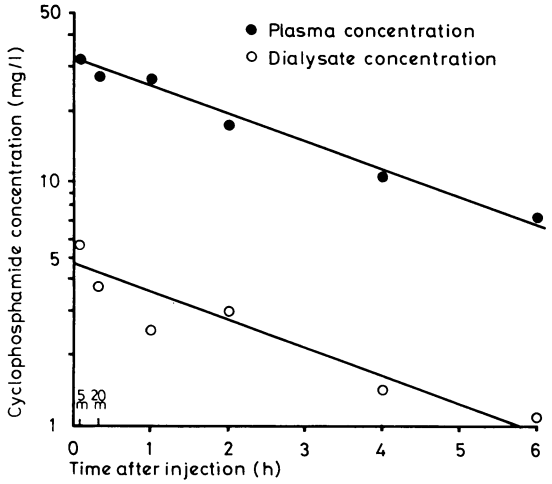
Case report

A 27-year-old man who had been diagnosed five years previously as having chronic glomerulonephritis, and was subsequently maintained on haemodialysis at home, presented with an enlarged left inguinal lymph node. On biopsy and further investigation he was found to have stage IV malignant lymphoma of diffuse histiocytic type. Despite histological evidence of liver disease the results of standard liver function tests were normal.

The first dose of intravenous cyclophosphamide (600 mg) was administered five minutes before haemodialysis was started and subsequently samples of plasma and dialysate were taken. Dialysis was maintained for six hours using a forearm arteriovenous fistula and a Gambro 1 square metre dialyser. Cyclophosphamide concentrations were measured by mass spectrometry-stable isotope dilution using tetradeuterated cyclophosphamide as an internal standard. The procedure was identical with that described[1] except that whole blood samples were centrifuged as taken and addition to citrate saline was omitted. After addition of the deuterated cyclophosphamide, plasma and dialysate were extracted with ethyl acetate. Cyclophosphamide concentrations in plasma and dialysate were plotted on semi-log paper (see fig). A half life of 2 h 35 min was found for plasma clearance of the drug.



Cyclophosphamide concentrations in plasma and dialysate after 600-mg injection.

Comment

Cyclophosphamide is a widely used bifunctional alkylating agent, which undergoes biotransformation in the liver to form an active metabolite.[2] The plasma half life shows considerable interpatient variation (1·8-9·2 h).[3] It has been suggested[4] that the rate of disappearance of unchanged drug is predominantly determined by the rate of its biotransformation in the liver. In our patient both plasma concentrations[1] and half life[3] for cyclophosphamide are within the range found for patients with normal renal function. The earlier study cited[3] also included one patient with renal impairment, who had a normal plasma half life. The present results show that little cyclophosphamide is lost in the dialysate, the concentrations being an order of magnitude lower than plasma concentrations. On the basis of our results, therefore, haemodialysis need not be interrupted during treatment with cyclophosphamide.

We are grateful to Dr T J McElwain, Dr A J Eisinger, and Dr D G Davidson for their help in preparing this paper.

[1] Jarman, M, *et al*, *Clinica Chimica Acta*, 1975, **58**, 61.
[2] Brock, N, and Hohorst, H J, *Arzneimittel-Forschung*, 1963, **13**, 1021.
[3] Bagley, C M, Bostick, F W, and De Vita, V T, jun, *Cancer Research*, 1973, **33**, 226.
[4] Mouridsen, H T, Faber, O, and Skovsted, L, *Acta Pharmacologica et Toxicologica*, 1974, **35**, 98.

