Plasmaphoresis and plasma exchange in the treatment of hyperlipaemia and xanthomatous neuropathy in patients with primary biliary cirrhosis

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SUMMARY Two patients with primary biliary cirrhosis who were increasingly incapacitated by xanthomatous neuropathy are described. Treatment with a low fat diet and cholestyramine was unhelpful but repeated plasmaphoresis by simple venesection in one and plasma exchange using an IBM blood cell separator in the other over a period of several months completely relieved the symptoms of the neuropathy, caused skin xanthomata to recede, and lowered plasma lipid levels in both patients. There was no evidence that this procedure was associated with any deleterious effects on the liver. The size of the cholesterol pool in xanthomata in one patient was estimated to be approximately 35 g, and from the plasma cholesterol response to plasmaphoresis at varying frequency it was suggested that the excess of cholesterol synthesis over degradation was less than 0.3 g/day in one patient and less than 0.4 g/day in the other. On the basis of the response in these patients it is suggested that the turnover rates of lipid pools are relatively slow in biliary cirrhosis and that cholesterol accumulation is more likely to be due to a reduced catabolic rate than to an increased synthetic rate of cholesterol. Plasmaphoresis or plasma exchange are useful methods of treatment for the rare patient afflicted by this resistant and distressing complication of biliary cirrhosis.

Disorders of lipid metabolism are common in patients with primary biliary cirrhosis (Sherlock, 1968). The characteristic elevation of plasma cholesterol and the presence of cutaneous xanthomata are diagnostically helpful features (Ahrens, Payne, Kunkel, Eisenmenger, and Blondheim, 1950), while Schaffner (1969a) has suggested that there may be an increased liability to coronary atheroma, emphasizing the seriousness of this aspect of the disease. Xanthomatous neuropathy, due to the excessive deposition of lipid in peripheral nerves, is a rare complication, but one which may add considerably to the misery of patients with biliary cirrhosis (Thomas and Walker, 1965).

Therapeutic manoeuvres aimed at reducing plasma and tissue lipid levels have been less successful in this disease than in patients with other forms of hyperlipaemia (Schaffner, 1969a). While a few

patients have shown a reduction in plasma cholesterol during cholestyramine treatment most have been unaffected (Datta and Sherlock, 1963; Schaffner, Klion, and Latuff, 1965). Treatment with clofibrate is contraindicated in patients with biliary cirrhosis since a paradoxical rise in plasma cholesterol has been reported in some of these patients (Schaffner, 1969b).

We report here two patients with primary biliary cirrhosis, who developed severe xanthomatous neuropathy which was successfully treated by repeated plasmaphoresis in one and plasma exchange in the other.

Cases

PATIENT 1

V.R., a 42-year-old housewife, presented at the Manchester Royal Infirmary in 1965 complaining of generalized pruritus and pigmentation. Splenomegaly was noted and liver function tests showed

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serum bilirubin 1.8 mg, alkaline phosphatase 110 KA units, cholesterol 400 mg, albumin 3.8 g, and globulin 4.2 g/100 ml, aspartate aminotransferase 67, alanine aminotransferase 100 U/ml, three-day faecal fat 131 g. An intravenous cholangiogram showed a normal gallbladder and biliary tree. During the following two years she became increasingly jaundiced, serum bilirubin rising to 9.6 mg/100 ml. Her stools became pale, her urine dark, and xanthelasma appeared on her eyelids. An antimitochondrial antibody test, positive to a titre of 1/2048, supported the clinical diagnosis of primary biliary cirrhosis.

She was treated with cholestyramine 12 g/day, parenteral injections of vitamins A, D, and K, and a low fat diet. Symptoms of a xanthomatous neuropathy appeared in June 1969 when she complained of pain in her hands and over the elbows and malleoli. The pain in her hands was particularly distressing when she gripped hard objects such as taps, keys, and knives and forks, and soon became severe enough to prevent her carrying out her normal

housework. Coincidentally multiple small xanthomata, 2 to 3 mm in diameter, appeared in the skin of the palms and fingers. Larger xanthomata appeared over the elbows and shins. There was a slight diminution to pinprick over the finger tips but other forms of sensation were normal as were the motor system and reflexes.

Investigation revealed that the serum cholesterol, which had remained between 400 and 580 mg/100 ml for three years, had risen to 1200 mg/100 ml in eight months. Nerve conduction studies in the sensory fibres of the hands and motor fibres of median and ulnar nerves were normal. Serum cholesterol, free, was 1000 mg, esterified, 200 mg, and serum phospholipid 2000 mg/100 ml. Cellulose acetate electrophoresis of lipoproteins showed a dense diffuse band in the β and pre- β region. Analytical ultracentrifugation of plasma revealed the presence of large amounts of an abnormal lipoprotein (LpX).

