Plasma lipids and coagulation in patients with arteriosclerotic dementia

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SYNOPSIS Plasma lipids and lipoproteins, glucose, uric acid, and haemocoagulative parameters were studied in a group of 22 elderly hospitalized patients with arteriosclerotic dementia, and compared with those of a control group of a similar age. No significant differences were found in lipids, lipoproteins, glucose, or uric acid but the fibrinogen level was significantly raised in the group with arteriosclerotic dementia. A comparison of the metabolic parameters of the dementia patients with those of a group of subjects with peripheral occlusive arteriosclerosis showed, on the other hand, that this latter group had significantly raised plasma triglycerides as well as a significantly higher incidence of the Fredrickson phenotypes of hyperlipoproteinaemia. These findings indicate that the common laboratory parameters used to evaluate arteriosclerosis are not adequate to point out any pathogenic mechanism for arteriosclerotic dementia, and research should therefore be focused in other directions.

Cerebral arteriosclerosis may produce dementia characterized by the loss of higher intellectual capacities, loss of memory and initiative, irritability, and, often, behavioural modifications, such as depression, confusion, and agitation (Mayer *et al.*, 1959). Studies on the biochemical and haemocoagulative parameters of patients with cerebral arteriosclerosis have yielded conflicting results, and no clear-cut pattern has been determined. Mayer *et al.* (1959) denied that hypercholesteraemia is more frequent in patients with cerebral arteriosclerosis, whereas Heyman *et al.* (1961) found a very high percentage of hypercholesteraemia among their patients. In a recent study by Acheson and Hutchinson (1972), in patients with cerebral arteriosclerosis showing plasma cholesterol levels above 250 mg per 100 ml, clofibrate treatment lowered serum cholesterol but failed to modify prognosis. According to Pendefunda *et al.* (1966) in 70% of patients with cerebral arteriosclerosis increased triglyceride levels could be ascertained, other lipid parameters being normal. Drobinski and Palamarchuk (1969), in a group of 361 young patients (aged 33-35 years) with neurological symptoms

of cerebral arteriosclerosis, found increased plasma cholesterol levels and decreased lecithins in 38% of the cases; arterial pressure was generally normal.

Brancale (1970) found a high frequency of hypercoagulability in 120 patients with cerebral arteriosclerosis, apparently dependent also upon the subject's age, the severity of the process, and concomitant diabetes. Ethnic differences between arteriosclerosis of the circle of Willis in the United States and Japan, indicating that the Japanese have strikingly more severe lesions (Resch *et al.*, 1969), have not been adequately explained. In patients with arteriosclerotic dementia no conclusive data are reported concerning biochemical parameters.

Patients with peripheral occlusive arteriosclerosis tend to have higher blood triglyceride levels than controls, according to Greenhalgh *et al.* (1971), whereas, according to Cotton *et al.* (1972) these patients have a practically normal plasma lipid pattern, but exhibit marked alterations in several haemocoagulative tests.

It was our purpose to perform biochemical and haemocoagulative tests in elderly patients

with arteriosclerotic dementia, admitted to a neuropsychiatric hospital. Dementia generally develops in very severe forms of cerebral arteriosclerosis and it represents one of the more advanced stages of the arteriosclerotic process. The clinical diagnosis was supported by signs of neurological deficit, by mental tests and psychiatric rating scales. These patients were compared with a group of subjects of the same age, without symptoms of cerebral arteriosclerosis. Part of the biochemical investigations were also carried out in a sample of patients with peripheral occlusive arteriosclerosis, and these data were compared with those of the patients with arteriosclerotic dementia.

METHODS

SUBJECTS Twenty-two hospitalized patients with arteriosclerotic dementia, 33 control subjects with diagnoses other than arteriosclerotic dementia, and 21 patients with peripheral occlusive arteriosclerosis were considered from the Neuropsychiatric Hospital, Verona-Ponton, and the Second Surgical Clinic, University of Milan. Details of age and sex are given in Table 1. All patients were kept on a standard hospital diet, the number of calories being between

a 24 hour basis with determinations every two hours.

