Uric acid and serum lipids in cerebrovascular disease

Part 2: Uric acid—plasma lipid correlations

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A significant proportion of patients suffering from atherosclerotic coronary artery disease have elevated levels of lipid fractions in the blood (Schrade, Boehle, and Biegler, 1960; Albrink, Meigs, and Man, 1961; Albrink, 1962). Similar observations in patients with cerebrovascular disease have been sparse, and have yielded conflicting results. Of studies measuring serum cholesterol, Heyman, Neftzger, and Estes (1961) showed significantly higher cholesterol levels in patients with cerebral infarction than in patients with 'non-atherosclerotic illnesses'. Robinson, Higano, and Cohen (1963) described higher β lipoprotein cholesterol concentrations and $\beta:\alpha$ lipoprotein ratios in patients with cerebral thrombosis than in matched controls. However, others have failed to demonstrate significant elevation of serum cholesterol in cerebral thrombosis (Meyer, Waltz, Hess, and Zak, 1959).

Considering other serum lipids, Katsuki, Uzawa, Fujimi, Shiratsuchi, and Ito (1964) reported significantly higher triglyceride concentrations in patients with cerebrovascular disease than in normal controls. Feldman and Albrink (1964) studied 63 male patients, aged 37 to 73, with transient ischaemic attacks and with completed strokes. They found serum concentrations of cholesterol and triglycerides to be increased. The elevated triglyceride concentration was more closely associated with cerebrovascular disease than was the serum cholesterol concentration. Furthermore, a relatively high serum cholesterol was usually not associated with cerebrovascular disease unless the triglyceride was also elevated, while a low serum cholesterol concentration could be associated with cerebrovascular disease if the triglyceride was increased. This finding of a relationship between serum triglycerides and strokes, but less striking correlation with other lipid fractions, is in agreement with the findings of Katsuki *et al.* (1964) in Japanese subjects.

In a related study (Pearce and Aziz, 1969), we have been able to show that about 25% of patients

suffering from strokes have hyperuricaemia. This accords with the known predisposition to atherosclerosis observed in subjects suffering from gout (Bauer and Klemperer, 1947). Gertler, Garn, and Levine (1951) have shown that there is some relationship between serum cholesterol, lipid phosphorus, and uric acid in determining the occurrence of coronary artery disease. They were able to produce a simple formula relating these three fractions, and they produced an index (uric acid ratio) incorporating these observations which was effective in separating the coronary heart disease group from control subjects in 94% of cases.

Against this background, the present study was designed to investigate the relationship of plasma uric acid and various lipid fractions in patients with cerebrovascular disease. The index mentioned above has been applied to these patients, and the values obtained for the various lipid fractions have been subjected to a statistical analysis, applying correlation coefficients calculated by a computer.

MATERIAL AND METHODS

Sixty subjects, of whom 42 were male and 18 were female, formed the basis for this study. The patients had been admitted for neurological study on account of an acute cerebrovascular incident, which was ultimately diagnosed as a cerebral infarct (95%) or cerebral haemorrhage (5%). These patients were included in the separately reported study of uric acid levels in cerebrovascular disease (Pearce and Aziz, 1969). Venous blood was taken in the fasting state, 12 hours after the last meal, at 9.0 a.m., in all subjects. Uric acid levels were estimated by the phosphotungstic sodium cyanide method; serum cholesterol by the method of Pearson, Stern, and Mackett (1953); serum free fatty acids by the method of Peters and Van Slyke (1946); phospholipids as lipid phosphorus by the method of McDonald and Hall (1957); serum triglycerides by the method of Van Handel, Zilversmit, and Bowman (1957). It is important to utilize a conservative range of normal values, in attempting to detect abnormalities of plasma lipids,

since these fractions are affected by such a wide variety of physiological, dietetic, and racial variations.

The following values were taken to represent the upper limit of normal in the fasting state for the age group investigated (mean age for both sexes, 60.6, S.D., 11.2):

- Serum uric acid: 6 mg/100 ml. in females
- Serum uric acid: 7 mg/100 ml. in males
- Serum cholesterol: 300 mg/100 ml. in females
- Serum cholesterol: 270 mg/100 ml. in males
- Serum free fatty acids: 450 mg/100 ml. (male and female)
- Serum triglycerides: 180 mg/100 ml. (male and female)
- Serum phospholipids: 320 mg/100 ml. (male and female)

These figures were derived from the literature describing the methods cited above, and from current epidemiological data (Oliver, 1968).

