Antibody-mediated tissue damage

Hyperviscosity and other complications of paraproteinaemia

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The association between hypergammaglobulinaemia and raised serum viscosity has been recognised for more than 40 years. Waldenström (1944) described three patients in whom macroglobulinaemia was associated with increased serum viscosity, and even earlier than this there had been reports of raised plasma viscosity in myelomatosis (Albers, 1937). Since these early reports many of the clinical features of macroglobulinaemia have been recognised to be a direct consequence of the increased plasma viscosity, and in 1965 Fahey and his colleagues defined the condition now known as the hyperviscosity syndrome (Fahey *et al.*, 1965). Initially it was believed that the hyperviscosity syndrome (HVS) was almost invariably associated with Waldenström's macroglobulinaemia and that it was a rare complication of myelomatosis. During the last few years, however, it has become increasingly recognised as a complication of certain types of myelomatosis (Preston *et al.*, 1978; Tuddenham *et al.*, 1974).

Concept of viscosity

Viscosity is best considered as the resistance offered by a liquid to attempts to change its shape (Phillips and Harkness, 1976). It is thus a measure of its resistance to flow. It is defined as the ratio of shear stress to shear rate. Shear stress is the tangential force exerted across a unit area between two parallel planes of the fluid, unit distance apart, with one plane moving at unit velocity relative to the other. Shear rate is the velocity gradient.

The relationship between fluid flow and viscosity was established by Poiseuille in 1840. He showed that

$$Q = \frac{\pi}{8} \times \frac{\Delta P}{l} \times \frac{r^4}{\eta}$$

where Q is the flow rate, ΔP is the pressure gradient, l is the tube length, r is the tube radius, and η is the viscosity. Although Poiseuille's biological studies were concerned primarily with blood flow through

the mesenteric circulation his formula was derived from studies of the dynamics of the flow of water through capillary tubes. For simple fluids the relationship between shear stress and shear rate is constant, and such fluids are described as having Newtonian flow characteristics. Blood, however, does not behave as a simple fluid and its anomalous flow characteristics are described as non-Newtonian. Blood can be considered as a suspension of erythrocytes in plasma, and it is these that are primarily responsible for the non-Newtonian behaviour of this biological fluid (Whitmore, 1968). Unlike Newtonian fluids, in which the viscosity is independent of the rate of shear, there have been a number of reports showing that the viscosity of the blood depends on the shear rate, with non-Newtonian characteristics becoming more pronounced at low rates of shear (Phillips and Harkness, 1976; Dintenfass, 1965).

Factors affecting blood viscosity

The haematocrit is the most important single factor influencing whole blood viscosity. Most workers agree that there is a linear relationship between the haematocrit and the logarithm of the blood viscosity (Virgilio *et al.*, 1964; Dormandy *et al.*, 1973). The importance of this should be borne in mind when transfusing patients with increased blood viscosities from other causes, since the increase in haematocrit may raise the whole blood viscosity to a level associated with the clinical features of HVS. Erythrocyte flexibility is also a factor influencing blood viscosity. This may relate to the internal structure of the red cell, as in sickle-cell anaemia, but in addition there is evidence to show that red cell flexibility may be influenced by plasma fibrinogen levels.

Plasma fibrinogen is another important factor influencing plasma and therefore whole blood viscosity. It also contributes to the non-Newtonian behaviour of blood with its viscosity effects becoming more prominent at low rates of shear.

Pathophysiology of HVS in paraproteinaemias

In macroglobulinaemia the raised serum viscosity relates to the physical properties of the IgM molecule, which has a molecular weight of 1 million. In addition it also has a high axial-length/width ratio which is associated with a high intrinsic viscosity of the molecule. A given concentration of IgM is consequently associated with a higher serum viscosity than that produced by the same concentration of the smaller IgG molecule (MW 160 000).

There are two main mechanisms whereby hyperviscosity effects may be produced in myelomatosis. Firstly, extremely high concentrations of serum paraprotein, regardless of class or subtype, will raise the blood viscosity to clinically significant levels. Secondly, there are certain immunoglobulins which by virtue of their physicochemical properties have high intrinsic viscosities. Moderate concentrations of these immunoglobulins may raise the blood viscosity enough to produce clinical effects. For example, HVS is not usually seen in patients with IgG₁ myeloma until the paraprotein concentration exceeds 80 g/l, when the serum viscosity may be sufficiently raised to produce symptoms.

Certain immunoglobulins, notably IgA and IgG₃, may produce increased blood viscosity at much lower concentrations than IgG₁. This relates to the tendency of both paraproteins to form complexes of high intrinsic viscosity. Although IgG₃ myeloma constitutes less than 10% of IgG myelomas there is a disproportionate number of reports of IgG₃ myeloma complicated by HVS (Somer, 1975). This undoubtedly relates to the tendency of this protein to form concentration- and temperature-dependent aggregates. With this type of myeloma a smaller increment in paraprotein concentration produces a greater increase in serum viscosity than a corresponding rise in IgG₁ protein. Significantly raised viscosity levels are thus associated with lower concentrations of IgG₃ protein.

