Individual values for two patients for erect and supine blood pressure, terminal latency (TL) and motor nerve conduction velocity (MCV) of ulnar and peroneal nerves, and Valsalva ratio (VR)⁵ at presentation and after withdrawal of perhexiline

Variable	Normal ranges	Patient 1				Patient 2				
		14 June 1976	21 June 1976	28 June 1976	5 July 1976	21 June 1976	5 July 1976	19 July 1976	13 September 1976	14 February 1977
Blood pressure (mm Hg):										
Supine		110/60	120/80	110/70	110/70	110/70	105/70	110/60	110/70	115/75
Erect		70	90/70	100/60	100/70	90/70	85/60	90/60	105/70	110/70
Ulnar nerve:										
TL (ms)	2.1-3.4	4.8	4.0	3.8	3.9	6.1	5.8	4.5	3.9	4.0
MCV (m/s)	46.5-72.6	42.5	44.4	50.8	49.1	46.6	44.8	45.5	54.9	52.4
Peroneal nerve:										
TL (ms)	3.7-6.1	9.1	8.2	8.4	8.1	12.4	10.5	9.6	6.5	5.8
MCV (m/s)	42.1-63.5	30.3	35.2	34.0	34.1	31.6	36.3	38.4	40.2	44.3
Valsalva ratio	>1.50	1.10	1.04	1.09	1.09	1.28	1.35	1.62	1.84	1.80

coronary angiography was carried out. He subsequently died after a further attempt at surgical revascularisation.

Case 2—A 60-year-old man presented in 1968 with symptoms of angina pectoris that progressed despite treatment with propranolol. In 1973 after coronary angiography he underwent triple aortocoronary saphenous vein grafts, but there was no real improvement in his symptoms, and he remained severely incapacitated. In July 1975 he started treatment with perhexiline (200 mg increased to 400 mg/day) with some relief of angina. He returned in June 1976 with a two-month history of weakness and paraesthesiae in both legs and numbness in both feet, and distressing symptoms of postural dizziness. Examination showed sensory blunting below the knee with weakness of all muscle groups in the legs. Systolic blood pressure was 110 mm Hg lying and 90 mm Hg erect. MCV in both arms and legs was delayed and VR reduced (table). Four weeks after withdrawal of perhexiline, his postural hypotension had resolved and VR had become normal. The symptoms of neuropathy had also improved, although three months after discontinuing the drug he still had paraesthesiae in both feet with reduced MCV in the peroneal nerve. He remained incapacitated by angina.

Case 3—A 61-year-old man with insulin-dependent diabetes mellitus of 30 years' duration was diagnosed as having autonomic neuropathy in 1975 because of clinical features (impotence, dizziness on standing, and intermittent nocturnal diarrhoea) and test results showing abnormal autonomic function (VR 1.10, blood-pressure response of 10 mm Hg to sustained hand-grip, and postural fall in systolic blood pressure of 50 mm Hg). He was started on fludrocortisone 0.1 mg daily, and after six months his blood pressure was satisfactory at 130/80 mm Hg lying and 105/70 mm Hg standing, with no symptoms of postural hypotension. During the next year he developed severe angina with no relief from increasing doses of oxprenolol, so in May 1976 this drug was stopped and he was started on perhexiline (400 mg/day). After a few weeks the patient noticed paraesthesiae in both feet and hands and recurrence of his symptoms of postural hypotension. He stopped perhexiline, and when seen two weeks later the paraesthesiae had completely resolved and he no longer felt dizzy, blood-pressure readings being 110/70 mm Hg lying and 90/60 mm Hg standing.

Comment

Three patients developed clinical features of peripheral and autonomic neuropathy on perhexiline maleate. In two cases the features

developed after prolonged treatment, and the diagnosis was confirmed by abnormal results of motor nerve conduction velocity and autonomic function tests. In the third case deterioration of known autonomic neuropathy secondary to diabetes mellitus occurred after a short period on the drug. In all three cases there was symptomatic improvement within a few weeks of discontinuing treatment, suggesting a direct association with the drug. Improvement in motor nerve conduction velocity and autonomic function test results lagged behind the symptomatic improvement in these patients, but in patient 2 results of these tests were almost normal three months after discontinuing the drug.

Lhermitte *et al*³ have postulated that peripheral neuropathy may represent individual susceptibility perhaps secondary to some latent inborn metabolic disorder. Further information on the incidence of test results showing impairment of motor nerve conduction velocity and autonomic function in patients taking perhexiline without symptoms or signs of neuropathy is needed before accepting this theory. The development of symptomatic autonomic neuropathy, particularly postural hypotension, is obviously an undesirable side effect in any patient with angina pectoris.

