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Capillary microscopy and hemorheology in children during antiepileptic monotherapy with carbamazepine and valproate

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Summary The interactions of epilepsy and antiepileptic therapy an one hand and cardiovascular system on the other hand are multiple and complex. Antiepileptic drugs (AEDs) cause alterations of serum lipids and of the fatty acid composition of the membranes. Homocystein, known to induce vascular endothelial damage was found to be elevated in patients on valproate (VPA) and carbamazepine (CBZ) therapy. Marked coronary artherosclerosis and myocardial infarction may already occur in children treated with CBZ. Community based studies corroborated a higher incidence of myocardial infarction, peripheral vascular diseases hypercholesterinemia, left ventricle hypertrophy and stroke in patients with epilepsy. In this context, we wanted to elevate changes of microcirculation related to AEDs commonly prescribed such as VPA and CBZ.

Capillary microscopy is a non-invasive technique for measuring the velocity of red blood cells and for determining nutritional blood flow in the capillaries of the skin. It can easily be performed in children.

The aim of this study was to look for possible effects an antiepileptic monotherapy with carbamazepine or valproate has on the peripheral microcirculation in epileptic children.

We were able to examine 14 children with CBZ and 24 children with VPA, recruited in our neuropediatric Unit. The results were compared to normative values, determined in former analyses of 207 healthy children. We found significant differences in capillary density, tortuous index of the capillaries, capillary diameter and flow rate of erythrocytes for both antiepileptic drugs. Additionally, there were changes in plasma viscosity and the aggregation of erythrocytes.

These microcapillary effects could be of special interest in the relationship of a long-term antiepileptic therapy and the development of vascular diseases.

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We suggest that the influence of AEDs on microcirculation should also be considered in further studies on cardiovascular changes in patients with antiepileptic long-term medication.

Introduction

The interactions of epilepsy and antiepileptic therapy on one hand and cardiovascular system on the other hand are multiple and complex. Antiepileptic drugs (AEDs) cause alterations of serum lipids and of the fatty acid composition of the membranes.[1] Homocystein, known to induce vascular endothelial damage was found to be elevated in patients on valproate (VPA) and carbamazepine (CBZ) therapy.[2] Marked coronary artherosclerosis and myocardial infarction may already occur in children treated with CBZ.[3] Community based studies corroborated a higher incidence of myocardial infarction, peripheral vascular diseases hypercholesterinemia, left ventricle hypertrophy and stroke in patients with epilepsy.[4] In this context, we wanted to elevate changes of microcirculation related to AEDs commonly prescribed such as VPA and CBZ. The interest in microcirculation began in the 17th century.[5] In vivo studies of the capillary circulation using a microscope were first described 45 years ago by Lombard.[6] In 1974 Bollinger introduced a method for actual measurements of the flow velocity in nutritional skin capillaries.[7] Capillary microscopy is a non-invasive technique for measuring the velocity of red blood cells and for determining nutritional blood flow in the capillaries of the skin. Because of its parallel course to the surface, nailfold-microscopy is especially easy to perform. The use of a video technique expanded the diagnostic possibilities, of not only the density of capillaries, tortuous index and diameter of erythrocyte columns, but also dynamic measurements such as flow rates of erythrocytes became possible. Various studies have shown that there is a significant change of skin capillary circulation in patients with polycythaemia, diabetes mellitus and hypertension.[8–10]

An effect of VPA on capillaries was shown in analysis of the cerebellar cortex[11] the effect of CBZ on the cerebral blood flow was shown by Sechi and Valmier.[12,13]

Method

The skin is illuminated by a microscope lamp at an angle of 45° to the surface. To improve contrast between the microvessels and the surrounding tissue a blue filter is used. The morphology of nailfold capillaries is studied by intravital capillaroscopy (Zeiss, Axioskop FS) at a magnification of 50×. Room temperature was maintained between 22 and 24 °C, the patient's arm was bedded on a warm (28 °C) microscope table with a sliding surface. Patients were examined in a sitting position after a resting time of at least 20 min. The capillaries were evaluated in accordance with the criteria as described by Jung et al.[14] The measurements were videotaped underlayed with a 1/100 s display.

The results were compared to standard values of rheologic parameters in children established by Engelmann.[15] The measured parameters included capillary density, diameter and tortuous index of the capillaries. The flow rate of erythrocytes was measured, as a dynamic parameter.

All of the patients in this study were outpatients in our neuropediatric Unit and were on valproat or carbamazepine, because of an epileptic disease (focale or generalized). Their ages ranged from 8 to 15 years (Table 1).

Results

We were able to examine 14 children with CBZ and 24 children with VPA, recruited in our neuropediatric Unit. The results were compared to normative

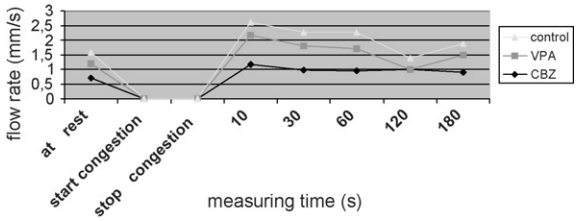

Figure 1 Flow rate of erythrocytes.