A clinical diagnosis of xanthomatous neuropathy was made, this complication having developed while she was receiving cholestyramine continuously.

Fig. 2 A Xanthomata over one elbow in V.R. before treatment and B after 26 weeks of treatment.

Plasmaphoresis

In view of the failure of other treatments and because of the severity of the symptoms an attempt was made to deplete the body pool of lipid by plasmaphoresis. Five hundred ml of blood was removed, centrifuged, the plasma taken off, and the cells were returned to the patient under aseptic conditions using JD2 Fenwal double blood packs (Baxter Laboratories). This was repeated daily for five days, weekly for 14 weeks, and at varying intervals thereafter.

Clinical response

After four weeks her symptoms improved; within 16 weeks the pain in her hands had completely resolved. The small xanthomata in the skin of her hands slowly decreased in size, most disappearing, and large xanthomata became smaller (Fig. 2). The xanthelasma around the eyes remained unchanged. As her symptoms were much improved plasmaphoresis was performed only four times during the next three months but at the end of this time the pain in her hands recurred but improved again after a further 10 weekly venesections.

Plasma lipid changes (Fig. 2)

The serum cholesterol fell rapidly from about 1000 mg/100 ml to 740 mg/100 ml during the initial five days of plasmaphoresis and then fell slowly during the period of weekly venesections. Biweekly venesections caused a more rapid fall to 350 mg/100 ml but levels rose again to 1000 mg/100 ml when the frequency of venesections was reduced. Cholesterol levels fell only slowly when weekly plasmaphoresis was re-introduced. Plasma phospholipid values followed a similar pattern to the changes in plasma cholesterol. The initial level of 1340 mg/100 ml fell to 730 mg/100 ml after 12 weeks.

A total of 105 g of cholesterol, and approximately 150 g of phospholipid, were removed during this period. Cholesterol was being removed at an overall rate of 0.3 g/day when xanthomata were regressing and plasma levels were falling; the average removal rate was reduced to about 0.1 g/day when the frequency of venesections was reduced and this rate allowed plasma levels to rise again. At 16 weeks, when the xanthomata had markedly regressed, 44 g of cholesterol had been removed.

The serum albumin and globulin remained unchanged despite this constant removal of protein, and, although the serum bilirubin and alkaline phosphatase levels fluctuated, there was no consistent change.

Since the patient's symptoms referable to the neuropathy had resolved plasmaphoresis was then stopped. In the following six months neither the

Fig. 1 Response of V.R. to repeated plasmaphoresis. Frequency of plasmaphoresis is shown at the top of the figure and the clinical response is shown diagrammatically below that. The changes in serum cholesterol and the cumulative amount of cholesterol removed is also indicated.

neuropathic symptoms nor the xanthomata re-appeared and the serum cholesterol remained between 520 and 710 mg/100 ml. However, hepatic function then deteriorated with the development of ascites and deepening jaundice. Plasma cholesterol fell spontaneously to 430 mg/100 ml when the patient lapsed into hepatic coma and died in March 1972.

PATIENT 2

P.E., a 58-year-old housewife, first noticed a generalized pruritus in November 1969 and within six months had developed pale, loose stools, dark urine, and mild icterus. On examination she was icteric and had a firm palpable liver 2 cm below the costal margin. Investigation revealed serum albumin 4.1 g, globulin 2.9 g, bilirubin 2.5 mg, alkaline phosphatase 112 KA units, and 5'-nucleotidase 215 IU per 100 ml, and aspartate aminotransferase 32 and alanine aminotransferase 26 U/ml. At laparotomy the extrahepatic biliary tree was found to be normal and the liver to be finely granular. A liver biopsy showed changes consistent with primary biliary cirrhosis

and this diagnosis was supported by a positive antimitochondrial antibody titre of 1/32.

She was treated with parenteral vitamins A, D, and K, a low fat diet, and cholestyramine. In the three months between December 1970 and March 1971 the serum cholesterol level rose from 430 mg to 1175 mg per 100 ml and during the following three months symptoms of xanthomatous neuropathy and cutaneous xanthomata developed. Pain in the fingers and hands on gripping hard objects was accompanied by the appearance of xanthomata in the palmar creases and the finger pulps which appeared exquisitely sensitive to pressure. Superficial pain sensation in the hands was slightly impaired and vibration sense was lost over both ankles and knees. Radiographs of the hands were normal and nerve conduction studies, both motor and sensory, in the hands and forearms were normal. Analytical ultra-centrifugation revealed the presence of large amounts of the lipoprotein, LpX, in the plasma and this lipoprotein was further identified immunochemically using a specific antiserum.