¹ Burns-Cox, C J, *et al*, *British Medical Journal*, 1971, **4**, 586.

² Boussier, M G, *et al*, *Nouvelle Presse Médicale*, 1976, **5**, 652.

³ Lhermitte, F, *et al*, *British Medical Journal*, 1976, **1**, 1256.

⁴ Tomlinson, I W, and Rosenthal, F D, *British Medical Journal*, 1977, **1**, 1319.

⁵ Levin, A B, *American Journal of Cardiology*, 1966, **18**, 90.

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SHORT REPORTS

Leukapheresis for papilloedema in chronic granulocytic leukaemia

Although retinal vein distension, fundal haemorrhages, and blurring of the optic disc margins are well-recognised features of chronic granulocytic leukaemia (CGL), true papilloedema is relatively rare.¹ We report a case where bilateral papilloedema was present at diagnosis and improved after repeated leukapheresis on a continuous flow cell separator.

Case history

A 33-year-old woman was admitted to hospital with a 12-month history of anorexia, weight loss, and fatigue. She admitted to recent deterioration in vision. She was pale and thin with splenomegaly to below the umbilicus. Both optic fundi showed venous distension, haemorrhages, and papilloedema consistent with leukaemic retinitis. The findings of full neurological exami-

nation were otherwise normal. Peripheral blood findings were as follows: Hb 7.4 g/dl; platelets $470 \times 10^9/l$; total WBC $260 \times 10^9/l$ (neutrophils 44%, metamyelocytes 9%, myelocytes 18%, promyelocytes 18%, eosinophils 2%, basophils 1%, lymphocytes 2%, blast cells 6%, nucleated RBCs 4/100 WBC). Leucocyte alkaline phosphatase score 5 (normal 20-120). Bone marrow examination yielded initially a dry tap, but a later aspirate showed gross myeloid hyperplasia, and an increase in eosinophils and megakaryocytes, consistent with a diagnosis of CGL. The Philadelphia chromosome was present. Trephe bone marrow biopsy showed no features of myelofibrosis. Immunoglobulin concentrations were normal and no paraprotein band was detected. Whole blood viscosity, measured at 37°C in an Ostwald viscometer,² was approximately twice normal (ratio patient's blood/water = 7.7; ratio control blood matched for haematocrit value/water = 4.2). An EMI brain scan showed no abnormality—in particular, no dilatation of the ventricular system to suggest raised intracranial pressure. Fluorescein angiography confirmed swelling of the optic nerve head.

CGL was diagnosed and, because of the very high WBC count, primary treatment was by leukapheresis, initially daily and later twice weekly, on a continuous flow cell separator. A total of 3.22×10^{12} leucocytes, of which 1.86×10^{12} were immature myeloid cells, were removed over a period of 26 days. By day 21, after eight such treatments, there was considerable improvement in the eye signs, with disappearance of most of the haemorrhages and

Appearances of fundus after eight leukaphereses showing resolving papilloedema.

reduction in venous calibre. Disc swelling improved although the margins remained blurred (see figure). Whole blood viscosity fell immediately to within normal limits (patient ratio 3.56; control ratio 4.0), although the WBC count remained fluctuant between 50 and $190 \times 10^9/l$. The spleen regressed in size by 4.5 cm and at the same time there was subjective restoration of normal vision. Treatment was then continued with busulphan. The patient remained well with no new retinal or neurological signs five months later. Total WBC, platelets, and Hb levels were within normal limits, although some early myeloid cells were still seen in the peripheral blood. The spleen was now palpable at the costal margin.

Comment

Leukaemic retinitis was first described in 1861 by Liebreich¹ and is at its most florid in CGL, where papilloedema and true retinal infiltration by leucocytes may occur. Papilloedema may also occur where anaemia is very severe from any cause, and is a cardinal feature of meningeal leukaemia where there is raised intracranial pressure, leading to diverse neurological signs and dilatation of the ventricular system. Leukaemic retinitis is most severe when the Hb level is low and WBC count high.¹ Although there is disagreement, some reports suggest that whole blood viscosity may be raised as a result of a large increase in the WBC count, but only where the count is greater than $50 \times 10^9/l$.³ Leucocyte thrombi and aggregates have been demonstrated at necropsy in patients with various types of leukaemia.⁴ These are most frequently in lung and brain and are again associated with very high WBC counts, especially where there is a high proportion of immature forms, as in our patient. It is therefore reasonable to postulate that this patient's papilloedema was a direct result of the extremely high peripheral blood white cell count, with formation of leucocyte thrombi and aggregates in the retinal vessels, and subsequent infiltration of the optic nerve by leucocytes.