Table 1 Test persons—overview

	Carbamazepine	Valproate
Number	14	23
Ø Age	13	11.5
Gender f—m	6—8	8—15

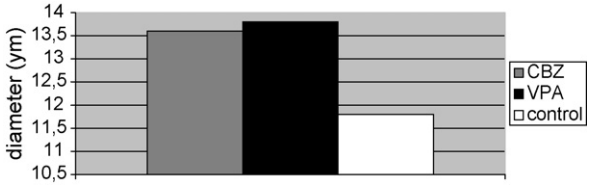

Figure 2 Capillary diameter.

values, determined in former analyses of 207 healthy children.

The patients were not examined before the anticonvulsive therapy was initiated, but according to the results of the normative values, it is not presumable, that the variances/differences in capillaries existed before therapy.

The duration of antiepileptic medication in the patients differs from 9 months to 4.5 year. The number of patients is to small, to divide them into subunits. The duration of the therapy tends to result in more pronounced changes of microcirculation.

We did not find a significant reduction in capillary density in our patients compared to the control group (CBZ 5.6 ± 1.1, VPA 6.0 ± 1.2, control 6.1 ± 1.1 *capillaries per mm epidermical edge*). Children treated with VPA or CBZ showed a significant increase in the tortuous index of the capillaries (CBZ 0.8 ± 0.6, VPA 1.4 ± 1.3, control 0.3 ± 0.3) [$p < 0.001$] and there was also a significant change in the capillary diameter, with an extension in the venous loop of the capillaries (Fig. 2) [VPA: $p < 0.001$, CBZ: $p < 0.009$]. There was no difference in the arterial loop.

Furthermore, there was a major difference in the flow rate of erythrocytes, with a significant increase in the rate for VPA [$p < 0.004$] and CBZ [$p < 0.001$] (Fig. 1).

Hemorheological differences could be shown for CBZ and VPA with a decreased plasma viscosity and aggregation of erythrocytes (Table 2).

Discussion

Changes of cardiovascular risk factors have been described in patients with epilepsy. The risk of coronary heart disease was found to be greatly increased (Karabiber et al.[2]). The influences of AEDs on serum lipids and on lipid metabolism are usually focused upon as an explanation of these findings.

We hypothesized that the influence of AEDs on the cardiovascular system may be broader and the changes of microcirculation may also be involved.

To the best of our knowledge, this issue (e.g. extension of the capillary diameter) has not been addressed in the past.

1. *Extension of the diameter in the venous loop of the capillaries*: The extension of the venous diameter could be seen as a result of vasomotoric instability in the form of spasms or atony,[16] but additionally the increased erythrocyte flow rate could lead to the found venous extension.
2. *Increased erythrocyte flow rate*: There is a known change in the constellation of serum lipid due to CBZ therapy, with an increase of the HDL-fraction (high density lipoprotein), especially the HDL-C and HDL3-C concentrations.[17] In the literature, patients on valproate showed significantly lower cholesterol, LDL-c and triglyceride levels but the differences in HDL-c levels were non-significant.[18] Additionally, there is a known pre-capillary vasodilatation in patients with epilepsy and VPA, leading to a hyperperfusion. An AED triggered reduction of central sympathotonus or a restriction of noradrenalin release were discussed as possible mechanisms.[19,20] At least, a reduced aggregation of erythrocytes and platelets, mainly due to hypofibrinogenemia[21] leads to the increase in erythrocyte flow rate.
3. *Elevated density of capillaries and tortuous index*: This raised index in patients with anticonvulsive therapy could be seen as (an effect)/(a result) of the underlying disease due to neurovascular dystonia and vasomotoric instability in the form of spasms or atony, as seen by Hauptmann in 268 of 304 neurological patients.[22] The latter authors included patients with a large range of neurological disorders in their study, ranging from epilepsy to schizophrenia. A second point is a raised MCV (mean corpuscular volume) as result of the AEDs.[5]

In summary we found changes of microcirculation in the terminal vascular bed in children with epilepsy and either VPA or CBZ monotherapy. By various mechanisms, VPA and CBZ may enhance degenerative mechanisms in vascular endothelium.[6] In the context of a reduced morbidity of patients with

Table 2 Aggregation of erythrocytes and plasma viscosity

	CBZ	VPA	Control
Aggregation of erythrocytes	14.98 ± 6.11	14.94 ± 5.25	16.2 ± 7.0
Plasma viscosity (mPa s)	1.26 ± 0.27	1.27 ± 0.31	1.30 ± 0.1

coronary heart disease and concomitant antiepileptic medication with phenytoin or phenobarbitone,[3] microcapillary effects could be of special interest in further investigations.

We suggest that the influence of AEDs on microcirculation should also be considered in further studies on cardiovascular changes in patients with antiepileptic long-term medication.

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