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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,