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Serum lipids and anticonvulsants

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The serum lipid levels of 200 epileptics (aged 20 to 40 years) undergoing long-term treatment with anticonvulsants were measured and compared with the levels of a normal population of the same age. The epileptics had higher serum lipid levels (especially of apolipoprotein B and HDL-cholesterol) but no higher incidence of hyperlipemias. A correlation between LDL-cholesterol and vitamin E has been found in epileptics, but it was not as significant as in normals. In male epileptics, positive correlations between the average daily dose of anticonvulsants (especially of those with a well-known enzyme-inducing effect) and triglycerides, cholesterol and LDL-cholesterol were found; in females there were no significant correlations.

Key words: Anticonvulsants – hyperlipemia – risk of cardiovascular diseases – serum lipids – vitamin E.

The different types of hyperlipemias and their importance as a risk factor in cardiovascular diseases have been known for many years. In 1975, new attention was drawn especially to the high-density-lipoproteins (HDL), when *Miller & Miller* (1975) postulated that these lipid fractions are a protective factor against atherosclerosis. In the following years many authors confirmed the fact of a low level of plasma-HDL in patients with cardiovascular diseases (*Berg et al.* 1976, *Castelli et al.* 1977, *Fuller et al.* 1978, *Gordon et al.* 1977, *Miller et al.* 1977, *Steinberg* 1978). In various previously reported studies (*Livingston* 1976, *Luoma et al.* 1979, *Mertz* 1979, *Pelkonen et al.* 1975, *Reunanen & Sotaniemi* 1977) elevated levels of serum lipids had been found in epileptics undergoing long-term treatment with anticonvulsants. Diphenylhydantoin (DPH) and barbiturates especially increase the cholesterol as well as the triglyceride level, possibly via an inducing effect on hepatic enzymes (*Reunanen & Sotaniemi* 1977) or an altered bile acid metabolism (*Miller & Nestel* 1973). Some authors postulated a high risk of cardiovascular diseases (*Pelkonen et al.* 1975, *Reunanen & Sotaniemi* 1977).

On the other hand, *Linden* (1975) and *Livingston* (1976) suspected a low incidence of myocardial infarction in a large number of epileptic patients. Since the discovery of the above-mentioned protective effect of HDL these observations were thought to be due to an increased HDL-

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level in epileptics. *Nikkilä et al.* (1978) found elevated HDL-levels in a small number of epileptics.

The present study was undertaken to compare the serum lipid levels of a larger number of epileptics with the levels of an unselected population of the same age in order to find out whether there is a connection between anticonvulsant drug therapy and hyperlipemias, the single lipid parameters, and the risk of cardiovascular diseases. In addition we tested to see if the highly significant correlation between LDL-cholesterol and vitamin E, shown in healthy adults (*Brubacher et al.* 1974), also exists in epileptics undergoing anticonvulsant treatment.

MATERIAL AND METHODS

A total of 200 epileptics (127 males and 73 females) aged 20 to 40 years were investigated. Each of them had been undergoing anticonvulsant therapy for at least 1 year. Because most of the epileptics were undergoing a combination therapy with several anticonvulsants, a calculation of equivalent units (modified after *Richens & Rowe* 1970) was made*; the anticonvulsants were divided into those with a well-known enzyme-inducing effect (phenytoin, phenobarbital, primidone, carbamazepine, mephenytoin) and others. The daily intake as well as the total amount of equivalent units since start of therapy were calculated and compared with the lipid levels.

The fasting serum levels of triglycerides and cholesterol were determined following the procedure of the *Lipid Research Clinics* (1974); the determination of the phospholipids after ashing with trichlor-acetic-acid-precipitates followed the method of Boehringer (*Zöllner & Eberhagen* 1965). The fractionation of the lipoproteins was carried out by ultracentrifugation (*Technicon Instruments* 1972); apolipoprotein B was measured by immunonephelometric quantitation (*Heuck & Schlierf* 1979).

The lipid levels of the epileptics were compared with those of a normal population of the same age from the same area (*Arab et al.* 1981). 2 lipid fractions (phospholipids, LDL-cholesterol) were not measured in the group of normal males. For these cases, the normal values of the medical laboratory Heidelberg were used.

Statistical analysis of the data employed Student's *t*-test and regression analysis.

