Current concerns in haematology 1

Is the painful crisis of sickle cell disease a "steal" syndrome?

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Introduction

All genotypes of sickle cell disease are characterised by recurrent attacks of pain, which are most frequent and most severe in homozygous sickle cell disease and sickle cell β^0 thalassaemia. The pain may be localised to the abdomen but the causes of most abdominal painful crises are unknown. Bone pain is much more common, and results from avascular necrosis of the bone marrow, as evidenced by the aspiration of necrotic bone marrow from sites of pain,¹⁻⁵ the behaviour of bone marrow on scintigraphy,²⁻⁶ and the close correlation between the sites of pain and that of erythropoietically active bone marrow. In children below the age of 5 years, active bone marrow occurs in the metacarpals, metatarsals, and phalanges, and avascular necrosis results in the characteristic dactylitis or hand-foot syndrome. At older ages, active marrow disappears from peripheral bones to become localised in the juxta-articular areas of long bones, and the clinical picture of dactylitis is replaced by the classic painful crisis. In this the most common sites of pain are the long bones, spine, and joints, the latter usually resulting from the long bones adjacent to the joint being affected.

If active erythropoiesis with its high metabolic and oxygen demands is one of the essential conditions of the painful crisis, what precipitates the avascular necrosis? An acute increase in oxygen demand must be unlikely and it is presumed to follow a fall in oxygen delivery. This reduced delivery is usually attributed to the vaso-occlusion characteristic of sickle cell disease, and the terms painful crisis and vaso-occlusive crisis are often used interchangeably. Observations which are inconsistent, or difficult to reconcile with this interpretation, include the role of skin cooling in precipitating crises, the bilateral symmetry of pain, and the failure of factors inhibiting sickling to reduce the number of painful crises.

Precipitating factors

Painful crises are episodic and most Jamaican patients recognise clear precipitating factors which precede painful crises. Contrary to what might be expected, these are not factors such as lowered oxygen tension and acidosis, which under laboratory conditions promote sickling.

The commonest precipitating factor, recognised by 200 Jamaican patients with sickle cell

disease in a recent questionnaire study, was skin cooling which was volunteered by 74% of patients and admitted on direct questioning in 90% of patients. Seasonal patterns of painful crises have been reported in Jamaica⁷ and elsewhere.⁸⁻¹⁰ There is evidence that this may be a direct result of skin cooling,^{11,12} and getting caught in the rain or swimming in the sea or a river were volunteered in 24% and 13% and admitted on direct questioning in 50% and 40%, respectively. The association of exposure to cold and bone pain is less obvious in North America and Europe where "manipulation" of environment is more common: air conditioning in the summer and central heating in the winter diminish the apparent seasonal effect. Exposure in northern climates is further reduced by warm clothing, whereas in Jamaica patients tend to wear a thin shirt regardless of the climate and the skin is more directly exposed to environmental temperature.

In the Jamaican questionnaire other precipitating factors included exercise (volunteered by 47%, obtained on direct questioning in 66%), infections (2% and 24%, respectively), and psychological stress (9% and 22%, respectively). These are broadly similar to precipitating factors observed elsewhere,⁸ although their prevalence and the proportion where no factor was recognised has varied between studies.

As cold is the most important precipitating factor in the Jamaican environment it is on this that the ensuing discussion will focus in the development of a new hypothesis for the painful crisis.

Bilateral symmetrical pain

The distribution of bone pain in many painful crises is bilateral and symmetrical, affecting both knees, both ankles, and both shoulders. Many Jamaican patients volunteer that pain affects symmetrical joints either simultaneously or within a period of less than six hours. The blood supply to the bone marrow of one distal femur could be impaired by a vaso-occlusive event, but were this a truly random process, the chances of involvement of the contralateral femur should be no greater than any other bone or joint. Even a general increase in circulating sickled, or less deformable, red cells might explain the simultaneous onset of bone pain at random sites but not the symmetrical pattern so frequently observed.

