Epilepsy Research (2014) **108**, 1087—1094

journal homepage: www.elsevier.com/locate/epilepsyres

Vascular function and risk factors in children with epilepsy: Associations with sodium valproate and carbamazepine

Ngaire Keenan, Lynette G. Sadlier, Esko Wiltshire*

Department of Paediatrics and Child Health, University of Otago Wellington, P.O. Box 7343, Wellington South, Wellington, New Zealand

Received 26 December 2013; received in revised form 3 April 2014; accepted 27 April 2014
Available online 14 May 2014

KEYWORDS
Child;
Epilepsy;
Anti-epileptic drug;
Vascular function;
Vitamin

Summary
Aim: To investigate biochemical cardiovascular risk factors and vascular endothelial function and structure in children with epilepsy on antiepileptic drugs (AEDs), particularly sodium valproate (VPA) and carbamazepine (CBZ).
Background: Individuals with epilepsy have increased risk factors for vascular disease, particularly lipid abnormalities and elevated total plasma homocyst(e)ine (tHcy). AED induced B-vitamin deficiencies have been suggested to contribute to this risk. Vitamin B supplementation has consequently been recommended for children on AEDs. Early vascular endothelial dysfunction and atherosclerosis are detectable by measuring flow-mediated dilation (FMD) and intima-media thickness (IMT).
Methods: Thirty children with epilepsy on AEDs (13.3 ± 2.3 years, 14 male) and 30 controls (13.9 ± 2.9 years, 14 male) were recruited. Fasting tHcy, folate, pyridoxal-5-phosphate (PLP), vitamin B12, glucose and lipids were measured. Vascular function and structure were assessed using FMD (brachial artery) and IMT (carotid/aortic arteries).
Results: No differences were found between children with epilepsy and controls for tHcy, folate, PLP, lipids, FMD, carotid or aortic IMT. Vitamin B12 levels were elevated and glucose reduced in children treated with VPA. Elevated total cholesterol, cholesterol/HDL ratio and triglycerides occurred in children treated with CBZ. Aortic IMT correlated with weight ($r = 0.75$, $p < 0.001$), BMI ($r = 0.54$, $p = 0.01$), and HDL cholesterol ($r = -0.58$, $p = 0.006$).

Abbreviations: AED, anti-epileptic drug; BMI, body mass index; CBZc, arbamazepine; CCAc, ommon carotid artery; ECGe, lectrocardiogram; EDTA, ethylene-diamine-tetra-acetic acid; FMD, flow mediated dilatation; GTNg, lyceryl-trinitrate; IMT, intima media thickness; LDLl, ow density lipoprotein; PLP, pyridoxal-5-phosphate; tHcy, total plasma homocyst(e)ine; VPA, sodium valproate.

* Corresponding author at: University of Otago Wellington, P.O. Box 7343, Wellington South 6242, Wellington, New Zealand. Tel.: +64 4 3855999; fax: +64 4 3855898.
E-mail address: esko.wiltshire@otago.ac.nz (E. Wiltshire).

http://dx.doi.org/10.1016/j.eplepsyres.2014.04.006

Conclusion: We found no early changes in vascular function or structure in children on valproate or carbamazepine. We were also unable to confirm previous reports of tHcy abnormalities in this group. This may be due to higher B-vitamin intake, which compensates for loss of vitamins induced by this AED therapy. Vitamin supplementation in children with epilepsy on valproate and carbamazepine is not required in populations with adequate dietary intake of B vitamins.

Introduction

Epilepsy is a common neurological condition which may require long term antiepileptic drug (AED) therapy. Patients with epilepsy have vascular risk factors (Elliott et al., 2007; Hamed et al., 2007) including abnormal lipids, insulin, elevated oxidative stress and elevated total plasma homocyst(e)ine (tHcy). This increase in vascular risk is postulated to result from AED therapy (Apeland et al., 2002; Apeland and Mansoor, 2003; Attilakos et al., 2006; Aydin et al., 2005; Elliott et al., 2007; Hamed et al., 2007; Isojärvi et al., 1994; Karabiber et al., 2003; Pylvänen et al., 2006; Tomoum et al., 2008; Verrotti et al., 1998, 2000; Vilaseca et al., 2000).

