Lipid and homocysteine levels in epileptic children treated with valproic acid – a preliminary data

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Abstract

Introduction: The problem of epileptic seizures is especially heavy for children as it concerns their daily activity as well as education. The use of antiepileptic drugs (AEDs) may increase the levels of some biochemical parameters like lipid parameters and homocysteine, which were confirmed to be risk factors for cardiovascular diseases, both in adults and in children.

Objective: To assess relationship between treatment with valproic acid in monotherapy, by at least 6 months, and levels of lipid and homocysteine in epileptic children.

Methods: The study group comprised of 4 children with epilepsy and 5 sex – and age-matched healthy children recruited from the Department of Pediatric Neurology in Medical University of Silesia in Katowice. Serum lipids and plasma homocysteine levels were measured in all children. Statistical analyses were made with Statistica 12.0 software.

Results: We observed higher level of plasma homocysteine in children with epilepsy treated with valproic acid than in healthy children. There were also found higher concentrations of total cholesterol, triacylglycerols, LDL-cholesterol and HDL-cholesterol in patients compared to controls.

Conclusions: Valproic acid used for at least 6 months may cause elevation of plasma homocysteine level as well as serum lipids levels in children with epilepsy. Further studies are needed to confirm this preliminary findings.

Key words:

epilepsy, children, antiepileptic drugs, valproic acid, lipids, homocysteine

Introduction

Epilepsy is a relatively common disorder worldwide. To diagnose epilepsy at least two unprovoked epileptic seizures must be found in patient's medical history, regardless of the treatment with antiepileptic drugs (AEDs). In almost 70% of epileptic cases, the seizures can be controlled in monotherapy. Antiepileptic drugs can be distinguished into two general groups, i.e. cytochrome P-450 inducers including among others carbamazepine (CBZ), phenytoin (PHT), primidone (PRM) or valproate inhibitor (VPA), and drugs that do not affect cytochrome P-450, as a second group, with gabapentin (GBP), vigabatrin (VGB), levetiracetam (LEV), oxcarbazepine (OCBZ) or topiramate (TPM). According to the current recommendations lamotrigine and CBZ should be used as first-line drugs for the treatment of partial seizures in children and adults, while sodium valproate is used for treatment of generalized seizures [1]. Children are prone to epilepsy and the problem of epileptic seizures is especially heavy for their daily activity as well as education. In the Lithuania, the epilepsy rate in children was established as 4.25 per 1000 children [2] while in Norway – 5.1 per 1000 [3].

The study of Ünver et al. [4] showed higher frequency of partial seizures than of generalized seizures in the group of over 500 Turkish children (56.5% vs 43.5%, respectively). The authors observed also that partial seizures were more common during late childhood [4]. In Spanish children focal seizures were observed in 52.9% of the patients while generalized epilepsy in 43.5% of the study cohort [5]. Similarly, in German children, focal epilepsies were more prevalent than generalized ones (58% vs 39%) [6]. In the study of Lithuanian children, the highest rate of diagnosed epilepsy was found in the 10-14 years age group while undetermined cause was found in 60.3% of cases [2]. In contrary, in Estonian study, the incidence rate was the highest in children aged from 1 month to 4 years with significant decrease after the age of 15 years [7].

The use of AEDs may influence number of biochemical processes in the patient body, including mainly increasing the levels of some biochemical parameters like lipid parameters and homocysteine (HCys), both in adults and children [8,9]. The elevated levels of HCys as well as dyslipidemia were previously confirmed as risk factors for coronary heart disease, venous and arterial thrombosis or vascular disease, both in adults and in children [10-13].

The problem regarding impact of AEDs on levels of cardiovascular biomarkers in children is not fully understood thus we made an attempt to analyze this effect. The aim of the present study was to assess relationship between treatment with valproic acid in monotherapy, by at least 6 months, and levels of lipid and homocysteine in epileptic children. The study is on the preliminary stage due to the fact that gathering biological material for research can be a problem in this age group. The inclusion criterion of 6 month monotherapy with valproic acid also limits our study as in many pediatric patients, the second AED is included much earlier if the seizures are not satisfactorily controlled. Children treated successfully by monotherapy with valproic acid are in minority since they were recruited in tertiary level center.

Methods

Participants

The study group comprised of 4 children with epilepsy (3 girls and 1 boy; age: 3-18 years) and 5 sex – and age-matched healthy children (3 girls and 2 boys; age: 3-18 years). All children were white, Polish Caucasians and were recruited from the Department of Pediatric Neurology in Medical University of Silesia in Katowice.

The inclusion criteria for patients were as follows:

- diagnosis of epilepsy based on history data and examinations results, including in particular electroencephalography and neuroimaging studies: magnetic resonance imaging (MRI) and computer tomography (CT);
- age of the patients from 3 to 18 years;
- monotherapy with VPA for at least 6 months.