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Factors inhibiting sickling

FETAL HAEMOGLOBIN CONCENTRATION

Fetal haemoglobin persists for longer in sickle cell disease and higher concentrations are associated with less sickling and generally less severe clinical disease.¹³⁻¹⁵ Although HbF molecules inhibit the growth of polymers of deoxy HbS molecules and although high concentrations of HbF are associated with low, irreversibly sickled cell counts,¹⁶ patients with high HbF concentrations may experience frequent severe bone pains while others with low concentrations rarely develop pains. Populations characterised by high HbF concentrations such as in central India and the eastern province of Saudi Arabia, have painful crises as a major symptom^{17,18} although other features are often benign. Finally, statistical analyses of the incidence of painful crisis and HbF concentrations in both the United States of America and Jamaica failed to show any protective effect of high HbF concentrations.^{19,20}

EFFECT OF GENOTYPES OF SICKLE CELL DISEASE

Sickle cell β^0 thalassaemia and the interaction of sickle cell disease with homozygous α^+ thalassaemia are both associated with a lower mean corpuscular haemoglobin concentration and are therefore less likely to manifest intravascular sickling. Red cell survival is prolonged in sickle cell disease with homozygous α^+ thalassaemia.²¹ Persistence of splenomegaly as well as other indices of clinical improvement occur in both genotypes, but neither the number nor severity of painful crises is reduced.^{22,23} Indeed, there is some anecdotal evidence that the frequency of pains may be increased.

CYANATE TREATMENT

Sodium cyanate carbamylates HbS and inhibits its polymerisation, reducing sickling and improving red cell survival, but this agent failed to reduce painful crises in a double blind cross-over study.²⁴

All of the above conditions seem to inhibit sickling yet have no discernible effect on the numbers of painful crises. In each case the reduction in sickling has been attended by an increase in total haemoglobin concentration which is a risk factor for painful crisis.²⁰ Flow in the capillary beds is influenced predominantly by the characteristics of individual red cells and should be improved by inhibition of polymerisation and a reduced intracellular viscosity. The major effect of a higher total haemoglobin is on flow in larger vessels and is consequent on the raised viscosity. These observations support the concept that painful crises result principally from changes in larger vessel flow.

A new hypothesis

It is difficult to envisage a mechanism whereby skin cooling promotes multiple and symmetrical sites of vaso-occlusion, but this stimulus could induce a reflex shunting of blood away from the bone marrow with the same result of avascular necrosis. In healthy people skin cooling leads to cutaneous vasocon-

striction with diversion of the blood to the deeper vessel systems²⁵ in the muscles and bones. The extent to which these changes are accommodated by a fall in total limb flow or by a redistribution of blood flow within the limb is still unclear. There is evidence, however, that muscle blood flow is increased in response to skin cooling and it is assumed that some of the flow shunted away from the skin is accommodated by vessels within the muscle and bone marrow. In sickle cell disease the erythropoietic expansion is likely to be associated with increased bone marrow blood flow and there may be a limited capacity to accommodate further flow. Furthermore, if preferential channels in muscle open up and offer less resistance to flow than intramedullary vessels it is theoretically possible that these could compromise blood flow to the bone. Even small areas of bone marrow necrosis will induce an inflammatory response, increasing the intramedullary pressure and favouring a vascular bypass of the bone marrow. Such a shunting away from metabolically active areas is also supported by the increase in oxygen tension in the superficial veins of the forearm observed during the painful crisis.²⁶

Peripheral blood flow in sickle cell disease is two to three times that in normal controls (Mohan JS, unpublished observations), and cardiac output is increased one and a half to two times, implying that a greater proportion of the cardiac output is diverted to the periphery. There is also some evidence that the vascular reflexes behave differently in sickle cell disease.^{27,28}

Because skin cooling does not induce bone marrow necrosis in other conditions with erythropoietic expansion such as β thalassaemia or hereditary spherocytosis, cells containing HbS must play a part in the painful crisis but they may contribute to the process only after major blood flow shifts away from the marrow have occurred.

Several observations cast doubt on the traditional vaso-occlusive concept of the painful crisis. Centrally mediated reflexes, initiated by skin cooling and resulting in shunting of blood away from the bone marrow, could explain the commonly observed bilateral and symmetrical distribution. This is more consistent with the total haemoglobin effect on larger vessel flow, and they would be largely independent of the determinants of intravascular sickling. Such a "steal" syndrome is a hypothesis worthy of exploration because it may lead to new initiatives in the prevention and treatment of painful crises.

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