In view of the lack of response to other therapy, the severity of the symptoms and the similarity of this patient to V.R., a decision to perform plasma exchange was made.

Plasma exchange

In this patient an NCI/IBM blood cell separator was used since it is possible to exchange large volumes of plasma with this apparatus, and thereby reduce the frequency of venesections. Between 1 and 2 litres of plasma were exchanged with fresh plasma during three to four hours at two weekly intervals for one month and monthly intervals thereafter for six months.

Clinical response

After four plasma exchanges her symptoms had improved and after five she was able to perform her normal housework without discomfort. The xanthomata in her hands regressed but the xanthelasma around her eyes did not change.

Plasma lipid change (Fig. 3)

Three plasma exchanges at two weekly intervals lowered plasma cholesterol from 1200 mg to 400-560 mg per 100 ml. Repeated plasma exchange maintained cholesterol levels between 420 and 700 mg per 100 ml. Sixty-two g of cholesterol was removed during this five-month period, and the overall average removal rate was 0.4 g/day.

Plasma lipoproteins were measured by the nephelometric method of Stone, Thorp, Mills, and Dick (1970), which is based on the degree of light scattering produced by the larger lipoprotein

Fig. 3 Response of P.E. to repeated plasma exchange. The clinical response is depicted diagrammatically at the top of the figure and the changes in plasma cholesterol and the cumulative amount of cholesterol removed is also shown.

particles. This technique has been validated for lipoproteins by comparison with analytical ultra-centrifugation methods (Stone *et al.*, 1970). Concentrations of three different classes of lipoprotein were determined: 'L' or large particles representing chylomicrons, 'M' or medium sized particles which represent very low density lipoproteins (Sf20-400), and 'S' or small particles which represent low density lipoproteins (Sf0-20). In this patient the 'S' particles were almost entirely made up of LpX and allowance was made for the particular composition of this abnormal lipoprotein in calculating concentrations. 'L' particle concentrations were normal and not influenced by plasma exchange. 'S' concentrations fell to approximately half their initial values, the pattern followed being similar to that taken by cholesterol, a not unexpected finding since these lipoproteins carry most of the cholesterol (Fig. 4). 'M' concentrations fell to within the normal range after two plasma exchanges.

Fig. 4 Changes in plasma 'S' and 'M' particle concentrations in P.E. induced by repeated plasma exchange. The dashed line indicates the upper limit of normal for 'M' particle concentration. The upper limit of normal for 'S' particles is 550 mg/100 ml.

Discussion

The symptoms of xanthomatous neuropathy in biliary cirrhosis are so characteristic as to be pathognomonic of the disorder (Thomas and Walker, 1965). The extreme discomfort in the hands on gripping such hard objects as door handles, taps, and knives and forks is a marked feature and may make life intolerable for afflicted patients. The association with multiple small tuberous xanthomata in the skin over the elbows, shins, finger pulps, and planar xanthomata in the palmar creases and the high serum lipid levels confirms the diagnosis. The neuropathy is thought to be due to an interference with peripheral nerve function by the deposition of lipid in the perineurium in the presence of high plasma lipid concentrations (Thomas and Walker, 1965). The pain may be produced by distortion of small terminal branches of sensory nerves in the skin by xanthomatous deposits.

Attempts to lower plasma lipid levels in primary biliary cirrhosis had been only partially successful (Schaffner, 1969a). Low fat diets are usually unhelpful and although corticosteroids can induce a

dramatic response (Howat, Ralston, Varley, and Wilson, 1966) the grave complications, especially osteoporosis, which accompany prolonged therapy with corticosteroids prohibit their use. Treatment with cholestyramine has sometimes been successful but, as in our cases, lipid levels may rise during such therapy. Clofibrate, so successful in certain forms of hyperlipaemia, may be dangerous in biliary cirrhosis, since paradoxical elevations of plasma lipid levels have been reported during its administration to such patients (Schaffner, 1969b). Because of the failure of previous treatment and in view of the severity of these patients' symptoms it was felt justified to attempt to reduce plasma levels by plasmaphoresis. It was uncertain whether this measure would remove sufficient lipid to overtake the synthesis rate, which theoretically could have increased in response to plasmaphoresis to maintain the initial lipid pool size. During the course of treatment the neuropathic symptoms virtually disappeared, the plasma lipid levels fell, and the skin xanthomata regressed, suggesting that the body pools were being depleted of lipid. That this reduction in the hyperlipaemia was not a spontaneous occurrence or associated with deteriorating liver function was borne out in V.R. by the recurrence of symptoms and rise in plasma lipid concentrations when plasmaphoresis was temporarily stopped and the absence of clinical or biochemical evidence of worsening hepatic function at this stage.