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Divisions of Chemistry and Medicine, Institute of Cancer Research, Sutton, Surrey

R A V MILSTED, MB, MRCP, Hamilton Fairley research fellow
M JARMAN, MA, PHD, member of scientific staff

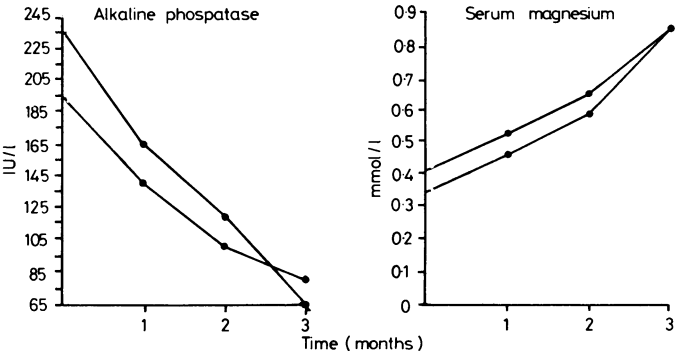
Apathetic hyperthyroidism with hypomagnesaemia and raised alkaline phosphatase concentration

Thyrotoxicosis may exist in two forms: the well-recognised hyperkinetic hyperthyroidism, and apathetic thyrotoxicosis, described by Lahey in 1931.[1] In the latter form patients present with wrinkled and pigmented facies and with severe weight loss and apathy. They have the typical demeanour of hypothyroidism. Fairclough and Besser 1974[2] reported a case of apathetic hyperthyroidism with a normal T4 yet raised T3 concentration. We describe two patients with apathetic hypothyroidism and appreciable hypomagnesaemia.

Case reports

Case 1—A 36-year-old unmarried woman complained of chronic anxiety, palpitations, and weight loss. She was prescribed diazepam (Valium), 5 mg thrice daily, and three years later realised that she was continually tired and unable to work properly. She had lost 19 kg in weight and noticed pigmentation on her skin; she had had no diarrhoea. Examination confirmed the pigmentation, and showed her pulse rate to be 60 per minute; she had evidence of a proximal myopathy and also generalised weakness; the thyroid gland was just palpable. The results of investigations were normal save for serum concentrations of magnesium of 0·34 mmol/l (0·83 mg/100 ml), of alkaline phosphatase of 194 IU/l, and of thyroxine of 220 mmol/l (17·1 μg/100 ml). She had no radiological bone disease. Carbimazole (Neomercazole), 10 mg thrice daily, was started and one month later her serum alkaline phosphatase concentration was 140 IU/l and magnesium 0·46 mmol/l (1·12 mg/100 ml). After two months' treatment the respective values were 104 IU/l and 0·59 mmol/l (1·43 mg/100 ml), and after three months 80 IU/l and 0·85 mmol/l (2·1 mg/100 ml), both normal. She was much improved clinically, having lost her anxiety, gained 7 kg, and had adequate energy.

Case 2—A 32-year-old unmarried woman complained of weight loss of 19 kg, and increased sweating. She disliked hot weather. Her serum thyroxine concentration was 194 nmol/l (15·1 μg/100 ml). She was treated with carbimazole, 15 mg thrice daily, and then lost to follow-up for six years. During this period she took no treatment and presented again with pigmentation and slowness in her movements, but no diarrhoea. She had an obvious lack of energy; her pulse rate was 60 and she had the appearances of hypothyroidism save for her thinness. The thyroid gland was palpable and soft. The serum concentrations were: thyroxine 207 nmol/l (16·1 μg/100 ml), magnesium 0·41 mmol/l (0·99 mg/100 ml), and alkaline phosphatase 234 IU/l. She had no radiological bone disease. After one month's treatment with carbimazole, 15 mg thrice daily, she felt better, and the serum concentrations of magnesium had risen to 0·52 mmol/l (1·3 mg/100 ml) and of alkaline phosphatase had fallen to 170 IU/l. The respective concentrations after two months were 0·65 mmol/l (1·6 mg/100 ml) and 120 IU/l, and after three months' treatment (when she had adequate energy and felt well), 0·85 mmol/l (2·1 mg/100 ml) and 65 IU/l. She has remained well for two years.



Serum magnesium concentrations after carbimazole treatment for thyrotoxicosis was begun.

Conversion: SI to traditional units—Magnesium: 1 mnol/l ≈ 2·4 mg/100 ml.

