SICKLE CELL TRAIT: A RARE CAUSE OF POST-OPERATIVE DEATH IN NORTHERN IRELAND

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OWING to the increase in the immigrant population in Northern Ireland, the medical profession, and especially anaesthetists, should be alerted to the necessity of investigating certain patients for sickle cell trait before anaesthesia. Although usually harmless, it may cause sudden death after even minor surgery.

Case Report

The patient who was a six-year-old negro child of mixed parentage with no recorded previous medical history was admitted for a minor plastic operation. At the time of admission his haemoglobin was 11.5 g. per 100 ml. Neither of the parents, both of whom were medically qualified, were aware of any haematological abnormality. Premedication was administered in the hour before being taken to theatre and consisted of seconal 50 mg per rectum, and morphine 5 mg and atropine 0.6 mg intramuscularly. The anaesthetic which was uneventful was induced with Althesin and maintained with nitrous oxide and oxygen (50/50) and methoxyfluorane (1%–0.2%). Post-operatively, the child was awake and restless and was sedated with 5 mg of Physeptone. Approximately four hours after completion of the operation the patient suddenly collapsed and resuscitation was unsuccessful.

At post-mortem examination, the body was that of a 4-feet tall negro child weighing 21 kg. On the posterior surface of each pinna there was a 4-cm long sutured surgical incision. There were no other significant findings on external examination.

On gross examination of the organs a small amount of blood-stained mucus was found in the trachea. Anterior to the hilum of the left lung there were two openings approximately 0.4 cm in diameter which were produced by needles during the attempt at resuscitation. The right lung showed a 1-cm long segment of collapse on the anterior border. On section, both lungs were congested and oedematous. The brain was cyanosed and soft. It weighed 1350g, an increase above the normal weight, due to cerebral oedema. The spleen weighed 60g which was within normal limits for the age of the patient. It showed no scarring or any other abnormality.

On microscopic examination, the most striking feature was in the spleen where there was distortion and congestion of the sinusoids around the lymphoid follicles. The lymphoid follicles were prominent, some containing active germinal centres. The bone marrow was active and showed no abnormality. The brain showed engorgement of the small vessels. The glomerular and peritubular capillaries of the kidneys also showed engorgement. The lungs were congested and showed focal collapse and oedema of some alveoli with compensatory expansion of others. Other organs showed no histological abnormalities. The sickle shape of the red blood cells seen microscopically may have been due to the patient's disease but can also be produced artefactually by fixation of tissue in formalin.

Examination of a blood specimen by electrophoresis showed the presence of haemoglobin A and haemoglobin S, confirming that the patient suffered from sickle cell trait and subsequent examination of the father's blood showed that he also carried the trait.

Pathology

The red blood cells in a patient with this condition, when deprived of oxygen, assume a sickle shape and sludging of blood with blockage of vessels may occur (Edington and Gilles, 1969). This is due to an abnormal haemoglobin, haemoglobin S, crystalling out in the deoxygenated state when it is less soluble than normal haemoglobin A. The abnormality in haemoglobin S is replacement of glutamic acid by valine at the sixth position of the beta chain. In the deoxygenated state the valine residues in each molecule form apolar bonds with adjacent haemoglobin molecules; several of these polymers twist upon each other and these long crystals of haemoglobin S distort the cell giving it the characteristic shape. Red cells so affected are also prone to haemolysis.

The essential pathology of the disease arises mainly from capillary thrombosis which can cause micro-infarcts and ischaemic atrophy, and the clinical effects depend on the organ or organs affected. The usual complications encountered (Rapaport, 1971) are splenic infarction after exposure to a high altitude, gross haematuria secondary to renal papillary necrosis and ulceration, cerebral thrombosis and sudden death.

At post-mortem, if death has resulted quickly the findings may not be specific. The spleen is the most likely organ to be affected and it is often enlarged and dark purple in colour with areas of congestion and haemorrhage around the central arterioles. The kidneys may appear grossly normal although occasionally papillary haemorrhages are present. On microscopic examination the diffuse intravascular sickling and agglutination of distorted erythrocytes may be well demonstrated in peritubular capillaries and in large glomeruli, particularly near the corticomedullary junction (Kissane and Smith, 1967). If the patient survives 24-hours or so focal ischaemic necrosis of glomeruli may be seen. In the brain diffuse cerebral hyperaemia and oedema are common. Engorgement of small vessels is always present. True thrombi may form in microscopic vessels, and occasionally in dural sinuses, resulting in cerebral infarcts.

Evidence of previous sickling episodes may be present. The spleen may be distorted due to scarring and weigh only a gramme in young adults. The kidneys may be coarsely scarred and the papillae may be shrunken and fibrotic and microscopically show dilated vessels and disruption of collecting ducts.

It may be difficult or impossible to determine the exact initiating cause of a sickling episode. This is because of a variable time lag between the period of relative hypoxia and death. In the reported case, with which the authors were concerned, the patient died within six hours of the operation. In another case, that of a 12-year-old negro boy who had a tonsillectomy, 33 days elapsed before he succumbed to a superior longitudinal sinus thrombosis.

