Serum Lipid Studies in Multiple Sclerosis

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The lipid pattern of blood serum has been studied in 32 patients with multiple sclerosis, in whom the disease was either remittent or slowly progressive. Although total lipids, free and esterified cholesterol, α- and β-lipoproteins and chylomicrons were found to be normal in patients, minimal and maximal values showed wider ranges than in controls.
Cholesterol esters were slightly reduced (71,6 $\pm$ 31,7 mg/100 m*l*) in patients with clinical exacerbation as compared to patients with "inactive" disease or healthy controls (160,4 $\pm$ 58,1 mg/100 m*l*).
Treatment with corticotrophin and hydrocortisone derivatives did not alter significantly any of the studied lipid constituents of the serum.

Bei 32 Patienten mit Multipler Sklerose (in Remission oder langsamer Progredienz) wurde das Lipidmuster im Serum untersucht. Gesamtlipide, freies und verestertes Cholesterin, α- und β-Lipoproteine sowie die Chylomikronen waren bei diesen Patienten normal, Minimal- und Maximalwerte zeigten eine größere Streuung als die Kontrollen. Bei Patienten mit klinischer Exacerbation waren, verglichen mit Patienten mit „inaktiver" Erkrankung oder gesunden Kontrollpersonen (160,4 $\pm$ 58,1 mg/100 m*l*), die Cholesterinester leicht vermindert (71,6 $\pm$ 31,7 mg/100 m*l*).
Keine der untersuchten Lipidfraktionen des Serums war bei Behandlung mit ACTH bzw. Hydrocortisonderivaten signifikant verändert.

An intensive neurochemical study of the brain and the analysis of the lipid composition of body fluids in multiple sclerosis have shown lowered tissue concentration of various lipids in demyelinating areas and increased content of some of them in the cerebrospinal fluid (1—4). Within remission of the disease, the serum level of total lipids, free and esterified cholesterol, lipoproteins, phospholipids and several fatty acids was described as largely normal (5—8). However, in exacerbations of the disease or after loading of patients with fats some alterations in the lipid metabolism were observed (9—12). On the grounds of conflicting results in these studies and a lack of information on the effect of corticotrophin and hydrocortisone derivatives on serum lipids in multiple sclerosis the present study was undertaken. The purpose of this study was to compare the levels of serum lipids in multiple sclerosis and healthy controls, as well as to evaluate the effect of clinical exacerbation and corticotrophin treatment on the lipid composition of the blood serum in multiple sclerosis.

Material and methods

The subjects of the present study comprised 32 patients with multiple sclerosis. In all cases the diagnosis of multiple sclerosis was made after complete clinical examination and only virtually certain cases were included in the study. The ages of patients ranged from 16 to 63 years (mean age 33,2 years). The course of the disease varied from 1 to 44 years. In 8 cases the estimations of serum lipids were carried out within exacerbations. Fourteen cases were found to be in remission and in 8 cases the estimations were done during a slowly progressive stage of the disease.
Blood (10 m*l*) was drawn from each subject from the antecubital vein after an overnight fast. The total serum lipids were estimated according to the method of Swahn (13). Cholesterol esters and free cholesterol were determined using the chromatography procedure described by Krawczynski and coworkers (14). Serum lipoproteins, chylomicrons and serum proteins were analysed by paper electrophoresis according to the method of Bogdanikowa (15).

Results

In the first stage of this study a comparison was made between the serum levels of total lipids, esterified and free cholesterol, lipoproteins and chylomicrons from a series of 32 patients with multiple sclerosis and in healthy controls (Tab. 1).
Table 1 shows the mean values and the standard errors of the means for different serum lipids. Statistical examination (Student's test) of the values obtained showed that there was no significant difference between these two groups. However, two facts were noteworthy: In multiple sclerosis serum cholesterol esters did show standard deviations of far wider range ($\pm$ 63,5), than did controls, and the percentage of chylomicrons was slightly increased in this patient group (23,16%) as compared with the control group (10,0%). These results suggest greater fluctuations of cholesterol esters and the tendency to increased concentration of

Tab. 1
Serum lipid levels in 32 patients with multiple sclerosis and in healthy controls

	Multiple sclerosis Mean value mg/100 m*l*	Controls Mean value mg/100 m*l*	p
Free cholesterol	47.4 $\pm$ 34.6	49.0 $\pm$ 2.0	Not significant
Esterified cholesterol	137.1 $\pm$ 63.5	121.9 $\pm$ 2.4	Not significant
Total lipids	620 $\pm$ 190	860 $\pm$ 125	Not significant
	Mean value %	Mean value %	
α-lipoproteins	34.72 $\pm$ 9.29	30.0 $\pm$ 6.4	Not significant
β-lipoproteins	42.12 $\pm$ 13.33	60.0 $\pm$ 5.1	Not significant
Chylomicrons	23.16 $\pm$ 13.99	10.0 $\pm$ 5.2	Not significant

low density lipoproteins (chylomicrons) in the serum of patients with multiple sclerosis.

