17-ketogenic steroids, and 17-hydroxysteroids (determined by Dr. J. D. Nabarro) was within normal limits. The 24-hour urinary output of gonadotrophins was between 20 and 80 mouse units. Reports on vaginal smear (Dr. G. I. M. Swyer): "Mainly mucus and debris. The few cells are of basal type—that is, very hypo-oestrogenic."

Bone x-ray films showed delayed epiphyseal fusion. There was marked diffuse osteoporosis affecting both central and peripheral bones. This was most gross in the pelvic bones, spine, and long bones of the limbs, but the skull and small bones of the hands and feet also showed definite though less marked changes. There was no specific evidence of osteomalacia or hyperparathyroidism—that is, no signs of cyst formation or subperiosteal erosion and no Looser's zones. Report on biopsy from cortex of tibia (Dr. H. Sissons): "Osteoporosis. The cortex is thinned but is otherwise normal. No evidence of osteomalacia is present, and the histological appearance of the intracellular matrix of the bone is normal."

The patient's genetic sex was determined by Dr. Swyer by examination of the skin nuclei and those of the polymorphonuclear leucocytes, and proved to be male.

Course and Treatment.—In an attempt to exclude an endocrine deficiency as the cause of the tetany, methyltestosterone, 20 mg. daily for two periods of six days, and stilboestrol, 2 mg. daily for two periods of six days, were given. The calcium and phosphorus levels rose and fell slightly during this time, but the changes did not seem to be related to the treatment. The simultaneous calcium balance study also showed no significant changes, but was unfortunately very inaccurate owing to curious fluctuations in bowel function. Neither form of therapy nor the raising of the plasma calcium level to 9.7 mg./100 ml. with intravenous calcium gluconate succeeded in abolishing the Chvostek or Trousseau sign.

Discussion

There can be little doubt that this patient has gonadal agenesis in association with some of the other congenital defects of Turner's syndrome. Although such patients not infrequently have osteoporosis limited to the spine, generalized and marked osteoporosis such as this has not been mentioned, nor has the tetany. In the few cases in which serum calcium levels have been recorded they have been normal or slightly raised, as found by Albright *et al.* (1942).

The cause of this patient's tetany remains obscure. Although the serum calcium level was somewhat low, it was hardly low enough to produce tetany without the operation of some additional factor. Also the tetany persisted even when the calcium level was raised almost to normal. None of the other known causes of tetany was apparent in this case.

Although it seems reasonable to suppose that the co-existence of the rare condition of gonadal agenesis with the equally rare conditions of marked clinical tetany and generalized osteoporosis could hardly be a chance occurrence, no cause for the association could be shown.

Summary

A case of gonadal agenesis is described in which, in addition to many of the usual features, spontaneous tetany and generalized osteoporosis also occurred. No metabolic explanation for this association can be offered.

I am grateful to Dr. C. E. Dent, in whose department the balance studies were performed, for permission to publish this case and for assistance with the preparation of this paper.

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HAEMOLYTIC ANAEMIA IN SICKLE-CELL TRAIT

BY

A. A. CHAZAN, M.B., Ch.B.

Senior Registrar

AND

J. G. A. McSORLEY, M.B., M.R.C.P.Ed.

Consultant Haematologist

Group Laboratory, Whittington Hospital, London

It is generally accepted that cases of sickle-cell trait show no haematological abnormality other than sickling (Chernoff, 1955). Edington and Lehmann (1955), however, suggested that the trait itself may be "by no means harmless," and ascribed the cause of death in an African woman with the sickle-cell trait to a haemolytic crisis possibly precipitated by a superadded infection. Griffiths (1955) has referred to a sickle-cell crisis occurring in a case of sickle-cell trait during pregnancy. No details were given.

We give below an account of a patient with the sickle-cell trait in whom a haemolytic episode developed during a superadded infection.

Case Report

The patient, a 35-year-old Jamaican, was admitted to Whittington Hospital on February 17, 1955, complaining of general malaise and cough. Three days before admission he felt cold and hot in turn and had vague body pains. On the day before admission he had difficulty in breathing and developed a pain in the right side of his chest, with a cough which produced a small amount of white phlegm.

His previous history was difficult to obtain; all that could be elicited was that he had landed in England from Jamaica five months previously, that he had suffered from unspecified "fever" in his home country, and that he had been working with a fellow Jamaican who had a cough which produced a bloodstained sputum for which he was being treated as an out-patient at another hospital.

Physical examination showed the patient to be a well-nourished negro with a temperature of 105° F. (40.6° C.), pulse 100, and respiration rate 24. Examination of the chest suggested consolidation at the bases of both lungs, with scattered rales and crepitations over the lung areas. Abdominal examination revealed a barely palpable spleen. Examination of the other systems was negative.