We have adopted the following exclusion criteria for patients group:

- age under 3 years;
- VPA monotherapy for less than 6 months;

- polytherapy;
- non-epileptic seizures or lack of epilepsy;
- diagnosed cardiovascular diseases (ischemic stroke, hypertension, heart disease).

Children were excluded from the control group in the presence of clinical neurological symptoms.

The design of the work has been approved by Local Ethical Committees. The research was funded within the project KNW-1-126/K/6/K. All parents of the patients gave written informed consents.

Biochemical analyses

In all children, serum lipids as well as plasma homocysteine levels were measured. Lipid parameters levels (total cholesterol, LDL-cholesterol, HDL-cholesterol, triacylglycerols) were analyzed spectrophotometrically (UV/VIS Cecil CE apparatus) in fresh, blood serum using enzymatic methods with commercially available kits (POINTE SCIENTIFIC). The homocysteine levels in plasma were measured using high-performance liquid chromatography (HPLC) according to Young et al. [14] method.

Statistical analysis

Statistical analyses were made with Statistica 12.0 software (STATSOFT; Statistica, Tulsa, OK, USA). Mean values (M) and standard deviations (SD) were estimated for continuous variables. To compare continuous variables between the epileptic children and controls the U Mann-Whitney test was used. Significance level p was accepted at ≤0.05.

Results

Table 1 shows mean values and standard deviation of all analyzed parameters.

The preliminary analysis showed that mean level of homocysteine in plasma of children with epilepsy treated with valproic acid was higher compared to healthy children with no signs of vascular diseases.

In case of lipids concentrations in serum, we observed higher levels of all analyzed parameters in epileptic children than in controls, i.e.: total cholesterol, triacylglycerols as well as LDL-cholesterol. Surprisingly, the mean value of HDL-cholesterol level was also higher in epileptic patients compared to healthy children. Despite these differences, they were not statistically significant due to low sample sizes in each analyzed group at the present stage of the study. Figure 1 presents a comparison of the mean values of the tested lipid parameters between the patients and healthy children.

Discussion

Valproic acid is a very effective anticonvulsant drug for generalized seizure however it carries some side effects [16]. It is recommended not to be used to treat epilepsy or bipolar disorder in girls or in women of childbearing age because of the risk of teratogenicity [17]. The meta-analysis of five randomized controlled trials and four observational cohort studies (1732 cases) demonstrated that VPA was significantly better choice than lamotrigine [18]. The authors observed also that the risk of adverse effects did not significantly differ between the two analyzed groups [18]. The side effects of VPA may include also elevation of the selected biomarkers of cardiovascular diseases.

Previously, hyperhomocysteinemia was observed in over 15% children treated with AEDs with

Table 1.
Concentrations of homocysteine and lipids in the studied groups

Measured biochemical parameters	Epileptic children n=4	Controls n=5	p
Homocysteine (μM/L), M±SD	6.72±2.10	5.50±0.19	0.540
Total cholesterol (mg/dL), M±SD	182.55±79.84	112.40±27.74	0.178
Triacylglycerols (mg/dL), M±SD	73.82±34.66	45.79±13.25	0.270
LDL-cholesterol (mg/dL), M±SD	163.85±45.29	132.99±7.91	0.271
HDL-cholesterol (mg/dL), M±SD	110.57±41.38	67.56±30.81	0.111