In the second stage of the study the analysis of serum lipids was performed according to the estimated activity of the disease. The basal criteria on which the grading was made were the following: subacute, recent clinical deterioration (I group of patients with exacerbation), lack of evidence of any clinical deterioration (II group with stationary course) and slowly deteriorating neurological disability (III group with progressive course). The results of this analysis presents table 2.

There were no significant differences of the serum lipids in any group, although a slightly lower concentration of cholesterol esters was found in patients with clinical exacerbation. The number of patients with subacute, active disease was small and therefore these results are not completely convincing. In one of the cases from the present series showing recent and rapid deterioration, the concentration of serum free and esterified cholesterol was diminished to 3 and 20 mg/100 m*l* respectively (normal means 49,0 and 121,9 mg/100 m*l*).

In the third part of this study another comparison was made between the levels of serum lipids before and after treatment with corticotrophin or hydrocortisone derivatives. The results of this comparison are shown in table 3.

As in previous comparisons the figures from table 3 show no statistical differences. Corticotrophin slightly increased the content of total lipids (from 576 up to 696 mg/100 m*l*) and cholesterol esters (from 116 up to 133 mg/100 m*l*) and diminished the percentage of serum γ-globulins, but this influence did not reach the level of statistical significance.

Discussion

After an overnight fast in multiple sclerotic subjects as well as in healthy controls, serum chylomicrons were identified only occasionally. Among 32 patients, chylomicrons were not identified in 7 and in 25 these low density lipoproteins were found to be in ranges between 16, 64 and 44, 49%. CSÖGÖR and coworkers (12) stated that in multiple sclerosis, the serum concentration of chylomicrons rose to greater extent after loading with fats and persisted for a longer time than in controls. According to SKILLEN and coworkers (16) the percentage of chylomicrons with a diameter exceeding 0,5 micron (S_f 10^4—10^5) did reach 55 in multiple sclerosis and was evidently higher than in controls (34%). Although the present study showed normal values of total serum lipids, mainly triglicerides bound with lipoproteins, and of chylomicrons in multiple sclerosis, there is a distinct possibility that in some cases there is an increased alimentary lipemia. Because of normal activity of lipoprotein lipase in multiple sclerosis, as was shown by SCHÄR (17), it may be supposed that in some conditions chylomicrons of post-absorptive serum are assembled and metabolized at a slower rate by hepatic cells than in healthy controls.

Lipoprotein molecules are probably rapidly synthesized de novo in the liver and their protein portion has a short half life, (18). The α- and β-lipoproteins in fasting serum were described in multiple sclerosis either as normal, or the α-fraction was found to be below normal concentration (12, 19). In the post-absorptive state the reduction of serum α-lipoproteins and the elevation of β-lipoproteins in multiple sclerosis are the reverse of that observed in healthy controls, where α-lipoproteins are probably involved in the lipid transport

Tab. 2
Serum lipid levels in remittent, slowly progressive and stationary multiple sclerosis*

	Remittent form 8 cases	Slowly progressive form 8 cases	Stationary form 14 cases
Values in mg/100 m*l*			
Cholesterol	30.5 ± 22.2	32.3 ± 12.6	58.9 ± 25.3
Cholesterol esters	71.6 ± 31.7	175.6 ± 63.7	151.1 ± 52.7
Total lipids	561 ± 140	717 ± 208	625 ± 185
Values in %			
α-lipoproteins	32.59 ± 8.42	42.51 ± 8.26	31.56 ± 8.39
β-lipoproteins	34.37 ± 18.30	35.42 ± 8.25	45.36 ± 13.20
Chylomicrons	23.94 ± 16.00	22.21 ± 13.98	23.05 ± 10.92

* All differences not significant

Tab. 3
Serum levels of lipids and proteins prior to and after treatment with corticotrophin or hydrocortisone derivatives in multiple sclerosis*