RESULTS

The total sample consisted of 60 subjects (41 male and 19 female). The males and females were compared on all variables and were found to differ significantly in age alone (mean ages: males 57.4 years, females 67.6 years, $P < 0.001$ by t test). Since sex and age were found to be unrelated ($P > 0.05$) to the lipid fractions considered in this study, it was appropriate to pool the data for both sexes in all further statistical analyses. The age range under investigation was small (mean age: 60.6 years for both sexes; S.D. 11.2), and this probably explains the absence of any obvious increase in higher levels which are known to accompany increasing age. With respect to sex differences, the females are significantly older than the males, and this factor probably obscures any sex difference in lipid levels at any particular age group. Means and S.D. of variables other than age are shown in Table 1.

In order to assess whether these results were different from those expected in normal subjects, estimates of the 95th percentile level for normals for each fraction were made. The percentage of

TABLE 1
MEANS AND STANDARD DEVIATIONS OF URIC ACID AND LIPID FRACTIONS IN SERUM

	Mean (mg/100 ml.)	Standard deviations (mg/100 ml.)
Uric acid	6.0	1.7
Cholesterol	214	72.6
Triglycerides	138	76.4
Phospholipids	234	88.5
Free fatty acids	443	206.2

subjects in the sample having levels over the estimated normal 95th percentile was then compared with the estimated 5% of normals. Details of these comparisons are given in Table 2, which shows that the percentage of subjects with high free fatty acid and triglycerides is very significantly above the expected 5%. Therefore, it can be concluded that the subjects show raised levels of these two fractions; there are also elevations of all the lipid fractions in more than the expected 5% of subjects.

In assessing the relationship between hyperuricaemia and elevated lipid fractions, intercorrelations (Pearson's product moment) were calculated by a computer between uric acid levels and the lipid fractions. These are shown in Table 3 and indicate that, while all the lipid fractions intercorrelate significantly—that is, a subject who has one high value tends to have high values for other fractions—uric acid fails to correlate to a significant degree with cholesterol, phospholipids, and free fatty acids. The correlation of 0.23 between uric acid and triglycerides just fails to reach the statistically accepted level of $P = 0.05$ (for this correlation, $0.10 > P > 0.05$ in a two-tailed test). This result may have clinical and pathological significance.

The uric acid ratio (Gertler *et al.*, 1951) is represented by:

$$k = \frac{\text{cholesterol (mg/100 ml.)} \times \text{uric acid (mg/100 ml.)}}{\text{lipid phosphorus (mg/100 ml.)}}$$

k = less than 119 in 94% of normal subjects (146 observations).

TABLE 2
ASSESSMENT OF ELEVATION OF SERUM LIPID FRACTIONS

Fraction	Estimated upper limit of normal, 95th percentile	(sex)	Patients above 95th percentile (no.)	(%)	Significance
Cholesterol	270 mg/100 ml.	M	6	15	N.S.
Cholesterol	300 mg/100 ml.	F	2	10.5	N.S.
Free fatty acids	450 mg/100 ml.	M and F	21	35	$P < 0.001$
Triglycerides	180 mg/100 ml.	M and F	15	25	$P < 0.001$
Phospholipids	320 mg/100 ml.	M and F	7	11.6	N.S.
Uric acid	7.0 mg	M	9	20	
Uric acid	6.0 mg	F	6	33	

Our results applying this formula are as follows:

60 observations, Mean $k = 143.4$ (S.D., 81.1)
Range 38.1 to 361.7

Using $k = 119$ as the cut off point, 30 subjects were above and 30 below this figure.

DISCUSSION

The results indicate that the patients in this study with cerebrovascular disease had serum lipid levels which were consistently higher than those anticipated in the normal population. The magnitude of this elevation was of a moderate degree, and was noted particularly in respect of serum triglycerides and free fatty acids (Table 4). The results extend the observations of Heyman *et al.* (1961), Feldman and Albrink (1964), Katsuki *et al.* (1964), and Jakobson (1967).

It is important to note, however, that attacks of cerebral ischaemia and cerebral infarction may occur in the presence of normal serum lipid levels as pointed out by Meyer *et al.* (1959). Inspection of our results, and consideration of the previous studies cited, show a general trend in which an elevated serum triglyceride concentration is more closely associated with cerebrovascular disease than are elevations of other serum lipid fractions. In general, these findings are similar to those observed in coronary artery disease although they are less marked (Albrink *et al.*, 1961).