The sickle cell trait is found in people who are heterozygous for the S gene. This is a Mendelian dominant and is an allele of the gene responsible for the

production of normal haemoglobin. Unlike the homozygous condition which usually presents as a severe congenital anaemia, the trait is usually asymptomatic (Browne, 1965). It is widely distributed but its highest incidence is usually found in tropical Africa. There, the heterozygote carrying the trait enjoys an advantage against the lethal effects of infection by the malarial parasite, *Plasmodium falciparum*. In a malarial-ridden country, this confers a selective advantage greater than any disadvantage. It is present in the descendants of West Africans in the United States where it reaches an incidence of 9 per cent and in the West Indies and South America. Isolated pockets of relatively high incidence are found in Sicily, Greece, South Turkey, South Arabia and the Indian peninsula.

Discussion

Until the present time death due to sickle cell trait has been virtually unknown in Northern Ireland. However, doctors in the province may expect to meet the condition more often if the immigrant population rises as it has done in England. At the last census in 1971, 936 people were recorded as having been born in Africa and 1284 in India; many of these were presumably closely associated with hospitals, as many posts are now filled by foreign graduates from regions where the condition is found. One of the great dangers of the trait is that it may go completely unnoticed and may pass as an unexplained cause of death unless specifically looked for at post-mortem. A case has been recorded of a negress dying after an uneventful anaesthetic for a 15-minute procedure although she had given birth to a child 5-months previously without complications. This stresses the point that a careful history should be taken, as an "operation" to a patient may not involve general anaesthesia. Furthermore, as in the case reported, a parent may be carrying the trait without realising it. Because of these facts one must be aware of the condition in certain ethnic groups.

During operation sickling may be caused by clinically undetectable hypoxia (Gilbertson, 1965). The level of oxygen desaturation required to produce sickling is variable both in different regions of the body in any one patient and in different patients. It has further been shown (Nunn and Payne, 1964) that a considerable degree of hypoxia may occur during and after an uneventful anaesthetic for a minor operation. These authors state that the average degree of hypoxia discovered post-operatively corresponds to that which occurs in an unpressurised air-craft flying at an altitude of 10,000 feet above sea-level and the lowest oxygen tension they found would be reproduced in a person in such an aircraft at 17,000 feet. In aircraft at these altitudes, however, passengers with sickle cell trait have suffered from splenic infarction (Smith and Conley, 1955) and so the same accident or consequences of sickling could be expected to occur post-operatively.

During operation a lowering of oxygen tension may cause an increase in viscosity without sickling. Due to the slowing of blood flow a local acidosis may then occur which initiates or enhances sickling. Thus a vicious circle may be set up, the initiating general hypoxia being exaggerated locally by factors resulting from it. Tissue hypoxia will be increased if there is accompanying dehydration or blood loss which cause circulatory stasis. It is logical to assume that any sedative drugs

which depress respiration could further increase tissue hypoxia. It has been stated (Searle, 1973) that there is little evidence to support the statement that anaesthesia may precipitate a sickle cell crisis in sickle cell trait. However the usual techniques to ensure adequate tissue oxygenation should be exercised with particular care.

Apart from the predisposing factors mentioned earlier, the position of the operating table should be carefully adjusted to prevent local stasis and tourniquets should not be used unless absolutely necessary. If they are, such as in orthopaedic operations, the limb must be carefully exsanquinated using an Esmarch bandage. Also, cooling and sepsis should be prevented because cooling increases blood viscosity and sepsis may be associated with an acute sickling crisis. However, it would seem that the ancillary methods suggested to prevent sickling in the homozygous condition are unnecessary. These include giving alkalies orally, low molecular weight dextran to reduce blood viscosity, urea to break down the hydrophobic bonds between the molecules of deoxygenated haemoglobin S and oxygen administration continuously for 24 hours after operation.

Sideroom and Laboratory Tests

A sickling test can now be carried out with a commercial preparation, Sickledex, and only takes a few minutes to perform (Loh, 1968). The test works on the principle that haemoglobin S is relatively insoluble when combined with a buffer and a reducing agent. When Sickledex Reagent Powder is mixed with Sickledex Test Solution and a blood sample is added, blood containing haemoglobin S will form a cloudy turbid suspension. Other haemoglobins are more soluble and will form a transparent solution when tested. This test has been found to be more sensitive and more reliable than the standard metabisulphite test.

The electrophoresis test is carried out in a specialised haematology department and works on the principle that haemoglobin S migrates in an electrical field at a different speed from normal haemoglobin A.

Summary

The authors wish to draw attention to the condition of sickle cell trait and to emphasise the increasing probability that serious manifestations may be seen in countries where previously it was unknown. It is particularly dangerous because there may be no prior clinical manifestations. It is suggested that screening for this condition should be performed in all negro, Indian and Mediterranean patients before any operative procedure requiring general anaesthesia. Blood for a simple sickling test or for electrophoresis should be sent routinely with specimens for blood grouping. Pre-medication and post-operative sedative drugs should be kept to a minimum and during anaesthesia particular attention should be paid to the prevention of hypoxia and the factors which may add to it such as circulatory stasis, blood loss, cooling and sepsis.

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