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* 1 equivalent unit = 50 mg phenytoin, 30 mg phenobarbital, 125 mg primidone, 50 mg CHP-phenobarbital, 200 mg carbamazepine, 50 mg mephenytoin, 250 mg ethosuximide, 300 mg valproate sodium, 2 mg clonazepan, 300 mg mesuximide, 100 mg sulthiam, 250 mg trimethadione.

Table 1. Mean range and standard deviation of serum lipids in epileptics and normals

	Triglyc.[1]	Chol.[1]	Phos-phol.[1]	LDL-chol.[1]	HDL-chol.[1]	APO-B[2]	
Epileptics ($n = 127$)	1.36 ±0.77	5.41[d] ±1.06	2.87 ±0.67	3.42 ±0.92	1.27[b] ±0.35	113[a] ± 31	♂
Normals ($n > 500$)	1.30 ±1.08	5.21 ±1.09	2.80 ±0.47	3.33 ±0.81	1.12 ±0.31	91 ± 22	♂
Epileptics ($n = 73$)	1.14[d] ±0.38	5.68[b] ±1.01	3.11 ±0.68	3.39[c] ±0.89	1.63[b] ±0.37	115[a] ± 35	♀
Normals ($n > 500$)	1.06 ±0.38	5.26 ±0.96	3.09 ±0.60	3.18 ±0.91	1.41 ±0.31	91 ± 23	♀

[1] mmol/l [2] mg/dl

Significances in the *t*-test:

[a] $P < 0.0001$ [c] $P < 0.005$

[b] $P < 0.001$ [d] $0.1 > P > 0.05$

RESULTS

Table 1 shows the mean range and the standard deviation of serum lipid levels of the epileptic patients in comparison with the normal population. All lipid fractions showed higher levels in the patients treated with anticonvulsants. The apolipoprotein B- and the HDL-cholesterol levels were most clearly elevated. In male patients, the HDL-cholesterol levels were elevated about 11 %, in females about 18 % when compared with the group of normals. The 14 epileptics with a high HDL-cholesterol > 2.0 mmol/l had a significantly higher cholesterol level (6.36 mmol/l), compared with the rest of this group (5.48 mmol/l). The triglyceride levels as well as the LDL-cholesterol levels were within normal ranges in these patients.

In epileptics the incidence of hyperlipemias was not higher than in normals: 4.7 % of the group had a type IV, 1.6 % a type IIa and 1 single patient a type IIb hyperlipemia.

The results of the statistical analysis of the lipid levels in correlation with the average daily and total intakes of equivalent units are shown in Table 2. In male epileptics we found positive correlations between the average daily dose of anticonvulsants (equivalent units/d) and the triglycerides ($P < 0.01$), the cholesterol ($P < 0.003$) and the LDL-cholesterol ($P < 0.003$). Taking only the daily dose of enzyme-inducing anticonvulsants into consideration, the significance becomes higher (triglycerides $P <$

Table 2. Regression analysis between anticonvulsants and serum lipids (N.S. = non significant)

		P ♂	*P* ♀
Total amount of anti-convulsants (equivalent units)	Tg., Chol., Pl., LDL-chol., HDL-chol., Apo-B	N.S.	N.S.
Total amount of enzyme inducing anticonvulsants (equivalent units)	Tg., Chol., Pl., LDL-chol., HDL-chol., Apo-B	N.S.	N.S.
Average daily intake of anti-convulsants (equivalent units/d)	triglycerides	0.010	N.S.
	cholesterol	0.003	N.S.
	LDL-cholesterol	0.033	N.S.
	HDL-cholesterol	N.S.	0.057
Average daily intake of enzyme inducing anticonvulsants (equivalent units/d)	triglycerides	0.0009	N.S.
	cholesterol	0.0003	N.S.

0.0009, cholesterol $P < 0.0003$). Because of the small number (11) of patients undergoing monotherapy with drugs without known enzyme-inducing effect, no statistical analysis of these cases was made. In females we found no significant correlations.

