FAVISM IN LONDON

BY

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(RECEIVED FOR PUBLICATION MAY 7, 1953)

Favism is an acute haemolytic anaemia caused by an acquired allergy to a protein of the broad bean (*Vicia faba*). Reports of the disease date from before the fifth century B.C. and in a good review of the literature Luisada (1941) points out that favism used to have a very wide distribution in the Mediterranean basin. It now occurs particularly in the Sardinians, who seem to have retained the more typical characteristics of the original Mediterranean race. In Sardinia many thousands of cases occur every year in a population of one million. The disease is found also in Sicily, on the mainland in parts of Italy, Greece and Turkey, in the Greek islands, in Cyprus and in north Africa. A few sporadic cases have been described in France and in Spain, and since 1933 nine cases have been described in Americans of Italian descent. I have been unable to find any reported cases in Britain.

There are now about 25,000 Cypriots living in London, and this number will probably increase. Many more examples of favism may be discovered in the future if this diagnosis is considered in Mediterranean patients presenting with acute haemolytic anaemia.

As well as being racial the condition is often familial. There must be some constitutional peculiarity in the people who develop allergy to the fava bean, for it has been shown that the susceptible subjects are sensitive to fava beans from any country, whereas people who are not susceptible can consume broad beans grown in Sardinia or elsewhere without ill effect.

The disease may arise by inhalation of the bean flower pollen (usually in April and May) and in this case the symptoms begin within a few seconds, sometimes with startling suddenness. The commoner cause is eating broad beans. The incidence is known to be less when the beans are well cooked. The symptoms begin in from five to 48 hours after ingestion of the beans.

Favism principally affects small children and is commoner in males. The severity of the condition generally decreases as age advances. The mortality

rate in untreated cases is stated to be 8%, the deaths occurring almost entirely in children. On first eating the beans or inhaling the pollen the child suffers no ill effects, but a second contact with the antigen can produce an illness which is very variable in degree. At one end of the scale is a mild attack of diarrhoea and vomiting and at the other end a rapid haemolytic anaemia with jaundice and haemoglobinuria.

The following cases illustrate this difference in degree.

Case Reports

Case 1. A Cypriot boy born in London three and a half years ago, had lived nowhere else, and had no previous history of any acquired disease. His only congenital abnormality was thick, horny palmar and plantar skin (tylosis) which he inherited dominantly through his father.

On the day before he was admitted to The Hospital for Sick Children (September, 1952) the child was being cared for by a friend. This woman noticed that his urine was red during the day. After returning home in the evening he complained of severe pain in the left iliac fossa. His parents noted that he was pale and was breathing rapidly. During that night the abdominal pain continued and the urine remained red.

Next morning they obtained a prescription for haematuria, but throughout the second day the boy gradually became more anaemic and the skin became jaundiced. Micturition was painful and the urine had the appearance of port-wine. A small amount of brown, formed stool was passed. He vomited once. Finally he became very weak and was unable to stand. At this stage, about 30 hours after the onset of symptoms, he was admitted to hospital.

On examination there was jaundice and severe anaemia. The temperature was 99.8° F. and the heart rate was 160 per minute. An apical systolic murmur was heard and the cardiac impulse was diffuse. Respirations were deep, and sighing and yawning were frequent. The liver and spleen could not be felt, and no lymph nodes were enlarged. There was general slight tenderness over the abdomen, but no rigidity.

The blood haemoglobin level was 30% (4.35 g. per 100 ml.). The serum was deeply coloured, and spectroscopically showed methaemoglobin. The leucocyte count was unfortunately not done.

The urine was very dark and slightly turbid. Direct microscopy showed many granular casts and a large amount of granular debris, but no red cells were seen. After centrifuging the supernatant urine was a beautiful deep red.

The direct Coombs test was negative.

It appeared that possibly as much as 70% of this patient's red blood cells had been haemolyzed in 30 hours and there was no evidence that the haemolysis was likely to cease. Therefore it was decided to transfuse Rh-negative blood. All the available stored blood which was tested against the patient's plasma showed some agglutination. However, transfusion was started because the child was so gravely ill.

On the following day the blood haemoglobin was 77% (R.B.C., 2.95 m. per c.mm.). Clinically there was still haemoglobinuria, and spectroscopic examination of the urine showed the characteristic bands of methaemoglobin.

This case bore an obvious and close resemblance to cases of favism in children which I had seen successfully treated in Cyprus. For this reason a request was made for details of the patient's diet during the two days preceding the onset of the illness. The parents questioned the neighbour who had cared for the boy, and she recollected that the only unusual item had been a plateful of broad beans. This she had given to the boy for lunch on the day before the onset of the haemoglobinuria. The parents could not remember the child ever having eaten broad beans before this occasion, but they thought he might have done so without their knowledge.

The patient was the only child. There was no history of episodes of acute anaemia in either the mother's or the father's large families in Cyprus.

A total of 1,500 ml. of stored blood was transfused over a period of 48 hours, and on the third day after admission to hospital the blood haemoglobin was 99% (R.B.C., 5.72 m. per mm.). Reticulocytes were 5.2%.

The blood serum was fully investigated for the presence of specific haemolysins, with completely negative results. The cold agglutinin titre was 1 in 16.

