis and coronary heart disease [19, 26, 97]. This relationship is mediated not only by changes in lipid profile, but also by hyperhomocysteinemia, hypertension, changes in the parameters of inflammation (increased C-reactive protein level), and a hypercoagulable state, as well as by a direct effect of thyroid hormones on the vessel wall [9, 19, 79, 95]. Controversy remains as to the increased cardiovascular risk due to SH, which is defined as an elevated serum thyrotropin (TSH) level concomitant with normal values of free thyroxine (FT4) and free triiodothyronine (FT3) [27, 97]. It has been observed that SH may be associated with hyperlipidemia [47]. Substantial evidence indicates altered cholesterol and lipoprotein metabolism when TSH serum levels exceed 10 mU/L, and the influence of SH on lipids is directly proportional to the degree of TSH elevation [27]. Observed abnormalities include elevated plasma TC, LDL-c, and TG levels, as well as increased TC/HDL-c and LDL-c/HDL-c ratios [27, 75, 79, 97]. Elevated Lp(a) levels have also been observed [75]. SH may also be associated with higher BMI and diastolic hypertension [67, 97].

It is well known that the commonly used AEDs may affect thyroid function [6, 32, 63, 102, 116], and many studies have reported the co-existence of thyroid hormone deficiency (particularly low FT4) and disturbed lipid metabolism among epileptic patients treated with AEDs, particularly with the EIAEDs [4, 20, 29, 63, 65, 129]. This has been attributed to the drug-related induction of the hepatic P450 enzyme system, and the consequent increase in the metabolism of thyroid hormones [20, 63]. The mechanism of increased LDL-c levels in patients on AEDs may be due to changes in the conversion cascade of IDL (intermediate-density lipoprotein) to LDLs, most likely as an indirect effect of decreased thyroid hormone levels [3]. Hypothalamic/pituitary dysregulation caused by epilepsy itself or by AEDs is also a possible mechanism [46, 139]. However, it has been demonstrated that although CBZ decreases the serum thyroid hormones levels, the TSH serum concentration and response to TSH-releasing hormone remain normal [65, 129]. The effects of AEDs on thyroid function in children with epilepsy have been investi-

gated less extensively, and the literature also lacks the specific focus on the "subclinical" side effects of thyroid hormone deficiency in children on AEDs.

According to plausible underlying mechanism, the majority of data suggest that treatment with EIAEDs, including PB, PHT, or CBZ monotherapy, decreases serum total thyroxine (T4), total triiodothyronine (T3), FT4, and FT3 in epileptic children, but it has no effect on TSH serum concentration [32, 34, 71, 118, 138–140]. However, Rousso et al. [103] reported a significant increase in serum TSH levels among children treated with CBZ or PHT. Similarly, in the study by Attilakos et al. [4], thyroid dysfunction with increased TSH and decreased T4, FT4, and T3 was found in epileptic children during CBZ therapy. Moreover, the authors revealed a significant association between serum LDL-c and TSH levels after 6 and 12 months of treatment. Although neither OXC nor its active monohydroxy metabolite induces the oxidative P450 enzyme system to a similar extent as CBZ [96], several reports documented reduced serum thyroid hormone concentrations in epileptic children under short- or long-term treatment with OXC [12, 52, 125]. It is interesting that in all of these studies, no evident clinical symptoms of thyroid hormone deficiency have been observed.

Reports on the effect of VPA treatment on serum thyroid hormone concentrations have been inconsistent [6, 12, 30, 32, 34, 65, 125, 129, 138, 139]. Verrotti et al. [129] did not observe any alterations in thyroid hormone metabolism, and the TSH response to thyroid-releasing hormone was also normal in epileptics treated with VPA-monotherapy in contrast to CBZ-treated children, who had significantly lower values of serum T4 and FT4. However, a few studies revealed varying grades of transient SH with increased TSH levels among children treated with VPA [4, 12, 15, 30, 84, 125]. Predictors of SH were younger age and combined drug therapy (VPA with EIAEDs) [84]. However, an association with the lipid profile has not been assessed.

The clinical significance of these results needs to be evaluated with future studies. However, since thyroid dysfunction and hypercholesterolemia are both associated with a higher atherosclerotic risk, thyroid function may need to be monitored closely in children under antiepileptic treatment, even in the short-term treatment interval [4, 12, 46]. It is reassuring that according to the results by Vainionpää et al. [125], it seems that AED-associated changes in serum thyroid hormone and TSH levels are reversible after discontinuation of treatment.