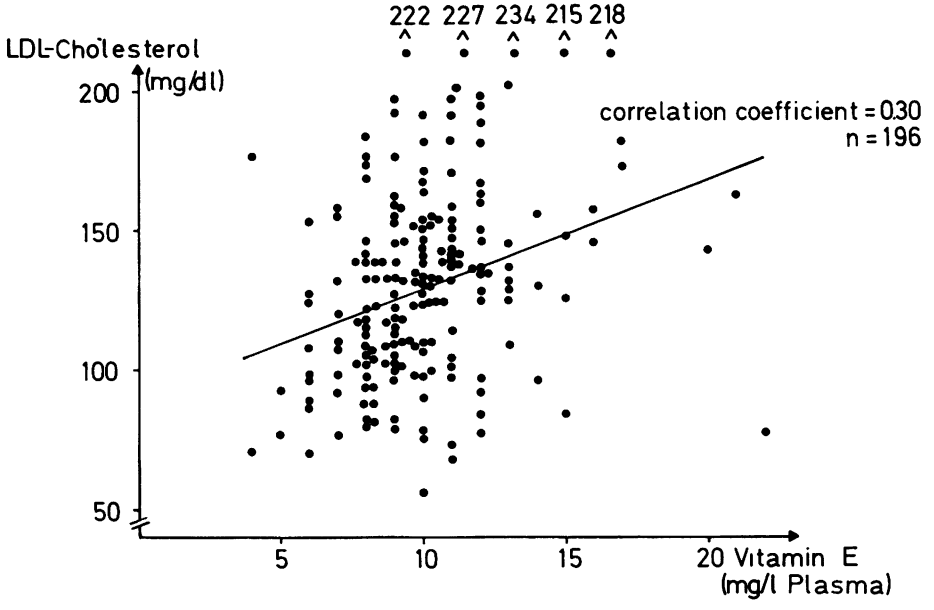

Fig. 1. Correlation between vitamin E and LDL-cholesterol in epileptics.

In addition, a correlation analysis between the LDL-cholesterol and vitamin E has been carried out. Testing these 2 parameters we found a significant correlation (coefficient 0.30, $P < 0.001$, Fig. 1).

DISCUSSION

While *Nikkilä et al.* (1978) found an elevation of HDL-cholesterol and VLDL-triglyceride as well as a lowering of LDL-cholesterol in their patients, in the present study all lipid fractions were elevated in patients of both sexes. These results suggest a general influence of anticonvulsants on the lipid status. The findings of significant positive correlations between some of the lipid fractions and the average daily dose of anticonvulsants (especially of those with a well-known enzyme-inducing effect) support this suggestion. There were different findings in female and male epileptics: only the male patients showed a significant correlation between triglyceride, cholesterol and LDL-cholesterol and the average daily antiepileptic drug dose. Probably this fact is due to the smaller number of females examined. But also one has to consider an interference from female sexual hormones, which are known to influence the enzyme induction (*Conney* 1967).

On the other hand, only women showed a probable correlation of HDL-cholesterol with the average daily drug intake. These results are consistent with those of *Luoma et al.* (1980) who described a significant elevation of HDL-cholesterol only in female patients. In contrast *Nikkilä et al.* (1978) found a more marked elevation of HDL-cholesterol in males. The evidence of sex-linked differences in the influence of antiepileptic drug treatment on the lipid status should be controlled with larger groups, taking constitutional factors, such as height, weight and Broca-index, into consideration.

The elevation of HDL-cholesterol in our patients was higher than that of cholesterol, but lower than the elevation of apolipoprotein B in males as well as in females. Since this apolipoprotein plays a role in the deposition of lipids into blood-vessels (*Fischer-Dzoga et al.* 1976), it is unlikely that the influence of anticonvulsants on the lipid status leads to a lower risk of cardiovascular diseases in epileptics. Corresponding to this prediction, *Hauser et al.* (1980) in their epidemiological study found no lowered mortality rates of cardiovascular diseases in epileptics. The increase of HDL-cholesterol seems to be part of an elevation of all serum lipids in patients undergoing anticonvulsant treatment. These findings are consistent with the observations of *Luoma et al.* (1979), who suggested that the increase of plasma HDL-cholesterol was influenced by the endogenous lipid metabolism.

Reviewing the connection between LDL-cholesterol and the vitamin E-plasma-level in treated epileptics we found a positive correlation, but it was not as significant as that of the normal group examined by *Brubacher et al.* (1974). This fact may be due to the altering of the lipid status by the anticonvulsants, but one also has to consider a possible influence of antiepileptic drugs on the vitamin E-metabolism.

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