The colour of the urine gradually changed from deep red through pink to pale yellow as the haemoglobinuria decreased during the three days following admission. On the fourth day there was less than 10 mg. % of protein in the urine and nothing abnormal in the spun deposit except for large numbers of epithelial cells. No bands of methaemoglobin were seen spectroscopically, Fouchet's test for bile was negative, and there was no excess of urobilinogen.

The patient remained well and returned home eight days after admission. The parents were advised never to allow him to eat broad beans again.

Case 2. This boy was a Cypriot. He was aged 9½ years when he was admitted to University College Hospital with jaundice and anaemia (August, 1951). His past history had been uneventful except that two years before he had been jaundiced for a week. This jaundice had been accompanied by abdominal pains and general malaise.

The illness for which he was admitted included no

pain and no diarrhoea. There was a history of having felt miserable for two days, with dizziness and vomiting. The parents stated that he had eaten a meal of broad beans a few hours before the onset of symptoms.

On admission the jaundice was moderate in degree and there was considerable anaemia. The spleen was not palpable. There was tenderness in the right iliac fossa.

The blood haemoglobin level was 43% (R.B.C., 2.32 m. per c.mm.). The leucocyte count was 9,200 per c.mm. with 12% monocytes. Reticulocytes were 8%. There were no target cells of Cooley's anaemia, and there was no sickling of cells. The fragility of the red cells was normal. Coombs test was negative. The blood bilirubin was 6.8 mg. per 100 ml. The urine contained no bilirubin and spectroscopically there was no haemoglobin.

A dark, formed stool was passed on the following day. The boy did not become ill enough to require a blood transfusion.

The jaundice gradually faded and the haemoglobin level gradually increased. The reticulocyte count rose for 12 days and then decreased again.

Skin tests using an extract of broad beans were inconclusive. About an ounce of cooked broad beans was prescribed for and eaten by this patient before he left hospital, but this was without effect on the haemoglobin level. He returned home four weeks after admission.

Discussion

The sensitization theory of aetiology is now on a secure foundation, largely owing to the work of Luisada (1941). The alternative theories of infection by a bean fungus and of poisoning by a bean toxin (the word 'favism' would be correct in a toxicological sense) have been thoroughly disproved.

Scratch tests with an extract from fresh broad bean are negative for about six weeks after favism (Pickering and Hurwitz, 1951). Similarly, giving beans to the patient after an attack produces no effect during this anergic period. Temporary unresponsiveness is well recognized in other forms of allergy. After six weeks the skin tests become positive in most cases.

A haemolytic crisis following the ingestion of fava beans in a young Mediterranean subject is probably always sufficient grounds for diagnosing favism in the absence of any other haemolytic disease. Even the youngest child could have been potentially sensitized. Luisada (1941) describes sensitization in infancy from the mother's milk after the mother had eaten fava beans.

Prognosis. In Luisada's experience the patient usually dies if the acute haemolytic process with haemoglobinuria lasts for more than three days. If a patient survives several attacks of favism then complete freedom from further attacks may develop spontaneously. Even when this immunity does not develop attacks in later life may become very mild.

The mild attacks may take the form of headache and diarrhoea, with an increased excretion of urobilin and stercobilin. A form may occur with pyrexia, vertigo and hypotension. Yet another manifestation is a headache closely resembling migraine.

In many cases there is a leucocytosis of between 10,000 and 40,000 per c.mm. for six or seven days. Sometimes a mononucleosis or an eosinophilia is found. Robinson (1941) regards the increase in eosinophils in the bone marrow as another argument in favour of an allergic aetiology. The serum potassium level may reach three times the normal during an attack of favism on account of the large and sudden destruction of red cells.

Pathology. Cadeddu (1950) described the necroses of eight fatal cases and concluded that the findings were those expected in any fatal haemolytic anaemia whatever the cause.

Treatment. The treatment of a severe case is the slow transfusion of the most compatible blood obtainable. Leone (1950) in Sardinia gave anti-histamine drugs to 21 children aged between 1 year and 12 years suffering from severe favism. The initial red blood cells counts ranged from 770,000 to 2.47 m. per c.mm., and these patients would otherwise probably all have required blood transfusion. Leone found, however, that only six of her 21 cases need transfusion. The symptoms in most cases were rapidly relieved after antihistaminics.

Diagnosis. Favism has in the past been mistaken for blackwater fever, Weil's disease, Lederer's anaemia, acholuric jaundice and infective hepatitis. Unless a history of recently having eaten broad beans is obtained by careful enquiry many cases may be missed.

It was pointed out by Jacobs (1950) that favism is probably a very suitable condition for the study of the acute haemolytic process. It may also be suitable for the study of the allergic mechanism in specific food allergy, and might bring to light unsuspected connexions between a disease and a food antigen. Coeliac disease is a much less dramatic condition than favism, yet it seems likely that sensitization by gluten plays a major part in its aetiology. It is tempting to wonder if any of the unexplained bouts of fever and vomiting in children will ever be found due to some specific food allergy.

Summary

Two cases of favism in Cypriot boys are described. The younger child had a severe attack with haemoglobinuria and required a large blood transfusion. The older child had a milder attack without haemoglobinuria but with jaundice.

The diagnosis is discussed, and attention is drawn to the importance of eliciting a history of the ingestion of broad beans within two days before the onset of the illness.

It is a pleasure to acknowledge my indebtedness to Dr. A. P. Norman under whose care Case 1 was admitted to The Hospital for Sick Children, and to Dr. Bernard Schlesinger for access to the notes of Case 2 in University College Hospital, and for his kind permission to publish this case.

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