Leukapheresis is being increasingly used in the initial treatment of CGL,⁵ and may, as in this case, provide a rapid and effective means of alleviating the potentially dangerous effects of leucocyte stasis in patients with grossly raised white cell counts.

¹ Borgeson, E J, and Wagener, H P, *American Journal of the Medical Sciences*, 1929, **177**, 663.

² Fahey, J, *Journal of Chronic Diseases*, 1963, **16**, 703.

³ Stephens, D J, *Proceedings of the Society for Experimental Biology and Medicine*, 1936, **35**, 251.

⁴ McKee, L C, and Collins, R D, *Medicine*, 1974, **53**, 463.

⁵ Goldman, J M, and Lowenthal, R M, *Leucocytes: Separation, Collection and Transfusion*. London, Academic Press, 1975.

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Factor V inhibitor and bullous pemphigoid

Although spontaneous inhibitors active against single clotting factors are uncommon, most of them are active specifically against factor VIII.¹ There are, however, sporadic reports of inhibitors against other clotting factors, and this report describes some clinical and laboratory observations on a patient who presented with bullous pemphigoid and who spontaneously developed an inhibitor against factor V.

Case report

A 73-year-old woman was admitted with a history of itchy "blistering" of the hands, scalp, and feet. She had had haematuria for two days and had finished a 3-week course of tetracycline four days before admission. She had also been taking nalidixic acid for seven days. On admission her haemoglobin level was 10.5 g/dl, but two weeks later she felt unwell and developed slight abdominal pain and distension. Her Hb dropped to 5.9 g/dl and a straight x-ray film of the abdomen showed gaseous distension of the colon. She was given 20 mg of vitamin K₁ intravenously and was transfused. Nevertheless, two days later she suddenly developed hypotension and died. At necropsy a large retroperitoneal blood clot surrounded the left kidney. No other abnormality was found.

Coagulation studies showed that the prothrombin time and the partial thromboplastin time were prolonged (see table) and neither was adequately corrected by the addition of an equal volume of normal control plasma. Assays for specific clotting factors showed a slight reduction in factor X and an almost complete absence of factor V. It was noticed that in the clot-weight technique for estimating fibrinogen there was slow generation of fibrin. Further investigations carried out to identify the nature of the inhibitor showed it to be specific for human factor V because there was no appreciable difference between the patient's plasma and normal plasma when each was incubated with bovine factor V. Antibody neutralisation tests using sheep anti-human IgG and IgM indicated that the inhibitor was an IgG antibody. Immunofluorescence tests against guinea-pig tissue were positive for basal lamina IgG but negative for intracellular substance IgG. LE cells were absent. Anti-pemphigoid antibodies were present (titre >1/400). The histological appearance of the bullae was consistent with bullous pemphigoid.

Results of coagulation studies

Studies	Patient		Normal range
Platelets ($\times 10^9/l$)	260		150-400
Factor VIII (% an*)	90		50-200
Factor X (% an)	38		50-200
Factor II (% an)	84		50-200
Factor V (% an)	<1		50-200
Plasma fibrinogen (g/l)	3.35		2.0-4.0
Calcium thrombin time (s diff)	+0.7		< +2.0
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Prothrombin time (s)			
Patient	92.5	97.2	12.1-16.1
Control	14.4	14.2	
50/50 mixture (incubated 37°C)	20.6	45.3	
(fresh mixture)	—	21.0	
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Partial thromboplastin time (s)			
Patient	233.4	250.0	33.5-45.9
Control	37.4	43.0	
50/50 mixture (incubated 37°C)	90.8	134.0	
(fresh mixture)	—	100.0	

*an = average normal; results from the patient were compared with those from a pool of six normal controls.

Discussion

Inhibitors active specifically against factor V are rare: only 12 other reports could be found.²⁻⁵ Some had had streptomycin or blood transfusion at a variable interval before the factor V inhibitor made itself apparent clinically.^{2,3,5} Nevertheless, our patient had not received streptomycin and was given a blood transfusion only after the onset of her bleeding disorder.

The poor generation of fibrin in the fibrinogen assay clot-weight system and the slow clotting of the blood transfusion sample raised the possibility of defibrination syndrome. Nevertheless, the normal fibrinogen level, thrombin time, and platelet count were all against this. The results of other investigations confirmed the presence of a factor V inhibitor. The reduced factor X concentration may have been an artefact caused by the presence of the factor V inhibitor interfering with the one-stage assay system.