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Noninvasive screening for preclinical atherosclerosis in children on phenytoin or carbamazepine monotherapy: A cross sectional study☆

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Summary
Purpose: This study was carried out to compare the carotid Intimal Media Thickness (IMT), and endothelial function using brachial flow mediated dilatation (FMD), in Epileptic children (6—12 years) on phenytoin (PHT) or carbamazepine (CBZ) monotherapy for ≥18 months with a control group of children.
Methods: In this cross-sectional study 30 children (aged 6—12 years) on PHT monotherapy and 28 children on CBZ monotherapy were compared with an equal number of apparently healthy age and sex matched children unexposed to antiepileptics. Fasting lipids, sugar, Hs-CRP levels and ultrasonographic assessment of carotid IMT and endothelial function using brachial FMD were conducted.

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Results: The age (years) of the children in the CBZ group (9.1 ± 2), PHT group (9.4 ± 2) and the controls (9.3 ± 2) was comparable. The duration of CBZ therapy was 30.8 ± 13.2 months and that of PHT therapy was 29.5 ± 13.6 months. The mean dose of CBZ was 18.18 ± 8.5 mg/kg and that of PHT was 5.5 ± 2.3 mg/kg body weight. The time since last seizure was 15.6 ± 8.4 months in the CBZ group and 17.3 ± 10.4 months in the PHT group. The fasting blood sugar was below 110 mg/dl in all children.

The height, weight, waist and hip measurements, waist hip ratio and blood pressures were similar in the groups. The total cholesterol levels (161.7 ± 24.8 vs 140.2 ± 20.8 mg/dl, $p = 0.001$), HDL (53.8 ± 10.5 vs 47.1 ± 8.8 mg/dl, $p = 0.017$) and LDL (85 ± 21.1 vs 70.9 ± 19.4 mg/dl, $p = 0.01$) were significantly higher in the CBZ group compared to the control group. The HDL levels (54.6 ± 9.4 vs 45.8 ± 7.7 mg/dl, $p < 0.0001$) were significantly higher in the PHT group compared to the control group. The right carotid (0.374 ± 0.04 vs 0.339 ± 0.05 mm, $p = 0.012$), left carotid (0.382 ± 0.05 vs 0.351 ± 0.05 mm, $p = 0.044$) and the overall average carotid intima media thickness (0.378 ± .048 vs 0.345 ± .052 mm, $p = 0.018$) of the children on CBZ was significantly higher than the carotid IMT in control group children. The right carotid (0.370 ± 0.04 vs 0.342 ± 0.05 mm, $p = 0.032$) and the overall average carotid IMT (0.374 ± 0.04 vs 0.348 ± 0.05 mm, $p = 0.035$) of the children on PHT was significantly higher than the carotid IMT in controls. The FMD were comparable in the children on CBZ or PHT and the control group.

Conclusions: The results are preliminary but could signal the increased vulnerability of epileptic children on long term antiepileptics to have subclinical atherosclerosis.

Introduction

Worldwide nearly 3.5 million people develop epilepsy annually. About 40 percent of these are under 15 years of age, and more than 80% of them live in developing countries (Forsgren, 2004). Most of these individuals receive anti epileptic drugs (AED's) for a variable duration. These drugs when given over a prolonged period can have several adverse effects (Eirís et al., 1995, 2000). Several studies provide evidence that AED's can alter serum lipids and apolipoprotein levels (Voudris et al., 2006; De Juan Frigola et al., 1996). Some reports indicate that long term AED therapy is proatherogenic. On the contrary many other studies report only minimal or transient changes in serum lipids in patients on AED's (Aynaci et al., 2001; Sonmez et al., 2006; Verrotti et al., 1997, 1998). In some early reports the mortality rate from heart diseases in epileptics was reported to be lower compared to control population (Muuronen et al., 1985). However, emerging data from some recent studies in adults suggests that long term AED intake may have a proatherogenic effect (Tan et al., 2009).

The recent studies have utilized ultrasonographic assessment of carotid intima-media thickening (IMT), as an early surrogate marker of atherosclerosis. Thickening of intima precedes clinical cardiovascular events of atherosclerosis by decades. Secondly, studies in adults have shown a close correlation between the endothelial function peripherally (at the brachial artery) and that of the coronary circulation (Kuvin et al., 2001). Ultrasound measurement of flow-mediated dilation (FMD) reflects on the peripheral endothelial functional integrity. Both the above techniques can pick up early atherosclerosis in children and allow institution of early intervention (Groner et al., 2006).

Recent studies have suggested that long term use of AED's may predispose to atherosclerosis later in life. Most of this data comes from adults (Chuang et al., 2012; Tan et al., 2009) and there are only a few studies evaluating vascular structural and functional correlates of early atherosclerosis in children on AED's (Erdemir et al., 2009; Tokgoz et al., 2012). So this study was conducted with the primary objective to compare carotid IMT and endothelial function using brachial FMD in epileptic children on phenytoin or carbamazepine monotherapy for ≥18 months with a control group of children.

Materials and methods

This cross-sectional study was carried from April 2008 to December 2008. Children aged 6—12 years with epilepsy, visiting the pediatric neurology outdoor clinic were evaluated for inclusion in the study. The study was approved by the Institutional Ethics Committee. Informed consent was obtained from the parents/guardians before the procedure. The inclusion criteria included (a) phenytoin or carbamazepine monotherapy for at least 18 months, (b) Compliance on the current dose for at least 3 months, (c) not more than four week of drug free period in the past 18 months, (d) absence of intake of other AED's for more than 4 weeks in the past 12 months. For the control group apparently healthy age and sex matched children who were not on any AED were chosen after clinical exclusion of chronic systemic or cardiovascular disease. Majority of these children were enrolled from among the siblings of the patients. Exclusion criteria included: (a) family history of premature (<55 years) coronary artery disease or stroke, (b) preexisting hypertension, coronary artery disease, stroke, chronic systemic disease, (c) breakthrough seizure in last 4 weeks, (d) intake of vasoactive medicines or folate or vitamin C intake in the past 4 weeks, (e) major infection in the last 3 months like — pneumonitis, cellulitis, peritonitis, or any febrile illness in preceding 4 weeks, (f) intake of statins or other drugs lowering or elevating lipids in 12 months for >4 weeks.

In those enrolled for study a detailed evaluation based on a predesigned proforma was carried out including history and general physical, systemic and neurological examination with emphasis on epilepsy type and details of antiepileptic