	ACTH Group 18 cases		Hydrocortisone Group 5 cases	
	Before	After	Before	After
Values in mg/100 m*l*				
Cholesterol	39.8 ± 24.0	35.1 ± 16.5	39.6 ± 13.4	27.8 ± 12.1
Cholesterol esters	116.9 ± 54.3	133.2 ± 53.7	129.4 ± 50.6	119.8 ± 4.2
Total lipids	576 ± 172	696 ± 211	693 ± 112	675 ± 230
Values in %				
α-lipoproteins	33.77 ± 7.54	36.99 ± 9.42	41.21 ± 6.72	30.73 ± 16.23
β-lipoproteins	43.84 ± 15.60	44.58 ± 15.45	33.69 ± 8.95	44.67 ± 6.04
Chylomicrons	22.31 ± 15.53	17.41 ± 13.45	25.12 ± 31.32	24.58 ± 30.20
Albumin	59.64 ± 8.43	60.67 ± 9.09	58.91 ± 9.63	63.91 ± 7.51
α_1-globulin	4.68 ± 6.06	5.08 ± 1.79	5.33 ± 1.25	4.84 ± 0.47
α_2-globulin	7.46 ± 1.96	7.78 ± 2.62	8.71 ± 3.04	6.86 ± 1.67
β-globulin	9.95 ± 2.75	9.79 ± 2.11	9.93 ± 3.49	8.48 ± 2.00
γ-globulin	18.04 ± 4.87	16.61 ± 7.95	16.88 ± 4.04	15.78 ± 6.17

* Both groups before treatment versus groups after treatment: difference not significant

from the intestinal mucosa to the liver. The Present paper, however, does confirm the normal concentration of serum lipoproteins, apart from one minor aspect. There was slight evidence of a greater percentage of serum chylomicrons. The electrophoretic analysis showed a normal distribution of serum lipoproteins both in active and inactive multiple sclerosis. Although these protein-lipid complexes have different immunochemical characteristics, they did not change quantitatively, even if brain antigens are released during clinical exacerbation.

The subject of the present study did not include serum fatty acids bound to albumin. Hypoalbuminemic states in multiple sclerosis and decreased capacity of serum albumin to bind congo red suggest that the transport of some fatty acids may be modified. BAKER and coworkers (10) found the reduction of linoleic acid (18:2), and TUNA and coworkers (20) gave a lower value for palmitic acid (16:0). In the cholesterol esters CUMINGS and coworkers (21) measured a decreased content of palmitic and stearic acid (18:0). This abnormality might be due either to a high level of oleic acid (18:1) in the diet, which is known as a suppressing factor in hepatic synthesis of linoleic acid, or to a failure in intestinal absorption. Both hypotheses seem to be unlikely.

The serum level of cholesterol esters in patients with clinical exacerbation was slightly lower than in other groups of patients, but this difference was not significant. BAKER and coworkers (11) found that the reduction of serum cholesterol esters and especially cholesterol linoleate was correlated with the extent and degree of recent clinical deterioration. No satisfactory explanation of this abnormality is yet in sight, but it may be suggested that immunologically active, toxic factors diminish the activity of serum fatty acid transferase, which is involved in the formation of cholesterol esters.

The concentration of free cholesterol in the serum was not altered, although a high standard deviation (± 34,6 mg/100 m*l*) and greater ranges of values (3—115 mg/100 m*l*) are worthy of note. GREEN and coworkers (1) found a lack of correlation between the levels of total cholesterol and γ-globulin in the cerebrospinal fluid from one side, and so did LIENHARDT (8) between serum total cholesterol and the titre of anti-brain antibodies from another. These observations weaken markedly the supposition that cholesterol fluctuations in multiple sclerosis are due to immunological mechanisms.

The analysis of serum lipids and proteins in patients prior to and after treatment with corticotrophin or hydrocortisone derivatives did not alter significantly any of the studied constituents in multiple sclerosis.

Addendum

Studies of EPERJESSY and coworkers (Symp. on the Pathology of Human Allergic Dis., Tirgu-Mures, 1967) showed the possibility that protein portion of serum lipoproteins in multiple sclerosis contains 19 amino acids instead of 14 in normal controls. BOLTON and coworkers (Lancet London, 1968/I, 99) found that low-density lipoproteins include qualitatively altered phospholipid, wich may cause increased plateled stickness in multiple sclerosis.

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