As recently as 1973 (*Lancet*, 1973) HVS was considered to be a rare complication of IgA myeloma. Since then, however, a number of workers have drawn attention to the relative frequency of the hyperviscosity syndrome in patients with IgA myelomatosis (Tuddenham *et al.*, 1974; Roberts-Thomson *et al.*, 1976; Preston *et al.*, 1978).

Studies of the physicochemical characteristics of IgA have clarified the viscosity effects of this paraprotein. An intrinsic property of the IgA molecule is its tendency to form high molecular weight complexes such as dimers, trimers, and tetramers with sedimentation coefficients of 10S, 12S, and 15S respectively. These complexes, particularly IgA trimer, are prominent in patients with IgA myeloma

complicated by HVS (Preston *et al.*, 1978). In patients without HVS the IgA is mainly in the form of monomer and dimer. The importance of the IgA complexes in raising serum viscosity levels in IgA myeloma is apparent from a study of the viscosity characteristics of these proteins. Data obtained for purified IgA monomer, IgA dimer, and IgA polymer show that the viscosity of the polymer is significantly greater than that of the larger IgM molecule (Preston *et al.*, 1978). The intrinsic viscosity of IgA monomer and IgA dimer occupies an intermediate position between IgG and IgM. For this reason the whole blood viscosity for a given concentration of paraprotein is higher in IgA myeloma than in IgG myeloma.

The incidence of HVS complicating myelomatosis remains uncertain since it has only recently become recognised as a complication of IgA myeloma. Hobbs (1969) reported an incidence of 4% for patients with IgG myeloma, but made no reference to IgA myeloma. More recently, Tuddenham *et al.* (1974) reported HVS in 14% of their IgA myeloma patients, while Preston *et al.* (1978) reported an overall incidence of 9.6% with 25% of patients with IgA myeloma being affected.

Clinical features

There is much individual variation in the clinical effects of raised blood viscosity in patients with paraproteinaemia. This was noted in the original description of HVS by Fahey *et al.* (1965). There is no correlation between measured blood or serum viscosity and clinical symptomatology. This is illustrated by two patients in the group described by Preston *et al.* (1978). Whereas one patient with myeloma consistently developed symptoms whenever his blood viscosity became abnormal, another was symptom-free until the blood viscosity was grossly raised. For any given patient, however, there is remarkable reproducibility in the type and degree of symptoms for any given viscosity. In many cases the viscosity level may be accurately predicted from the accompanying clinical picture.

GENERAL SYMPTOMS

Patients often complain of weakness, excessive fatigue, lethargy, and drowsiness. Although affected patients are invariably anaemic the symptoms are often greatly in excess of those normally associated with the degree of anaemia.

VISUAL DISTURBANCES

Ocular manifestations of HVS have been recognised for many years. They include haziness or blurring of vision, loss of near vision, and diplopia. The onset

is usually gradual and transient. Patients often complain of transient blurring of vision while reading newspapers or books. Occasionally visual acuity may suddenly deteriorate. Total blindness may also occur. The retina of patients with HVS is invariably abnormal and it is doubtful whether the diagnosis can be sustained in the absence of some form of retinopathy. The commonest abnormality is congestion and pronounced tortuosity of the retinal veins. In advanced cases sausage-like constrictions of the distended veins occur at sites of a-v crossings. Retinal haemorrhages and exudates may also occur and sometimes the fundal changes are indistinguishable from those observed in hypertensive encephalopathy.

NEUROLOGICAL FEATURES

Neurological signs and symptoms are very common. Patients often complain of headaches but vertigo, dizziness, auditory and visual disturbances, nystagmus, tinnitus, ataxia, and transient ischaemic episodes may also occur. Patients may complain of somnolence, and coma may be a presenting feature. On occasion there may be pyramidal signs and symptoms and, more rarely, peripheral neuropathies.

OTHER COMPLICATIONS

The effect of increased blood viscosity on cardiac function is poorly understood. Patients with myeloma and macroglobulinaemia are often middle-aged or elderly, when cardiac insufficiency is not uncommon. Nevertheless, there are a number of reports of improved cardiac function after successful management of the increased viscosity (Somer, 1975; Schwab and Fahey, 1960). Renal impairment is also often seen in patients with severe HVS and it often responds to plasmapheresis.

ABNORMAL BLEEDING TENDENCY

A bleeding diathesis often accompanies the other features of HVS. Epistaxis is particularly common and may be so severe that the unwary may be prompted to transfuse the patient rather than perform a more effective plasmapheresis. Other haemorrhagic manifestations include bleeding from venepuncture sites, spontaneous bruising, and vaginal and genitourinary haemorrhage. Gastrointestinal haemorrhage can also be particularly troublesome.

