

Familial hyperuricaemia and hypertriglyceridaemia

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An association of gout with elevated levels of plasma lipids is well documented (Barlow, 1968; Berkowitz, 1964; Feldman and Wallace, 1964). Conversely, patients with primary hyperlipoproteinaemia often have a raised plasma urate (Harris-Jones, 1957) and occasionally develop secondary gout (Strejček and Kučerová, 1969).

The mechanism of this interrelationship is not known but, as there is also evidence of a link between hyperuricaemia and ischaemic heart disease (Dawber, Moore, and Mann, 1957), its elucidation is of practical importance in preventive medicine.

We report on a family, originally described in 1960 (Duncan and Dixon, 1960) with familial hyperuricaemia, two members of which have had gouty arthritis; several members have now been found to have hypertriglyceridaemia.

Family history (see Figure and Table)

In the family, as originally described, both parents had hyperuricaemia (but never suffered from gout) and all six surviving children had hyperuricaemia. Two of the brothers (II6 and 7) subsequently died, at the ages of 22 and 25 years respectively, of renal failure, thought to be secondary to their hyperuricaemia. The eldest sister (III1) died at the age of 16 in renal failure and it is presumed that she too had severe hyperuricaemia; the histology of her kidneys supported this assumption. Her brother (II5) died at 6 months of pneumonia. Both parents have subsequently died: the father, aged 64, of carcinoma of the larynx and the mother, aged 58, following a cerebral hemorrhage. Of the four remaining children the two brothers (II4 and 8) and sister (II2) have hyperuricaemia which is adequately controlled by allopurinol, but have chronic renal failure and hypertension. One sister (II3), although originally having a plasma urate just above normal, now falls within the

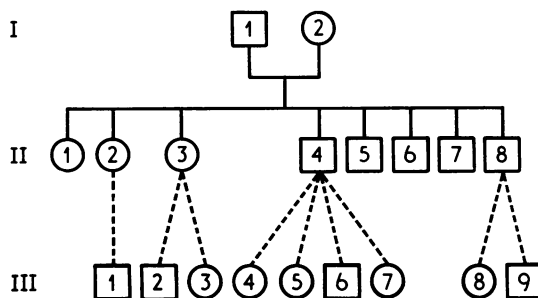


FIGURE Family tree.

normal range. Since the original description of this family, all surviving members have married and produced offspring.

Patients and methods

All the surviving members of this family, with the exception of III4 (an 8-month-old baby) were further studied in relation to their plasma lipids and lipoproteins, current medical status, and alcohol consumption. The two severely affected brothers were admitted for an intravenous fat tolerance test, bromsulphthalein (BSP) retention, and liver biopsies. Blood samples were obtained after an overnight fast.

Plasma triglyceride was measured by a semi-automated fluorimetric method (Cramp and Robertson, 1968) and lipoprotein electrophoresis was performed on cellulose acetate (Chin and Blankenhorn, 1968). In the intravenous fat tolerance test, 0.1 g. triglyceride per kg. body weight was injected intravenously in the form of 'Intralipid' (Vitrum, Stockholm, batch No. 191249), and its disappearance from the plasma was measured nephelometrically over the course of 40 minutes (Lewis, Boberg, Mancini, and Carlson, 1972). The rate constant for the disappearance curve, K_2 , gives a measure of the fractional turnover rate of triglyceride. The normal K_2 value for men is $0.056 \pm 0.016 \text{ min}^{-1}$ (mean \pm S.D.) (Lewis and Chait, unpublished data; Lewis, Sissons, and Chait, unpublished data).