Discussion

Thyroxine causes mitochondrial swelling,[3] resulting in loss of magnesium from the mitochondrion and hypomagnesaemia. This hypomagnesaemia is postulated as producing the apathetic form of hyperthyroidism, Neguib[4] claiming that thyrotoxic patients have shown an increase in muscular strength after treatment with magnesium chloride. Thyroxine is alone responsible for the induction of enzymes, such as glutamate dehydrogenase,[3] and similarly it regulates the induction of alkaline phosphatase in osteoblasts and to a lesser

extent in bone osteoclasts. In our patients, who had apathetic hyperthyroidism with low concentrations of serum magnesium and high ones of alkaline phosphatase which reverted to normal after three months' treatment, the interesting aspect is the possible role of hypomagnesaemia in producing this type of hyperthyroidism.

[1] Lahey, F H, *Annals of Internal Medicine*, 1932, **5**, 1123.
[2] Fairclough, P O, and Besser, G M, *British Medical Journal*, 1973, **1**, 364.
[3] Lehninger, A L, *Biochemistry, The Molecular Basis of Cell Structure and Function*, 2nd edn, p 825. New York, Worth, 1975.
[4] Neguib, M A, *Lancet*, 1963, **1**, 1405.

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Westminster Hospital, London SW1
PETER MARKS, MB, MRCP, senior research registrar
HASHMAT ASHRAF, MB, FRCS, surgical registrar

Association between HLA-BW40 and alcoholic liver disease with cirrhosis

Some alcoholics seem to develop cirrhosis more readily than others, and the influence of genetic and environmental factors on individual susceptibility has been discussed.[1] Autoimmune mechanisms have also been implicated, since an increased prevalence of autoantibodies and evidence of cell-mediated immunity to liver tissue have been reported in patients with cirrhosis,[2-4] particularly in women.[2]

Bailey *et al*[4] performed HLA typing on their patients with alcoholic liver disease and found an increased prevalence of HLA-B8. This is a known trait in several autoimmune disorders and has also been shown in chronic active hepatitis. Scott *et al*[5], however, could find no association between any HLA antigen and chronic active hepatitis or alcoholic cirrhosis. We report here the results of HLA typing in patients with alcoholic liver disease.

Patients, methods, and results

Forty-one patients with alcoholic liver disease were studied. Twenty-five patients (aged 37-74 years (mean 58); 8 women, 17 men) had cirrhosis. All of these patients had undergone liver biopsy and the diagnosis was based on clinical, biochemical, and histological criteria. Nine of the 25 also had the histological features of alcoholic hepatitis. The other 16 patients (aged 39-75 years (mean 56); 3 women, 13 men) had no evidence of cirrhosis on liver biopsy: four had alcoholic hepatitis, and 12 had fatty liver disease. Another 16 patients with different liver diseases also underwent HLA typing. Four had chronic persistent hepatitis, three had hepatitis B, two had hepatitis A, and three had minimal biochemical evidence of hepatic disease of unknown origin. Four patients were classified as having non-alcoholic cirrhosis. HLA typing was performed by recommended microcytotoxic techniques. Fifty-four typing sera were used, typing for 20 antigens. Three anti-HLA-BW40 sera were used. All patients were typed blind. The control samples were from blood donors in Oslo. Controls and patients were typed within the same period using the same set of typing sera. χ^2 values were calculated by two-by-two tables for each comparison separately.

The table shows all the antigens typed for, and the number of subjects positive for each. When computing the χ^2 value for each comparison (60 in all) we found only one significant deviation from the normal distribution. Thirteen of the 25 patients (52%) with alcoholic liver disease and cirrhosis were HLA-BW40 positive compared with 28 of the 153 (18%) controls ($\chi^2 = 13{\cdot}77$, 11·93 with Yates's correction; $P < 0{\cdot}001$; when multiplied with the number of antigens tested for (20), $P < 0{\cdot}02$). The prevalence of HLA-BW40 was not increased in the two other groups of patients, and the prevalence in the control group was the same as that in the Norwegian population. The prevalence of HLA-B8 did not differ significantly from normal in any group. Bailey *et al*[4] noted an absence of HLA-A28 in both types of alcoholic liver disease, which we also found, but our groups were too small to yield statistically significant results.