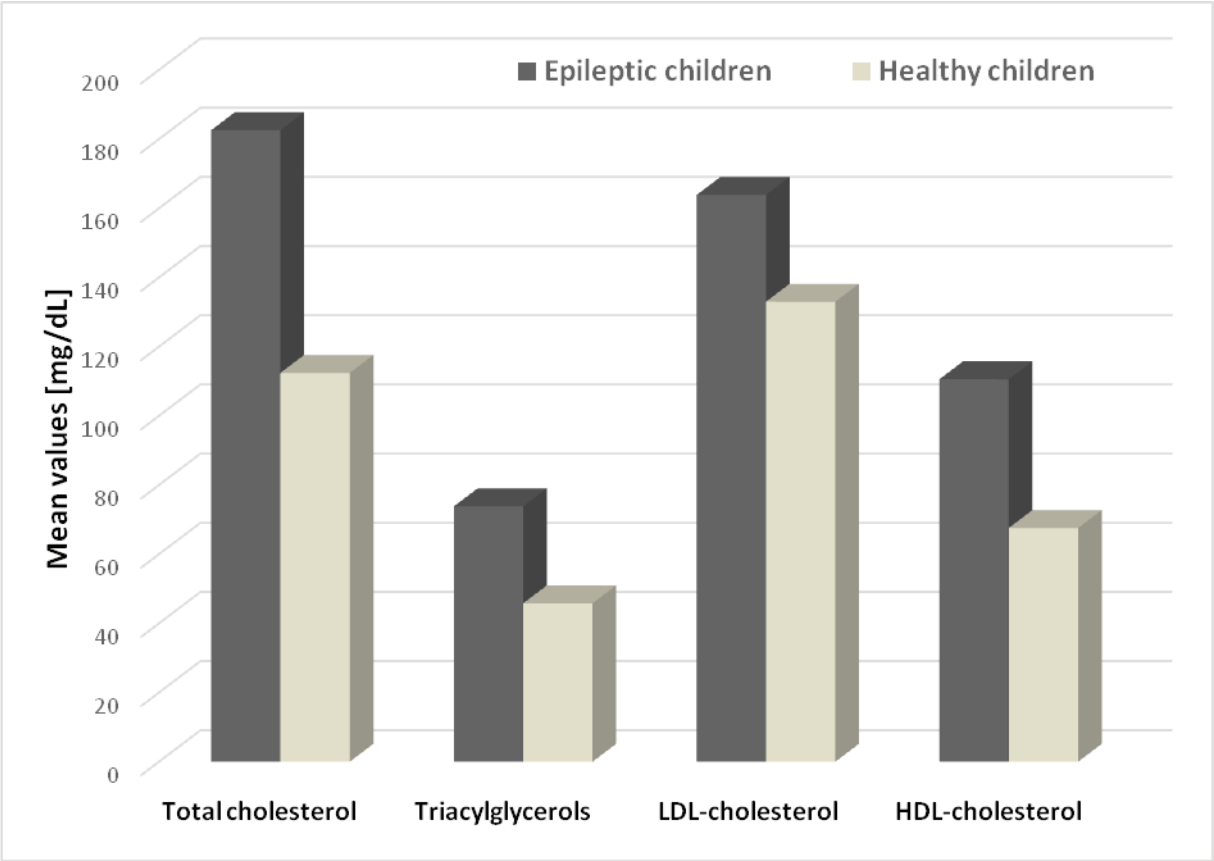

Fig. 1.
Comparison of mean lipid levels between patients and controls

particular increase the risk of HCys elevation during polytherapy [19]. The serum homocysteine level was significantly increased with simultaneous significant decrease of folate levels in epileptic children after valproate monotherapy as compared to the values obtained before therapy [20]. The results of the Sener et al. study [21] analyzing patients treated with AEDs for over 6 years in monotherapy, patients using no AED and healthy controls confirmed the effect of AEDs on plasma HCys in epileptic patients. In the present study we observed elevated level of HCys in epileptic children however it was still in the range of physiological concentration. The mean concentration of HCys in our patients was lower than previously obtained in Italian pediatric patients (12,11 μmol/L) [22]. It was demonstrated that treatment with AEDs is associated with reduced folate or vitamin B12 serum levels and is a risk factor for hyperhomocysteinemia [23]. After 20 weeks of monotherapy with valproate sodium and carbamazepine in two groups of children with epilepsy, HCys level increased significantly [8]. The meta-analysis of Gorjipour et al. [24] demonstrated that carbamezepine and sodium valproate increased HCys levels, with simultaneous decreasing folate levels in CBZ group and no effect of valproate on folic acid. Another meta-analysis also confirmed the significant effect of valproate on HCys levels, however it was not correlated with age and ethnicity [25].

Our data showed elevation of all lipid parameters in epileptic patients compared to controls. Similarly, Spanish children with epilepsy receiving carbamazepine or phenobarbital in monotherapy for 7 months to 10.5 years had higher TC, HDL – as well as LDL-cholesterol [26]. In the valproic acid group the authors found lowered mean levels of TC and LDL-cholesterol than in controls which is in opposite to our results. The same observation was made by Nikolaos et al. [27]. Adult epileptic patients treated with CBZ in monotherapy showed significant increase in TC, HDL-, and LDL-cholesterol while in contrast patients on valproate showed significantly lower TC, LDL-cholesterol and TG values [27]. In other study based on adults with epilepsy, monotherapy with

CBZ or VPA showed in turn, increasing concentrations of TC, TG and LDL-cholesterol compared to cases on lamotrigine monotherapy and the control group [28].

Limitation of the study is a low number of patients due to the difficulties with their recruitment. One of the way of enlarging patients groups is recruitment of the ambulatory epileptic patients. In this situation, the statistics should be treated with caution. However the initial results are interesting and suggest the usefulness of further research in the topic.

Conclusions

1. The use of monotherapy of valproic acid in epileptic children may cause elevation of plasma homocysteine level however in the range of physiological concentration.

2. Valproic acid used for at least 6 months may increase the levels of lipid parameters, i.e. total cholesterol, triacylglycerols, LDL-cholesterol and HDL-cholesterol in children with epilepsy.

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