Table *Clinical and biochemical findings in nineteen members of one family*

Code no.	Age (yrs)	Cholesterol (mg./100 ml.) (Normal 140-240)	Triglyceride (mg./100 ml.) (Normal 60-140)	Lipoprotein strip	Serum uric acid (mg./100 ml.) (Normal 2-7)	Urea (mg./100 ml.) (Normal 15-40)	Blood pressure	Outcome	Treatment
I1	58	—	—	—	9.4	32	Normal	Died age 69 CVA	—
2	69	—	—	—	7.6	51	Elevated*	Died age 58 cancer throat	—
III1	14	—	—	—	—	—	Elevated	Died age 14 renal failure	—
2	42	206	630	Both B and preB	5.4	83	Elevated	Symptomatically well	Allopurinol
3	41	252	164	preB	6.2	39	Normal	Well	None
4	37	337	1118	B, preB, and Chylo	5.6	72	Elevated	Symptomatically well	Methyldopa and allopurinol
5	6/12	—	—	—	—	—	—	Died age 6 mths pneumonia	—
6	25	—	—	—	16.0	106	Elevated	Died age 25 renal failure	—
7	21	—	—	—	12.7	50	Elevated	Died age 21 renal failure	—
8	26	290	670	preB	6.6	84	Elevated	Symptomatically well	Methyldopa and allopurinol
III1	21	208	235	preB	7.4	26	Normal	Symptomatically well	None
2	10	204	171	preB	4.4	26	Normal	Well	None
3	13	172	185	preB	5.4	20	Normal	Well	None
4	8/12	—	—	—	—	—	—	Well	None
5	3	155	75	Normal	4.6	25	Normal	Well	None
6	8	175	50	Normal	4.1	19	Normal	Well	None
7	11	190	75	Normal	4.2	26	Normal	Well	None
8	2	140	103	Normal	5.1	18	Normal	Well	None
9	2	133	98	Normal	4.5	17	Normal	Well	None

* > 160/95 before treatment.

An estimation of guanine phosphoribosyl transferase (G.PRTase) and Adenine phosphoribosyl transferase (A.PRTase) was performed on B8.

Results

Two siblings (II2 and 8) with treated hyperuricaemia had a preB-hyperlipoproteinaemia, II2 also having an excess of B-lipoprotein; II4 had elevated preB-lipoprotein and chylomicrons in his serum after a 14-hour fast as well as increased B-lipoprotein levels. The sister (II3) who is now normouricaemic (without treatment) has a triglyceride level at the upper limit of normal with a pronounced preB-lipoprotein band.

Of the children of II2, II3, II4, and II8, only one (III1), now aged 21, had both hyperuricaemia and hypertriglyceridaemia. However, the two teenage off-

spring of II3 were found to have a significant preB-hyperlipoproteinaemia in the absence of hyperuricaemia. None of the six children of the two severely affected males (II4 and 8) had either hyperuricaemia or hypertriglyceridaemia.

To exclude the possible diagnosis of familial lecithin-cholesterol acyltransferase deficiency (which is associated with renal failure and hypertriglyceridaemia), it was shown by thin-layer chromatography that more than 50 per cent of the cholesterol content of plasma was esterified.

The liver biopsies on II4 and II8 showed mild fatty change. BSP retention tests were normal.

The intravenous fat tolerance test for II4 was $K_2 = 0.016 \text{ min.}^{-1}$ and for II8, $K_2 = 0.015 \text{ min.}^{-1}$. Both values were subnormal.

Guanine PRTase was 94 nano moles/hr/mg. protein and adenine PRTase was 14.7 nano moles/hr/mg. protein (normal values) in the case of II8.

Discussion

The familial occurrence of gout has been known since the time of Hippocrates, although no clear-cut pattern of inheritance has emerged except in the Lesch-Nyhan syndrome (Lesch and Nyhan, 1964). The usual explanation for such an ill-defined inheritance pattern is either that of an autosomal dominant with variable penetrance or the combined expression of several contributory genetic loci. PreB-hyperlipoproteinaemia can be secondary to disorders such as diabetes mellitus, excess alcohol consumption, hypothyroidism, and glycogen storage disease Type 1. The primary form may be inherited as an autosomal recessive, which may not express itself in the phenotype until adult life (Fredrickson, Levy, and Lees, 1967).