Prevalence of HLA antigens in three groups of patients. Results are numbers of subjects positive for each antigen

HLA	Patients with: Alcoholic liver disease and cirrhosis (n = 25)	Alcoholic liver disease without cirrhosis (n = 16)	Other liver disease (n = 16)	Healthy controls (n = 153)
A1	8	5	2	40
A2	15	12	11	80
A3	5	2	3	36
A9	5	2	5	37
A10	3	2	1	13
A11	1	3	0	15
A28	0	0	1	8 (+1 ?)*
B5	4	0	1	9
B7	5	2	4	41
B8	4 (16%)	4 (25%)	5 (31%)	31 (20%)
B12	6	6	1	58
B13	4	0	0	3
B14	1	1	0	2
BW15	3	4	3	30
B17	2	0	1	8
B21	1	1	1	4
B27	0	5	5	15
BW35	3	4	2	23
BW37	1	0	0	2
BW40	13 (52%)	3 (19%)	3 (19%)	28 (18%)

*Anti-HLA-A28 cross-reacted with HLA-A2. One of the controls might therefore have been A2 homozygous, A2, A "blank," or A2, A28.

Comment

Many associations have been shown between HLA antigens and different diseases—mostly chronic diseases of uncertain cause and sometimes with immunological manifestations. Even if excessive consumption of alcohol is the main agent in the development of alcoholic cirrhosis, its cause is still uncertain, since we do not know why only some heavy drinkers develop cirrhosis. The association with HLA-BW40 may support the idea that individual susceptibility to the development of alcoholic cirrhosis is genetically determined.

We know of no previous reports of an association between liver disease and HLA-BW40. Scott *et al* did not find an increased prevalence of HLA-BW40 among 18 patients with alcoholic cirrhosis,[5] and Bailey *et al*[4] did not type for HLA-BW40. We were not able to confirm the findings of Bailey *et al*[4] of an excess of HLA-B8 among patients with alcoholic liver disease, which suggested that alcoholic disease might belong to the group of autoimmune diseases, in which several associations with HLA-B8 have been shown.

[1] Klatskin, G, *Gastroenterology*, 1961, **41**, 443.
[2] Krasner, N, *et al*, *British Medical Journal*, 1977, **1**, 1497.
[3] Mihas, A A, Bull, D M, and Davidson, C S, *Lancet*, 1975, **1**, 951.
[4] Bailey, R J, *et al*, *British Medical Journal*, 1976, **2**, 727.
[5] Scott, B B, *et al*, *Gastroenterology*, 1977, **72**, 122.

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Krohgstøtten Department of Oslo City Hospital, Oslo 1, Norway
H BELL, MD, university lecturer

Department of Immunology, National Blood Group Reference Laboratory and Tissue Typing Unit, National Institute of Public Health, Postuttak Oslo 1, Norway
R NORDHAGEN, MD, deputy director

Intracellular potassium after magnesium infusion

Potassium loss in the urine is a well-known side effect of treatment with most diuretics, and usually potassium supplements are provided to avoid this. During the last few years interest has focused on the increased renal excretion of magnesium resulting from the use of most diuretics.[1] A sustained increase in magnesium excretion may lead to a cellular magnesium deficiency, which by an insufficient activation of Na-K-ATP-ase may result in the inability of the cell to maintain the high intracellular potassium concentration. Thus the cell fails to attract potassium despite an abundant supply, as shown also in animal studies.[2] As the resting membrane potential is mainly a function of the logarithmic ratio between the intracellular and extracellular potassium, a change in only one of these factors results in a change in membrane potential: thus a decrease in intracellular potassium will lead to a less negative potential. In this way the resting membrane potential approaches the threshold potential and the cell becomes more excitable.