In patients with peripheral occlusive arteriosclerosis, digital plethysmography and oscillography were performed, as well as aortography by the Dos Santos technique, unless other clinical findings suggested it was better not to carry out this procedure. All patients were free from symptoms of liver and kidney damage.

BIOCHEMICAL AND HAEMOCOAGULATION PROCEDURES

Lipids Plasma cholesterol and triglycerides were measured after 12 hour fasting by a simultaneous automated procedure (Block *et al.*, 1965; Kessler and Lederer, 1965), and individual phospholipid classes were separated according to the method described by Rouser *et al.* (1966). Lipoprotein electrophoresis was performed on agarose gel by the method of Noble (1968); nephelometry according to Stone *et al.* (1970); lipoprotein separation by ultracentrifuge was carried out according to the NIH procedure (Fredrickson *et al.*, 1968).

Glucose and uric acid Glucose and uric acid were analysed by automated chemical procedures (Bittman and Manning, 1963; Musser and Ortigoza, 1966).

Coagulative parameters Fibrinogen was determined according to Fearnley and Chakrabarti (1966); partial thromboplastin time (PTT) according to Langdell *et al.* (1953); prothrombin time (PT) by Dade Thromboplastin reagent; platelet count was on a model F Coulter counter. Euglobulin lysis time (ELT) was measured according to Buckell (1958). Statistical differences between results were measured by the two-tailed *t* test.

RESULTS

CLINICAL FINDINGS Intelligence tests were applicable to only five subjects with arteriosclerotic dementia, and, according to the Wechsler Bellevue scoring system, their IQs ranged between 57 and 72. In the others the dementia did not allow verbal communication. The control subjects had IQs between 69 and 82, and no IQ was recorded for the patients with peripheral occlusive arteriosclerosis who, however, all seemed to have normal intellectual functions. Neurological deficits of varying degrees (from mild to severe) and signs of focal deficits were present in all subjects with arteriosclerotic dementia but in none of the controls or patients with peripheral occlusive arteriosclerosis. Hypertension (diastolic blood

TABLE 1

AGE AND SEX DISTRIBUTION IN THREE GROUPS
OF SUBJECTS CONSIDERED

Groups	Male	Female	Age (yr)
Arteriosclerotic dementia	12	10	70.77 ± 5.71
Controls	19	14	66.39 ± 6.24
Peripheral occlusive arteriosclerosis	21	—	62.14 ± 3.10

Means ± SD.

1,500 and 2,000 per day. The diagnosis of arteriosclerotic dementia was based upon clinical observation of the patients, the results of an intelligence test (Wechsler-Bellevue II), and a psychiatric rating scale (J. R. Wittenborn). Patients with psychiatric symptoms of dementia were included in the study only if the standard neurological examination showed signs of focal deficit. Eye ground observations were performed by two independent examiners.

Blood pressure measurements were carried out on

TABLE 2

LIPIDS, LIPOPROTEINS, GLUCOSE, AND URIC ACID PLASMA LEVELS IN PATIENTS WITH ARTERIOSCLEROTIC DEMENTIA AND CONTROLS (MG/100 ML)

	<i>Cholesterol</i>	<i>Triglycerides</i>	<i>sf 0-20</i>	<i>sf 20-400</i>	<i>sf 400</i>	<i>Glucose</i>	<i>Uric acid</i>
Arteriosclerotic dementia	207.50 ± 11.36	134.31 ± 21.96	383.27 ± 20.12	175.32 ± 25.45	7.26 ± 1.00	101.68 ± 6.76	4.75 ± 0.31
Controls	226.09 ± 11.38	124.39 ± 7.19	406.76 ± 9.94	143.03 ± 7.20	5.93 ± 0.54	93.04 ± 2.11	5.14 ± 0.25

Means ± SEM.

No significant differences.