Hyperhomocysteinemia, folate, and vitamin B status

Hcy is a sulfur-containing amino acid formed during demethylation of methionine [47, 124]. An increased plasma total Hcy concentration (p-tHcy) is recognized as an independent vascular risk factor that promotes atherosclerosis [18, 47, 123, 124, 127]. Suggested biological activities of Hcy that could explain the vascular risk associated with hyperhomocysteinemia include: a) oxidative modification of low-density lipoproteins [48, 49, 121], b) direct oxidative damage to endothelial cells [121, 127], c) impairment of the endothelial nitric oxide synthase (eNOS)/nitric oxide (NO) system with dysregulation of endothelium-dependent vascular tone [113, 119, 121], d) promotion of thrombosis due to loss of endothelial cell antithrombotic function and platelet activation [100, 104, 121], and e) induction of the inflammatory process of atherogenesis [121]. The endothelial damaging effect of Hcy has been attributed, in part, to its autoxidation, which leads to the formation of homocystine, disulfides, thiolactone, reactive oxygen species (ROS), and hydroxyl radicals. The formation of these metabolites results in the peroxidation of plasma and cell-membrane lipoproteins with induction of a prothrombotic environment [17, 48, 49, 113, 121, 127, 135].

In the pediatric population, cut-offs for hyperhomocysteinemia range from 8.3 to 11.3 μmol/L, depending on ethnic and age groups [59]. Hcy concentrations exceeding the 95th age percentile have been reported to be associated with a four-fold increased risk for ischemic cerebrovascular disease in the pediatric population [126]. In a study conducted by Tümer et al. [122], about 4% of children receiving AEDs had p-tHcy levels that exceeded 12 μmol/L, which is a critical concentration for atherosclerotic disease [106, 114]. 2% of epileptic children had p-tHcy levels greater than 15 μmol/L. This concentration threshold is linked to about a three-fold increased risk of myocardial infarction [114], and about a two-fold increased risk of carotid artery stenosis [106]. In some studies, hyperhomocysteinemia has been observed in as high as 40% of pediatric patients receiving AEDs

[59]. Hcy plasma concentrations exceeding the 90th age percentile have been observed in 13.8% of 81 Japanese children and adults taking AEDs [94], and hyperhomocysteinemia has been indicated in 40.4% of 136 Spanish pediatric patients treated with either CBZ or VPA [132]. Verotti et al. [131] compared p-tHcy levels in children receiving VPA and CBZ. The measurements were performed at the beginning of therapy and after 1 year of treatment. Patients treated with either VPA or CBZ monotherapy showed a significant increase in fasting and post-methionine loading p-tHcy levels when compared to baseline data and control values [131]. These observations were confirmed by Vilaseca et al. [132] who found that fasting p-tHcy levels were similarly increased in children treated with either VPA or CBZ, and the percentage of children with hyperhomocysteinemia was similar for both AEDs. These authors documented high p-tHcy levels ranging from 15 to 39.8 μmol/L in epileptic children aged 8 to 18, especially in the eldest groups. These results suggest that long-term CBZ or VPA administration may progressively increase p-tHcy levels [132]. Huemer et al. [59] found hyperhomocysteinemia in 15.5% of 123 pediatric patients receiving AEDs. High p-tHcy levels were predominantly associated with multidrug treatment. On the other hand, Tümer et al. [122] identified no significant difference in Hcy levels between the epileptic children on monotherapy or combination drug therapy.

Hcy accumulation and elevated p-tHcy levels may result from a deficiency in cofactors or genetic polymorphisms in genes coding for enzymes involved in Hcy metabolic pathways [35, 36]. Metabolism of Hcy is tightly connected to cobalamin (vitamin B_{12}), pyridoxine (vitamin B_6), folate (vitamin B_9), riboflavin (vitamin B_2), and choline metabolic pathways [33, 35, 36, 115]. Ono et al. [93] have reported a significant inverse correlation between p-tHcy and folate plasma concentrations in patients treated with CBZ, VPA, or PB, thus suggesting that folic acid depletion may induce hyperhomocysteinemia during antiepileptic therapy. This finding is consistent with other reports. Karabiber et al. [68] found significantly lower serum folate concentrations in groups of children aged 2 to 16 taking VPA or CBZ in comparison with healthy controls. Similarly, Verrotti et al. [131] observed a significant decrease in folate plasma levels after 1 year of therapy with VPA or CBZ when compared to baseline and control values. However, erythrocyte folate concentration, which is considered to be a more reliable indicator for long-term folate nutritive status [51], remained normal in those patients [131]. Vilaseca et al. [132] observed that a high percentage of children taking CBZ showed folate levels below reference value (< 8.6 nmol/L), but VPA had no effect on folate serum levels. This is in agreement with observations by Geda et al. [42], who also found that VPA therapy did not change folic acid concentrations. Thus, VPA seems to have a less dramatic effect on folic nutritional status than CBZ. Furthermore, it has been demonstrated that plasma and erythrocyte folate concentrations in pediatric patients treated with lamotrigine (LTG) were higher than in epileptic children treated with other AEDs. This observation was rather unexpected, since LTG shows an inhibitory effect on dihydrofolate reductase *in vitro* [85]. However, this inhibitory action seems to be less effective than other dihydrofolate reductase inhibitors, such as methotrexate [87].