Despite the removal of 1500 ml of plasma in one week and 300 ml per week for several months there was no obvious change in serum albumin in V.R., indicating that liver function was adequate to compensate for this loss of protein. The lack of any consistent change in serum bilirubin, alkaline phosphatase, or serum transaminase in either patient testifies to the safety of the procedure so far as liver function is concerned.

Disturbances of lipid metabolism, although common in biliary cirrhosis, are complex and ill understood. Elevated plasma cholesterol and low density lipoprotein levels as noted in the present cases are typical (Furman and Conrad, 1957). The abnormal lipoprotein, LpX, detected in these cases is also a characteristic finding (Seidel, Alaupovic, and Furman, 1969). There is little published information about lipid pool sizes or turnover rates in biliary cirrhosis. Ahrens *et al* (1950) originally speculated that an increased synthesis rate might be responsible for the hypercholesterolaemia although methods were not then available for measuring cholesterol turnover rates. However, their more recent sterol balance studies in subjects with biliary cirrhosis suggest that a decreased catabolic rate is more likely to be the cause (Ahrens, personal com-

munication). The observations in the patients reported here are of interest in this respect.

In V.R. the skin xanthomata had virtually disappeared when approximately 44 g of cholesterol had been removed. This figure includes about 9 g removed in lowering the plasma concentration, leaving 35 g to provide an indication of the upper limit for the size of the cholesterol pool within the xanthomata and other abnormal deposits. This figure compares with reported normal values for total body cholesterol of 1 to 2 g/kg body weight.

The finding that removal of relatively small amounts of lipid could effectively reduce plasma levels and xanthomata suggests that these presumably greater than normal lipid pools were turning over at a relatively slow rate. In the two patients with Frederickson type II hyperlipoproteinaemia, reported by Moutafis and Myant (1969), removal by cholestyramine of approximately 1 g of sterol above control daily faecal excretion rates failed to lower plasma cholesterol or influence xanthomata. This compares with a reduction in plasma cholesterol and xanthomata induced in our cases with biliary cirrhosis by removal at an average rate of 0.3 g/day in V.R. and 0.4 g/day in P.E. Although these figures are not strictly comparable since cholestyramine removes mainly bile salts, thus influencing plasma cholesterol predominantly, while plasmaphoresis and plasma exchange remove all lipids and lipoproteins, they do suggest that the mechanisms for the hyperlipaemia are different in the two disorders. Increased synthesis of cholesterol in response to therapy seemed to be responsible for the failure of xanthomata to change and plasma cholesterol levels to fall in the type II hyperlipoproteinaemia patients. In our patients with biliary cirrhosis any increase in synthesis which might have occurred in response to therapy was insufficient to prevent the fall in plasma lipid and reduction of xanthomata induced by treatment. This suggests that the turnover rate of cholesterol in these patients was relatively slow, and also supports the suggestion of Ahrens that accumulation of cholesterol in biliary cirrhosis is due to a decreased catabolic rate rather than to an increased synthetic rate. The alternative for the hypercholesterolaemia in our cases, of a relatively trivial increase in cholesterol synthesis, seems less likely. When cholesterol was being removed at an average rate of 0.3 g/day plasma cholesterol fell and xanthomata regressed in V.R., suggesting that the rate at which cholesterol was accumulating, that is, the excess of cholesterol synthesized over that catabolized, was something less than 0.3 g/day. This estimate is less than one third of the reported normal total cholesterol turnover of about 1 g/day (Lewis and Myant, 1967; Goodman and Noble, 1968).

One possible mechanism for decreased catabolism of cholesterol is a reduced conversion to bile salts consequent upon their retention in biliary cirrhosis. That plasma cholesterol levels are influenced by variations in bile salt excretion rates is borne out by the cholesterol-lowering effect of techniques which increase faecal excretion of bile salts. In addition recent investigators suggest, on the basis of studies in primates, that plasma cholesterol levels may rise solely as a result of a reduced excretion of bile salts (Lofland, Clarkson, St. Clair, and Lehner, 1972).

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