Although in general the relationship of gout to raised serum lipids is not known, there are two situations, namely glycogen storage disease Type 1 and over-indulgence in alcohol, in which common biochemical pathways have been proposed: in glycogen storage disease, the deficiency of glucose-6-phosphatase leads to an intracellular accumulation of glucose-6-phosphate. This acts as a substrate for *de novo* purine synthesis via the pentose shunt pathway; thus leading to an overproduction of both uric acid and fatty acids (Jakovic and Sorensen, 1967).

In excess alcohol consumption, the alcohol is thought to be oxidized in preference to fatty acids within the liver resulting in decreased levels of NAD. Consequently, an excess of fatty acids is available for triglyceride formation. In addition, the excess of available hydrogen atoms from NADH₂ favours the conversion of pyruvate to lactate, the resulting acidosis leading to hyperuricaemia by its inhibition of renal urate secretion (Lieber, 1965).

Although not numerically important in the context of the interrelationship of gout to lipid metabolism, these two diseases provide some insight into possible mechanisms of common biochemical pathways.

The low values found in the intravenous fat tolerance tests in these patients suggests that a decreased rate of triglyceride removal is of importance in the pathogenesis of the raised lipid levels. This might occur as a result of a deficiency of lipoprotein lipase activity, or from a defective triglyceride resynthesis within the cell (Fredrickson and others, 1967).

It appears from the family reported here that a genetic component to this association can occur, thus providing an incentive to search for possible common enzyme deficiencies. The actual inheritance of the

hyperuricaemia and the hypertriglyceridaemia in this family cannot be explained in simple Mendelian terms, although it is of interest that the hypertriglyceridaemia has only been passed on by the females. However, III4, III5, III8, and III9 are not yet old enough to exclude the possibility of their developing hyperlipidaemia or hyperuricaemia.

Patient II8, who was started on treatment at the age of 12 and has been normouricaemic since that time, has pronounced hypertriglyceridaemia. It thus appears that hyperuricaemia does not play a direct role in the genesis of the raised lipid levels. This is supported by the finding that a therapeutic reduction of plasma urate does not regularly alter the lipid abnormalities in gout (Bluestone, Lewis, and Mervart, 1971).

Hyperuricaemia, usually of mild degree, is a recognized feature of familial preB-hyperlipoproteinaemia, but this association is unlikely to account for the severely elevated urate levels and the chronic renal failure seen in this family. About one-third of patients with chronic renal failure due to primary renal disease have hypertriglyceridaemia, usually of moderate degree (Bagdade, 1970); in many but not all of these, the high carbohydrate content of the therapeutic diet may largely explain the hypertriglyceridaemia, on the basis of carbohydrate-induced lipaemia; however, three patients in the family have hypertriglyceridaemia despite normal urea levels and an unmodified diet.

It is also possible that in some cases the familiar relationship between gout and alcohol plays a role in elevating the lipid levels in these patients (Chait, Mancini, February, and Lewis, 1972). III4, with the highest triglyceride levels, drinks about ten pints of beer a day, but his younger brother, III8, is a teetotaler. It is conceivable that gout carried an inherited predisposition towards elevated serum lipids, the biochemical basis of which is not yet known, and that excessive alcohol consumption will exacerbate the tendency to hypertriglyceridaemia.

Summary

Three generations of a family with a strong tendency to hyperuricaemia are described in relation to abnormalities of serum lipid levels. Three of the four surviving siblings of the second generation had hyperuricaemia and pronounced hypertriglyceridaemia. In the third generation only one member had both hyperuricaemia and hypertriglyceridaemia, but two children had raised blood lipids in the absence of a raised serum urate. The lipid abnormality was transmitted only through the female members. The patient with the highest lipid levels had an excessive alcohol consumption; it is suggested that this may play a contributory role in the hyperlipidaemia of gout.

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