A variety of mechanisms have been suggested to account for the effect of long-term use of AEDs on folate deficiency. These include: a) impairment of folate absorption and gastrointestinal transport [61], b) increased folate metabolism in the liver due to induction of LME [72, 76, 83], c) competitive interaction between drugs and folate co-enzymes [43], d) increased demand for folate as a cofactor in the hydroxylation of AEDs [66], and e) altered activity of the folate-mediated one-carbon transfer pathway [76]. However, the precise mechanism remains controversial [72], and various AEDs may have differential effects on folate and Hcy metabolism [47, 59]. Furthermore, it has been postulated that genetic susceptibility may be implicated in folate deficiency among epileptics receiving AEDs. It has been suggested that homozygosity for the mutant allele of MTHFR (5,10-methylenetetrahydrofolate reductase) predisposes individuals to increased levels of p-tHcy and augments the severity of hyperhomocysteinemia in epileptic patients treated with AEDs [132, 137]. MTHFR is a hepatic enzyme involved in the metabolism of Hcy. A common MTHFR 677 C→ T mutation, which results in a mutant protein with 50% of the activity of the normal enzyme, seems to be a major determinant of hyperhomocysteinemia during therapy with AEDs. Patients with this homozygous thermolabile genotype of MTHFR were found to have a higher folate requirement to maintain a normal tHcy serum level during antiepileptic therapy [137].

CBZ has been shown to have an additional lowering effect on vitamin B_{12} and vitamin B_6 concentra-

tions in epileptic children [68, 132]. A significant negative correlation has been found between the duration of CBZ therapy and vitamin B_{12} concentrations, as well as between p-tHcy and vitamin B_{12} levels in epileptic patients during long-term treatment [132]. Vitamin B_{12} deficiency observed in patients under chronic medication with CBZ may be related to secondary malabsorption caused by low folate levels [96]. In contrary, some studies reported significantly elevated levels of vitamin B_{12} and low vitamin B_6 in VPA-treated children [22, 132]; however, the possible mechanisms remain unknown.

Elevation in p-tHcy levels induced by AED administration can theoretically increase not only the risk of vascular occlusive diseases, but also the risk of resistance to antiepileptics and development of refractory epilepsy [47, 108], since Hcy is a potential convulsant [74, 82, 89, 94, 105]. Moreover, increased p-tHcy levels concomitant with low folate status may contribute to the development of AED-related side effects, such as impaired cognitive performance and neuropsychiatric illnesses, as well as hematologic complications including megaloblastic changes in the bone marrow [16, 40, 53, 55, 77, 99]. Thus, it is recommended to periodically assess serum folate and p-tHcy levels in children receiving AEDs, especially in those receiving multidrug treatment. Clinicians may suggest folic acid supplementation in patients with low folate and high Hcy levels, but whether this approach could prevent the risk of atherosclerotic disease remains to be clarified [59, 122]. The Hcy Lowering Trialists' Collaboration [56] has concluded that folic acid supplementation at a daily dose between 0.5 and 5 mg reduces p-tHcy levels by 25%. However, 0.4–1 mg per day throughout the entirety of drug treatment seems to be sufficient for patients on AEDs [2, 59]. It has been also suggested to combine folic acid with vitamin B_6 and B_{12} supplementation, since low levels of these vitamins have also been reported among epileptic children on AEDs [47, 68]. However, initial data from recent large randomized controlled trials have shown that there is no clinical benefit of lowering plasma tHcy concentrations with folic acid and B vitamins. Moreover, results from the ongoing clinical trials are being eagerly awaited to clarify whether Hcy is a cause or rather the indicator of CVD [86, 134]. A special concern should also be paid to the interaction between vitamins and drugs. Folate overload may change the pharmacokinetics of some AEDs, particularly phenytoin [77, 107].

Conclusions

According to the presented results of clinical studies, dislipidemia, hyperhomocysteinemia with folate deficiency, and thyroid hormone deficiency may be relevant issues in epileptic children receiving AEDs.

The reviewed data should alert neurologists that children with epilepsy seem to be at increased risk for the development of atherosclerosis. However, it is important to point out that we do not yet have definite evidence of risk correlations, because we have no reports on cohort studies to document the follow-up of children taking AEDs. Monitoring vascular risk factors as well as folate and vitamin B supplementation may be beneficial, particularly in patients undergoing multidrug or long-term antiepileptic therapy, but up to this point, there is no documented need to administer specific prophylaxis together with AEDs unless new evidence is revealed. Newer anticonvulsant agents such as OXC, LTG, or TPM may be safer when prescribed to children with a high risk of developing atherosclerosis, as indicated by family history of occlusive vascular disease or genetic disorders that lead to hyperhomocysteinemia [29, 37, 64, 70], but whether the newer AEDs are clearly beneficial in this context remains to be evaluated.

In conclusion, long-term studies are needed to determine the cardiovascular risk in children on AEDs. Nonetheless, neurologists would do well to advise and engage epileptic children regarding the importance of physical exercise and healthy diet.

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