The various lipid fractions estimated in this study are transported in lipoprotein molecules. The α -lipoproteins are of high density, and are rich in phospholipids. The present investigation does not show any gross abnormality of α -lipoprotein metabolism. The β -lipoproteins are of low density, and largely represented by cholesterol. The very low density β -lipoproteins are reflected in triglyceride levels in the serum. Our results show predominant changes in the β -lipoprotein fractions of both low density and very low density. However, these are not of the magnitude seen in the genetically determined hyperlipoproteinaemic states described by Fredrickson, Levy, and Lees (1967).

The main purpose of this work was to assess the possibility of a correlation between plasma lipid fractions and hyperuricaemia. Theoretical reasons for such a relationship have been described in a previous communication (Pearce and Aziz, 1969). A clinical basis for such an association is provided by Harris-Jones (1957). He reported 22 patients and their relatives with essential hypercholesterolaemia and xanthomatosis, and found that all except one of the patients with uric acid levels of greater than 7 mg/100 ml. had serum cholesterol levels of 400 mg/100 ml. or more. He suggested that the conditions of hyperuricaemia and hypercholesterolaemia might be related by genetic linkage, on the basis of an autosomal dominant inheritance. He also considered the possibility that hypercholesterolaemia might inhibit

TABLE 3
INTERCORRELATIONS OF URIC ACID AND LIPID FRACTIONS IN SERUM

	Uric acid	Cholesterol	Triglycerides	Phospholipids
Cholesterol	0.066			
Triglycerides	0.230	0.375†		
Phospholipids	-0.002	0.445†	0.555†	
Free fatty acids	0.022	0.284*	0.323*	0.456†

*Correlation significant at 0.05 level.

†Correlation significant at 0.01 level.

TABLE 4
CORRELATION COEFFICIENTS OF SERUM URIC ACID, LIPIDS AND 'URIC ACID RATIO'

	Age	Uric acid	Cholesterol	Triglycerides	Phospholipids	Free fatty acids
Uric acid	0.123					
Cholesterol	0.195	0.066				
Triglycerides	0.022	0.230	0.375†			
Phospholipids	0.069	-0.002	0.455†	0.555†		
Free fatty acids	0.065	0.022	0.284*	0.323*	0.456†	
Uric acid ratio	0.163	0.515†	0.374†	-0.120	-0.492†	-0.047

*Correlation significant at 0.05 level.

†Correlation significant at 0.01 level.

the excretion of uric acid and hence produce hyperuricaemia.

Evaluation of our data by correlation coefficients, shows quite clearly that elevation of the lipid fractions intercorrelate to a significant level. However, uric acid levels do not correlate to a significant degree with free fatty acids, phospholipids, or cholesterol. The correlation coefficient between uric acid and triglyceride was 0.23 and has borderline statistical significance $0.10 > P > 0.05$. This observation may be clinically relevant.

On theoretical grounds, it would be valuable to obtain some biochemical parameter which would separate patients with cerebrovascular disease from control subjects of similar age, sex, and domestic background. Although never widely applied, the uric acid ratio (Gertler *et al.*, 1951) seems to offer a simple formula of high predictive value in coronary artery disease, in which it separated 94% of patients from controls. This formula has never been applied to patients with cerebral ischaemic attacks or cerebral infarction. Its application in our series of patients showed a very wide range of values, and 50% of the subjects examined were above the critical figure of 119 and 50% were below. We concluded, therefore, that this formula has no value in either the prediction or detection of cerebrovascular disease, but we are unable to explain the discrepancy between this group of patients and those with coronary artery disease.

In conclusion, we have shown a general trend consisting of an elevation in serum lipid fractions in patients with cerebrovascular disease. The abnormalities observed were not, however, of gross magnitude. The serum lipid fraction showing the highest degree of correlation with the clinical occurrence of a stroke was the serum triglyceride level in the fasting state. A small degree of correlation below the statistically acceptable limits of significance was shown between hyperuricaemia and hypertriglyceridaemia. The role of these abnormalities in the genesis of atherosclerotic disease of the great vessels and cerebral vascular tree remains uncertain, but there is no definitive evidence that such abnormalities are primarily responsible for cerebrovascular atherosclerosis.

We are, therefore, unable to provide any scientific basis for dietetic restriction or cholesterol lowering drugs in the management of patients with cerebrovascular atherosclerosis.

SUMMARY Measurements of four plasma lipid fractions and uric acid have been performed in a

series of patients with cerebrovascular disease. A modest elevation of the lipid fractions was noted, especially marked in respect of triglycerides. Correlation coefficients show that all the lipids tend to be elevated together, but these changes do not correlate with hyperuricaemia. The uric acid ratio was calculated and was of no value in detecting cerebral atherosclerotic disease. The significance of these findings is discussed.

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