TABLE 3

COAGULATION PARAMETERS IN PATIENTS WITH ARTERIOSCLEROTIC DEMENTIA AND CONTROLS

	<i>Platelets (per mm³)</i>	<i>PTT (s)</i>	<i>PT (%)</i>	<i>Fibrinogen (mg/100 ml)</i>	<i>ELT (min)</i>
Arteriosclerotic dementia	194,630 ± 14,820	29.15 ± 0.78	91.88 ± 2.57	499.90 ± 23.35*	210.90 ± 11.34
Controls	184,277 ± 16,060	31.53 ± 1.00	92.86 ± 2.05	425.71 ± 17.60	199.00 ± 12.85

Means ± SEM.

* Significantly different from controls: $P < 0.01$.

TABLE 4

PHOSPHOLIPID LEVELS AND PERCENTAGE OF PHOSPHOLIPID CLASSES IN PATIENTS WITH ARTERIOSCLEROTIC DEMENTIA AND CONTROLS

	<i>Total (mg/100 ml)</i>	<i>Pl + Lys. (%)</i>	<i>Sph. (%)</i>	<i>Le (%)</i>	<i>Pl (%)</i>
Arteriosclerotic dementia	204.60 ± 0.154	6.82 ± 0.47*	23.39 ± 0.69†	67.14 ± 0.73	2.51 ± 0.16
Controls	234.50 ± 0.100 NS	5.47 ± 0.36	21.04 ± 0.43	67.51 ± 0.76 NS	2.66 ± 0.30 NS

Means ± SEM.

* Difference from controls: $0.05 < P < 0.1$.

† Significantly different from controls: $P < 0.05$.

TABLE 5

LIPID, GLUCOSE AND URIC ACID PLASMA LEVELS IN PATIENTS WITH ARTERIOSCLEROTIC DEMENTIA AND PERIPHERAL OCCLUSIVE ARTERIOSCLEROSIS (MG/100 ML)

	<i>Cholesterol</i>	<i>Triglycerides</i>	<i>Glucose</i>	<i>Uric acid</i>
Arteriosclerotic dementia	207.50 ± 11.36	134.31 ± 21.96	101.68 ± 6.76	4.75 ± 0.31
Peripheral occlusive arteriosclerosis	218.52 ± 10.65	192.66 ± 24.55*	104.77 ± 9.41	5.42 ± 0.32

Means ± SEM.

* Significantly different from patients with AD: $P < 0.01$

pressure over 100 mmHg steadily in 12 measurements over 12 hours, together with retinal changes) was present in two patients with arteriosclerotic dementia, and six with peripheral occlusive arteriosclerosis ($P < 0.05$), and in none of the controls.

All subjects with peripheral occlusive arteriosclerosis had pathological findings documented by plethysmography, oscillography, and angiography. These tests were not carried out in either demented patients or in control subjects. Palpation of the peripheral arteries in these subjects gave, however, normal findings.

LIPIDS Comparison of the blood lipid findings in arteriosclerotic demented patients and controls showed that cholesterol, triglycerides, and lipoprotein fractions separated by nephelometry, were not significantly different (Table 2). Patients with arteriosclerotic dementia showed a higher percentage of phosphatidylinositol (PI) and lysolecithins (Lys), as well as sphingomyelins (Sph) (see Table 4).

GLUCOSE AND URIC ACID These were not significantly different in the three groups (Table 2, and Table 5). Diabetes (fasting blood sugar above 120 mg per 100 ml with pathological glucose tolerance test) was recorded in two patients with arteriosclerotic dementia and four with peripheral occlusive arteriosclerosis, and one control. Elevated plasma uric acid levels ($> 7 \text{ mg}\%$) were found in three patients with arteriosclerotic dementia and four with peripheral occlusive arteriosclerosis, but in none of the controls. None of the patients had clinical gout.

HAEMOCOAGULATION Platelet number, PT, PTT, and ELT did not differ significantly between patients with arteriosclerotic dementia and controls. Fibrinogen levels were, however, significantly elevated in the arteriosclerotic dementia group (Table 3).