Various haemostatic defects may be detected in these patients. It must, however, be emphasised that similar abnormalities may also occur in myeloma patients without an apparent bleeding tendency. According to Perkins *et al.* (1970) the most significant association between defects of haemostasis and abnormal bleeding is seen with tests which relate to platelet-plug formation. In HVS the bleeding time is

not infrequently prolonged, even in those patients who are not thrombocytopenic. Abnormalities of platelet function presumably occur as a result of platelet coating by the paraprotein. Thrombin and reptilase clotting times are the coagulation tests that are most often abnormal. This is usually a reflection of inhibition of fibrin polymerisation by the circulating paraprotein (Lackner *et al.*, 1970). Occasionally the prothrombin time or partial thromboplastin time may be unduly prolonged, and again evidence for inhibitory activity against one or more clotting factors should be sought.

HYPERVOLAEMIA AND HVS

There have been a number of reports of increased plasma volume in patients with paraproteinaemia, and various workers have emphasised the correlation between plasma volume and serum viscosity in patients with myelomatosis and Waldenström's macroglobulinaemia (Tuddenham and Bradley, 1974; Russell and Powles, 1978).

From what has been said it is to be expected that plasma volumes in patients with IgA myeloma and macroglobulinaemia would, in general, be greater than in patients with IgG₁ myeloma. This was confirmed by Tuddenham and Bradley (1974). The mechanism responsible for this relationship, however, is unclear. It is unlikely to relate to colloid osmotic pressure, since this is generally regarded as being inversely related to molecular weight. An important question is whether the increased plasma volume contributes to the clinicopathological features of HVS. In an attempt to study this Russell and Powles (1978) examined the relationships between plasma volume, serum viscosity, retinopathy, and a bleeding tendency in patients with myeloma and macroglobulinaemia. They concluded that the retinopathy of HVS was more closely related to raised viscosity levels than to hypervolaemia.

The relationship between bleeding and viscosity levels, however, is more difficult to define. These same authors showed that although the correlation between bleeding and viscosity is strong there are nevertheless patients who bleed whose blood viscosity is insufficient to be associated with a retinopathy. Russell and Powles (1978) conclude that although hypervolaemia in itself does not seem to be a critical factor it could perhaps influence the presence of symptoms when other factors causing bleeding are present, whether or not they are directly related to the high viscosity.

DIAGNOSIS OF HVS

HVS may often be diagnosed on clinical grounds alone since serum viscosity is invariably increased in

all patients with paraproteinaemias other than those with light chain myelomas. Clinicians should therefore be aware that there are certain groups of patients who are particularly susceptible to this complication. They include patients with the following: (1) macroglobulinaemia, (2) IgA myeloma, (3) IgG₃ myeloma, and (4) all patients with serum paraprotein concentrations over 80 g/l. HVS occurs particularly at initial clinical presentation and during relapse when paraprotein concentrations are high.

The development of CNS signs and symptoms, particularly headaches, or drowsiness, or visual disturbances, or a bleeding diathesis, should suggest the possibility of HVS. Retinal examination is essential and the characteristic features represent valuable, if not essential, diagnostic support.

Although the serum viscosity is often raised in patients with paraproteinaemia, irrespective of the presence or absence of HVS, some useful guide lines are available. Fahey *et al.* (1965) state that although there is great individual variation, no patient in their study with serum viscosities less than 4.0 had symptoms. Similarly Russell and Powles (1978) report that the retinopathy of HVS is always associated with serum viscosity levels greater than 3.8. There are inherent dangers in relying solely on serum viscosity levels for the diagnosis of HVS since the whole blood viscosity is influenced by the haematocrit and also by red cell aggregation. For these reasons it is perhaps more appropriate to measure whole blood viscosity levels at various rates of shear.

Treatment

Large amounts of paraprotein can be removed by plasmapheresis, which thus constitutes an effective method for treating HVS. The fall in paraprotein concentration is paralleled by a fall in serum viscosity, and this is often accompanied by a dramatic reversal of the patient's symptoms (Figure). The volume of plasma which requires to be removed depends upon its initial concentration and the type of paraprotein: 80% of IgM, for example, is confined within the intravascular space compared with 40% for IgG. Consequently plasmapheresis for macroglobulinaemia will effectively remove large concentrations of IgM and afterwards there will be only a minimal secondary rise in serum IgM from the extravascular compartment. A single plasmapheresis for IgG myeloma, however, will be less effective since there may be an appreciable secondary rise from the extravascular space. Further plasmapheresis may then be needed.

At clinical presentation symptoms are usually satisfactorily reversed by plasmapheresis, and ade-

Figure Treatment of IgA myeloma HVS by plasma exchange. The improvement in relative serum viscosity is paralleled by changes in 10S + 12S protein.

quate control can be maintained with standard chemotherapeutic regimens. During relapse, however, the problem is much more difficult. The rapid production of new paraprotein may rapidly negate the beneficial effects of plasmapheresis.

It should be remembered that patients with HVS are invariably anaemic, with hypervolaemia an important contributory factor. Thus blood transfusion may be hazardous, since the improved haematocrit may severely aggravate the clinical features of HVS by its effect on blood viscosity.

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