FAVISM IN A WHITE SOUTH AFRICAN CHILD

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Favism is uncommon in South Africa, and only one other case report, that of Senior and Braudo,[1] has been found in the literature. Since that report was published, considerable advances in the understanding of this interesting condition have been made, although there are still features which have not been adequately explained. It has been established that individuals who are sensitive to broad beans *(Vicia fava)* manifest the red-cell defect associated with primaquine sensitivity.[2] The erythrocytes in this hereditary condition appear normal to ordinary microscopic examination, but are characterized, among other biochemical abnormalities, by deficiency of the enzyme glucose-6-phosphate dehydrogenase, and by low levels of reduced glutathione, which is also unstable under certain

in vitro conditions.[3] The patient described by Senior and Braudo[1] was a Greek immigrant, and the present case appears to be the first reported in an Afrikaans-speaking White South African.

CASE REPORT

History

The patient, a 6-year-old White male child, was first seen by one of us (I.M.P.) on the morning of 23 September 1961, complaining of tiredness and intermittent abdominal pain of 4 days' duration. The symptoms had progressively increased, and the day before he was seen the parents noticed that he was pale and put him to bed. The next day the child was worse and medical aid was sought.

No history of significant previous illness was obtained. Seventeen days previously he had been given 3 doses of a sulphonamide suspension for a mild upper respiratory tract infection. The day before the commencement of the present illness (18 September) the family had eaten cooked broad beans which were subsequently identified as *Vicia fava*. These beans had been eaten regularly by the family, including the patient, for a month previously, and the patient had been seen to eat raw beans in the garden on several occasions before the present episode, without ill-effect. Although careful enquiry was made, no history of exposure to any other possible haemolytic agent could be obtained.

Examination

On examination there was marked pallor of the mucous membranes with slight icterus of the sclerae. The oral temperature was 99°F., the pulse rate 140 per minute, and the respiratory rate 30 per minute with prominent movement of the alae nasi. Examination of the cardiovascular and respiratory systems was negative. There was generalized abdominal tenderness, but no guarding, and the tip of the spleen was felt. The urine was dark-red in colour and albumin was present (++++).

Blood Investigations

On examination of the blood the haemoglobin concentration was 6·7 G. per 100 ml., and there were 2·8 million erythrocytes per c.mm. The reticulocyte count was 16·5%. The leucocyte count was 20,400 per c.mm., of which 74% were neutrophils. A normal number of platelets were seen, and no malarial parasites were observed. The red cells showed diffuse polychromasia, aniso- and poikilocytosis, and some spherocytosis. Occasional normoblasts were present. No Heinz bodies were seen. The Coombs' test was negative. Osmotic fragility was normal, and the Donath-Landsteiner and Ham tests were negative. The serum bilirubin was 3·1 mg. per 100 ml. (total) and Schumm's test was positive. The screening test for erythrocyte glucose-6-phosphate dehydrogenase (G6PD)[4] showed markedly deficient enzyme activity.

Urine

Porphyrins were not found in the urine, but oxyhaemoglobin was present in addition to the marked albuminuria. On microscopic examination granular casts were found, together with 8 pus cells and 3 red cells per high-power field.

Treatment and Course

By the evening of 23 September the child appeared even more distressed, and air hunger was present. A second blood count showed similar findings to those previously noted. A transfusion of 1,000 ml. of blood was begun and continued slowly over the succeeding 24 hours. In addition, cortisone was given parenterally for the first 24 hours and then replaced by oral prednisone. The patient's condition rapidly improved. The output of urine remained good, and by 27 September it was normal in colour and free of albumin. On 28 September the haemoglobin concentration was 9·5 G. per 100 ml. The glutathione (GSH) stability test[5] was negative, the initial level of 34 mg. per 100 ml. of erythrocytes not falling on incubation with acetylphenylhydrazine. A temporarily negative GSH stability test is not unexpected during or immediately after a haemolytic episode in sensitive individuals.[6] When the test was repeated 3 months later the initial concentration of 34 mg. per 100 ml. fell to 4 mg. per 100 ml. on incubation, a markedly positive result.