COMPARISON BETWEEN PATIENTS WITH ARTERIOSCLEROTIC DEMENTIA AND PERIPHERAL OCCLUSIVE ARTERIOSCLEROSIS It was soon evident that patients with peripheral occlusive arteriosclerosis had a significantly higher incidence of hypertriglyceridaemia than patients with arteriosclerotic

dementia (Table 5). Therefore, by using the N.I.H. protocol (Fredrickson, 1968) for the typing of hyperlipoproteinaemia, we could detect a significantly higher incidence of Fredrick-

TABLE 6
DISTRIBUTION OF FREDRICKSON HYPERLIPOPROTEINAEMIA PHENOTYPES AMONG PATIENTS WITH CEREBRAL ARTERIOSCLEROSIS AND PERIPHERAL OCCLUSIVE ARTERIOSCLEROSIS

Fredrickson types	Arteriosclerotic dementia	Controls	Peripheral occlusive arteriosclerosis
I	—	—	—
IIa	1	3	1
IIb	1	1	6
III	—	—	—
IV	2	3	8
V	—	—	—

son's phenotypes among the peripheral arteriosclerotic group than among controls or arteriosclerotic dementia patients (Table 6). We did not detect any floating beta-lipoproteins, although sinking pre-beta lipoproteins (Rider *et al.*, 1978) were detected in two patients in each group.

DISCUSSION

Our data show that plasma lipid and lipoprotein levels do not differ significantly between controls and patients with arteriosclerotic dementia. Only two phospholipid subclasses, sphingomyelin and phosphatidylinositol + lysolecithins were in a higher percentage in the latter group. Coagulative parameters were not markedly altered in either group, and only fibrinogen was significantly more elevated in patients with arteriosclerotic dementia. A comparison between demented and peripheral occlusive arteriosclerotic patients showed a significantly higher incidence of hypertension in the latter group, and we were also able to detect marked differences in plasma lipids and lipoproteins. In particular, peripheral occlusive arteriosclerotic patients had more elevated plasma triglycerides with a very high incidence of Fredrickson type IV hyperlipoproteinaemia while almost all the arteriosclerotic dementia patients had a normal lipid

lipoprotein pattern. Diabetes was more frequent in patients with peripheral occlusive arteriosclerosis but, on the whole, plasma glucose levels were not significantly different. Laboratory tests commonly used in the clinical diagnosis of atherosclerosis seem, therefore, to be of little value in evaluating arteriosclerotic dementia, the only exception being fibrinogen levels. Although coagulative parameters were not determined in our peripheral arteriosclerotic patients, it may be pointed out that fibrinogen was shown by Cotton *et al.* (1972) to be higher in such patients.

On the other hand, patients with peripheral occlusive arteriosclerosis had significantly higher triglyceride levels than control or arteriosclerotic demented patients. This finding, which confirms data by Greenhalgh *et al.* (1971), was not among the conclusions of the study by Cotton *et al.* (1972). This difference was probably due to the use of nephelometry as the only technique for estimating triglyceride-rich particles, while we determined cholesterol and triglycerides as did Greenhalgh *et al.* (1971), as well as the Fredrickson typing, thus probably providing more complete results.

Arteriosclerotic dementia is the consequence of severe, usually long-standing, anatomical damage to the cerebral arteries. Our study of the biochemical and haemocoagulative parameters in a group of patients with arteriosclerotic dementia failed to detect any significant alteration, with the possible exception of elevated fibrinogen levels. On the other hand, a group of peripheral occlusive arteriosclerotic patients of similar age showed evidence of markedly raised plasma triglyceride levels, a finding already shown by others; it may also be noted that signs of hypercoagulability have been reported in these latter patients. The authors feel that laboratory tests commonly used in the diagnosis of vascular diseases are not adequate in indicating any pathogenic mechanism in arteriosclerotic dementia. In spite of very severe vascular lesions, leading to dementia and focal deficits, laboratory tests did not indicate any abnormality. Studies in other directions, such as immunology, protein metabolism, and central mediators, are warranted.

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