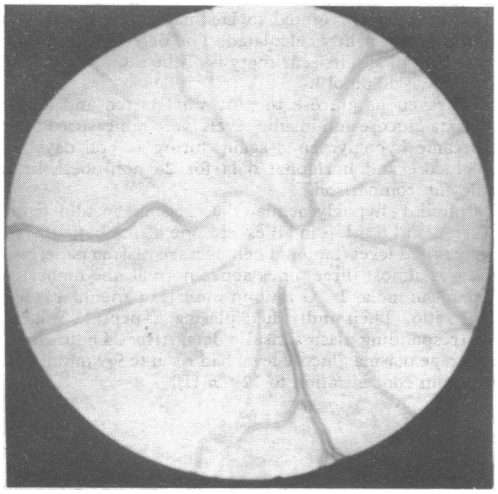

Appearances of fundus after eight leukaphereses showing resolving papilloedema.

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 190×10^9/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 Liebreich[1] 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 50×10^9/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.

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(*Accepted 15 April 1977*)

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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 K_1 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
	0 h	1 h	
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	
50/50 mixture (fresh mixture)	—	21·0	
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	
50/50 mixture (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.

The possible association with bullous pemphigoid has not been reported. The occurrence of factor V inhibitors seems to have been associated with "autoimmune" disturbances in at least three of the 12 patients reported[3]—for example, penicillin allergy and the presence of autoantibodies such as antinuclear and rheumatoid factors. Antibodies to factor VIII have occurred in patients suffering from diseases with an autoimmune basis, such as asthma, rheumatoid arthritis, ulcerative colitis, and allergic reactions to penicillin. The association with pemphigoid may therefore suggest that the inhibitor may be a manifestation of some generalised autoimmune disturbance.

We would like to thank Dr J W Beattie, consultant geriatrician, West Norwich Hospital, for permission to publish this report on his patient.

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(*Accepted 20 April 1977*)

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Plasma insulin, C-peptide, and glucagon levels in acute phase of ethanol-induced hypoglycaemia

The pathophysiology of ethanol-induced hypoglycaemia (EIH) is not fully established. Plasma insulin levels do not seem to be raised,[1] and there is only scanty information on plasma pancreatic glucagon concentrations in the pretreatment period.[2] We have therefore documented the insulin: glucagon (I : G) relationships during the acute phase of clinical EIH, in view of the current emphasis on the bihormonal nature of glucoregulatory activity.

Patients, methods, and results

Five non-obese patients (four men and one woman) who presented with the syndrome of EIH were studied. Their mean age was 39 years (range 26-60). Pertinent clinical features included a consistent background of long-standing excessive alcohol intake culminating in a preadmission "binge," no intake of food for several hours before admission in a stuporous condition, absence of florid liver disease or pancreatitis, and lack of other metabolic disturbances such as hypothermia, acidosis, or ketonuria.

As soon as the clinical diagnosis of EIH was suspected and before starting treatment venous blood was withdrawn into heparin tubes to measure "acute" plasma glucose (AutoAnalyzer) and plasma levels of insulin, C-peptide, and pancreatic glucagon by radioimmunological methods.[3] The glucagon tubes contained aprotinin. Plasma samples for the hormonal assays were deep-frozen and air-freighted to Denmark. The molar I : G ratio of each patient was subsequently calculated. The detection limit of the insulin assay system is 2 mU/l and its sensitivity is of the same order. The detection limit for C-peptide is 40 pmol/l.

Prolonged intravenous glucose therapy was started and all five patients recovered. Plasma glucose and insulin levels were remeasured after 24 hours. No patient became hypoglycaemic again during several days' observation. The fasting glucose and hormonal data for 24 non-obese healthy adults were available for comparison.

Despite profound hypoglycaemia the plasma insulin concentrations ranged between 3 and 6 mU/l in all except one of the patients (case 2), who had a distinctly raised level (table). Their average plasma pancreatic glucagon concentration was almost three times above normal, the highest again being in case 2. The mean molar I : G ratio in the EIH patients was less than half of the control ratio. Their individual plasma C-peptide values tended to parallel the corresponding plasma insulin data. After 24 hours on intravenous glucose the average plasma glucose level had risen to 9·9 mmol/l (179 mg/100 ml) and the insulin concentration to 12·6 mU/l.

Comment

In EIH the raised glucagon concentration probably represents a physiological adjustment to the hypoglycaemia. The preceding period of starvation may also be relevant. Pretreatment levels of insulin and C-peptide (released from the beta cell with insulin on an equimolar basis) were, on average, near normal, although at the extremely low glucose concentrations in our patients they should both have been virtually completely suppressed.[4] One explanation for this novel finding is that the hyperglucagonaemia produced some beta cell stimulation, and this is supported by the observation that the patient with the highest glucagon level also showed the highest insulin concentration. Another consideration is that the normal hepatic destruction of insulin might have been reduced, leading to spuriously high peripheral insulin concentrations. But peripheral levels of C-peptide, which is not metabolised significantly by the liver,[5] should then have been appropriately suppressed. Our results did not show this.

The pretreatment molar I : G ratio was uniformly depressed but despite this "hyperglycaemic set" blood glucose levels remained very low. Hepatic glycogen stores are depleted and neoglucogenesis is suppressed in patients with EIH,[2] however, and glucagon cannot overcome these metabolic effects of ethanol.[1]

The South African Medical Research Council and Atomic Energy Board provided financial assistance.

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(*Accepted 14 April 1977*)

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Plasma glucose and hormonal levels in five patients with ethanol-induced hypoglycaemia and in 24 fasting controls

	Glucose (mmol/l)	Insulin (mU/l)	Pancreatic glucagon (ng/ml)	Molar I : G ratio	C-peptide (pmol/l)
			Patients		
1	1·4	6	0·18	0·78	250
2	1·5	18	1·50	0·23	1000
3	1·1	5	0·19	0·61	120
4	1·0	3	0·40	0·18	40
5	1·1	3	0·32	0·22	120
Mean ± SE of mean	1·2 ± 0·1*	7·0 ± 2·8	0·52 ± 0·25*	0·40 ± 0·12*	310 ± 180
			Controls		
Mean ± SE of mean	4·7 ± 0·2	7·4 ± 0·9	0·19 ± 0·01	0·91 ± 0·11	350 ± 10

* Significantly different ($P \leq 0·05$) from controls.
Conversion: SI to traditional units—Glucose: 1 mmol/l ≈ 18 mg/100 ml.