On 2 October 1961 the child was discharged from hospital. He has since remained well, and a haemoglobin estimation on 24 January 1962 was normal for his age (12·9 G. per 100 ml.)

DISCUSSION

An acute haemolytic episode may be provoked in individuals with enzyme-deficient erythrocytes by exposure to a variety of extrinsic agents.[3] These include primaquine and pamaquine, phenacetin, water-soluble vitamin-K analogues, nitrofurantoin, certain sulphonamides, and broad beans. Haemolysis commences at varying intervals after exposure to these different agents, but in no case longer than 5 days. In the present case, therefore, the administration of the sulphonamide preparation 17 days before the child was seen can be excluded as a precipitating factor. The ingestion of the beans, however, occurred immediately before the onset of the illness, and this time relationship is characteristic of favism.[7] No history of exposure to any other known precipitating agent could be obtained. The absence of Heinz bodies in the erythrocytes during the acute haemolytic crisis is a further point in favour of the beans having been the precipitating factor. These structures, which are almost certainly derived from denatured haemoglobin,[8] are typical of the drug-induced haemolytic anaemias,[3] but are not seen in favism.[9,10]

Certain other members of the patient's family had eaten the beans without ill-effects, although they were subsequently found to be markedly enzyme-deficient.[11] The ingestion of fava beans by primaquine-sensitive individuals without provoking haemolysis has been well documented,[9,12] and represents a further point of difference between the haemolytic anaemia of favism and that produced by drugs, since primaquine and the other drugs in sufficient dosage will always cause haemolysis in G6PD-deficient subjects.

Sensitivity to fava beans may vary from time to time in the same individual. As in the present case, a G6PD-deficient subject may eat the beans without ill-effects on many different occasions, and then eventually haemolyse.[13-15] It has also been observed that individuals formerly sensitive to the beans may become resistant spontaneously.[7]

Consideration of these facts has led many workers to conclude that other factors in addition to the red-cell defect must be involved in the pathogenesis of favism, though the defective red cells seem to be essential. An allergic basis has long been postulated[7] and is still current.[3] The massive haemolysis which may follow within seconds after a sensitive subject inhales the pollen from flowering beans[7] seems difficult to explain on other than an allergic basis.

Recent work, however, has indicated that the additional factor distinguishing favism from primaquine haemolysis may be a protective plasma constituent, which is absent in those enzyme-deficient individuals who are sensitive to the beans. Thus, Roth and Frumin[12] were able to produce haemolysis *in vitro* by incubation of cells, from a patient

with favism, with an extract of the beans. This haemolysis was prevented by normal plasma, but not by the patient's own plasma. The patient's father had eaten the beans without ill-effect, although his erythrocytes were markedly enzyme-deficient, and it was of great interest that the father's plasma also prevented haemolysis in the *in vitro* system.

Further evidence is provided by the experiments of Vullo and Panizon.[16] These workers labelled erythrocytes from favism patients with ^{51}Cr and introduced them into the circulation of compatible normal recipients. When the recipient then ate fava beans there was usually no destruction of the labelled cells, although in a few experiments this did occur. When sensitive cells were introduced into other favism sufferers, however, consumption of the beans resulted in rapid disappearance of the tagged cells on every occasion. Greenberg and Wong[10] have confirmed these findings, and in addition showed that administration of primaquine, in contrast to ingestion of the beans, produced rapid disappearance of the enzyme-deficient cells from the circulation of a normal individual. These observations were compatible with the concept of a protective plasma factor, as suggested by the work of Roth and Frumin,[12] although other explanations (such as a different metabolic degradation of the beans in favism sufferers) are also possible.

It thus seems that the pathogenesis of haemolysis in cases of favism is complex. All cases so far investigated have manifested G6PD deficiency and GSH instability. However, since the beans do not cause haemolysis in all persons with these defective red cells, and since sensitivity to the beans varies in the same individual from time to time, other factors must clearly be operating.

SUMMARY

A case of favism in a White South African child is reported, and the pathogenesis of this disease is briefly discussed.

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