Elevated tHcy, a risk factor for atherosclerosis, is common in individuals on AED therapy (Apeland et al., 2002; Apeland and Mansoor, 2003; Attilakos et al., 2006; Belcastro et al., 2010; Chuang et al., 2012; Coppola et al., 2012; Hamed et al., 2007; Karabiber et al., 2003; Sener et al., 2006; Verrotti et al., 2000; Vilaseca et al., 2000). Elevations in tHcy may be due to AED induced B-vitamin deficiencies, particularly folate and vitamin B6 (pyridoxal-5-phosphate, PLP) as these are important cofactors in homocysteine metabolism (Maxwell et al., 1972; Welch and Loscalzo, 1998). Elevations of tHcy and B-vitamin deficiencies are particularly apparent in patients treated with enzyme inducers such as carbamazepine and phenytoin (Apeland and Mansoor, 2003; Attilakos et al., 2006; Eiris et al., 1995; Elliott et al., 2007; Hamed et al., 2007; Sonmez et al., 2006; Svalheim et al., 2010; Verrotti et al., 2000). Because of this, some authors have recommended that all children on AEDs receive vitamin B supplementation to decrease long term cardiovascular risk (Apeland et al., 2002; Huemer et al., 2005).

AED therapy is associated with other vascular risk factors. Elevated oxidative stress, hyperinsulinaemia and hyperlipidaemia are common in patients with epilepsy, and similar to B-vitamins, are particularly elevated in those treated with enzyme inducers (Aydin et al., 2005; Eiris et al., 1995; Hamed et al., 2007; Isojärvi et al., 1994; Pylvänen et al., 2006; Sonmez et al., 2006; Svalheim et al., 2010; Tomoum et al., 2008; Verrotti et al., 1998). Lipid abnormalities in these patients are associated with increased arterial intima media thickness (IMT) a measure of arterial lipid deposition and an early marker of atherosclerosis (Chuang et al., 2012; Erdemir et al., 2009; Hamed et al., 2007).

Endothelial dysfunction occurs early in the development of atherosclerosis (Berenson and Srinivasan, 1998). Degeneration of vascular endothelium (Gerstner et al., 2006) and arterial stiffness (Yildiz et al., 2010) in children on AEDs has been suggested by microscopic and pulse wave velocity techniques respectively. No studies however have investigated endothelial function in children with epilepsy. Endothelial function can be measured non-invasively using flow mediated dilatation (FMD) (Celermajer et al., 1992; Skilton and Celermajer, 2006) and predicts cardiovascular events (Gokce et al., 2003). It has been used in children with diabetes and obesity to demonstrate early endothelial dysfunction, which can occur within 12 months of diagnosis in these conditions (Skilton and Celermajer, 2006; Peña et al., 2006; Wiltshire et al., 2002). As vascular disease begins in childhood and early vascular disease is potentially reversible, it is important to understand cardiovascular risk factors and their impact on endothelial function in children with epilepsy (Berenson and Srinivasan, 1998; Celermajer et al., 1992). By assessing biochemical vascular risk factors, endothelial function and structure, this study aims to investigate early vascular disease in children with epilepsy receiving AEDs, particularly sodium valproate and carbamazepine.

Methods

Patients and controls

30 children with epilepsy were consecutively recruited from paediatric neurology and general paediatric clinics. Inclusion criteria included age between 8 and 18 years, two or more unprovoked seizures and at least 1 year of AED therapy. Children were excluded if they received vitamin supplementation, medication other than AEDs affecting homocysteine or lipid metabolism, had a history of smoking, or clinical evidence of acute illness, renal dysfunction, thyroid dysfunction, metabolic disease, chronic inflammatory disease, cerebrovascular disease or mental-motor retardation with an unknown aetiology. 30 age, sex and BMI matched healthy controls were recruited from friends or family members of three groups: subjects with epilepsy; children with diabetes from a previous study (Wiltshire et al., 2002); and staff of the Paediatric department at Wellington Hospital. Self-reported pubertal stage was recorded on all epilepsy subjects and controls using Tanner illustrations. Informed consent was obtained for each participant and/or their parent/guardian and ethical approval was provided by the Central Regional Ethics Committee, Ministry of Health, Wellington.

Results are presented for the whole group in comparison with controls and also for children treated with sodium valproate or carbamazepine (as numbers treated with other AEDs or polytherapy are small).

Biochemical methods

Fasting venous blood samples were collected in all subjects. tHcy was determined using the Abbott AxSYM Homocysteine