Special Investigations.—The initial blood count was: Hb, 60% (8.9 g.); red cells, 3,110,000 per c.mm.; P.C.V., 28%; M.C.V., 93 cubic microns; M.C.H.C., 32%; reticulocytes, 4%; white cells, 3,100 per c.mm. (Standard techniques as in Wintrobe, 1951.) Examination of the blood film showed marked anisocytosis and increased polychromasia of the red cells. Some target cells, "raspberry"-shaped and spiculated forms, together with one normoblast, were seen. A sickling test with 2% sodium bisulphite was positive in 10 minutes. The E.S.R. (Westergren) was 9 mm. in one hour. The serum bilirubin was 1.4 mg. per 100 ml. and the urine contained a great excess of urobilinogen. The direct Coombs test, cold agglutinin test, and specific haemolysis tests were negative. Complement-fixation tests with the antigens of influenza A and B, psittacosis, and Q fever were persistently negative, and the M.G. streptococcus titre was negative at 1 in 4. The Wassermann reaction and Kahn test were negative. Paper electrophoresis of a haemoglobin solution (barbitone buffer pH 8.6, 0.06 M solution) revealed a pattern of haemoglobin A plus haemoglobin S, the latter pigment comprising one-quarter to one-third of the total haemoglobin mass. Foetal haemoglobin tested for by the alkali denaturation technique (Singer *et al.*, 1951) was 0.12% (within normal limits). No other abnormal haemoglobins could be demonstrated. Sternal marrow showed slight hypoplasia with active normoblastic erythropoiesis. The myeloid series and

megakaryocytes were normal and there was a small increase in plasma and reticulum cells. No abnormal cells were seen. Culture of sputum yielded a growth of *Staph. aureus* sensitive to penicillin, chlortetracycline, chloramphenicol, and streptomycin. Blood culture yielded a coagulase-negative staphylococcus. Acid-fast bacilli were not detected in sputum, gastric washings, laryngeal swabs, or faeces. C.S.F. was normal and the Widal reaction was negative.

Despite treatment with "estomycin" there was no improvement in the clinical condition, but within 48 hours of starting chloramphenicol the patient felt better and his temperature returned to normal. The temperature stayed normal for only 48 hours on chloramphenicol alone and estomycin was restarted and chloramphenicol stopped. Two pints (1,140 ml.) of blood was transfused on February 26 as the haemoglobin had fallen to 52% (7.7 g.). The serum bilirubin indirect reaction was 1 mg. per 100 ml. on February 19 and increased amounts of urobilinogen continued to be excreted in the urine for a period of three weeks. The temperature continued to swing wildly, and on February 27 signs of an effusion developed over the right lower lobe. Paracentesis was performed and the fluid showed small numbers of leucocytes—almost all lymphocytes—with large numbers of red cells. No bacteria were seen in the films stained by the Ziehl-Neelsen method. Routine and Löwenstein-Jensen cultures were sterile. The patient's general condition improved slightly, but the chest signs remained unchanged. On March 16 signs of bilateral iridocyclitis developed.

Further Investigations.—X-ray examination of the chest on March 29 showed fine diffuse miliary foci throughout both lungs, and the appearances were reported as being suggestive of acute miliary tuberculosis. The E.S.R. was 30 mm. in one hour and the Mantoux test was positive at 1 in 1,000. On April 1 the total serum proteins were 6.4 g. per 100 ml. with an albumin:globulin ratio of 0.7:1. Paper electrophoresis of the serum proteins showed a marked increase in globulin. The serum calcium was 11 g./100 ml. and Sulkowitch's test on the urine showed moderate amounts of calcium. Liver biopsy was carried out on April 7, and this was reported on by Dr. C. C. Bryson as showing slight focal chronic inflammatory reaction, fine pericellular fibrosis, and one minute "miliary" epithelioid focus.

On cortisone, isoniazid, and streptomycin the patient's lung condition had practically cleared after one month, but the iridocyclitis was still active. The E.S.R. was now 6 mm. in one hour. The mean corpuscular fragility test (Parpart *et al.*, 1947), which was carried out on May 2 (65 days after transfusion), was 0.375% NaCl equivalent (normal range 0.400 to 0.438% NaCl). On June 13 the peripheral blood picture was as follows: Hb, 100% (14.8 g.); white cells, 6,700 per c.mm. (neutrophil polymorphs 82%, eosinophil polymorphs 1%, lymphocytes 15%, monocytes 2%); platelets, 213,000 per c.mm.; film: normal. No haematological abnormality other than sickling could now be detected.

Discussion

In thalassaemia minor, infection, sometimes of an obscure nature, has been reported to be associated with decreased activity of the bone marrow and a drop in the haemoglobin level steeper than usual, while during periods of freedom from infection the drop in haemoglobin level is more gradual (Matoth *et al.*, 1955).

Weiss (1953) concluded that the sickle-cell trait was associated with a significantly increased incidence of the acute exudative form of pulmonary tuberculosis in American negroes, and stated that "the sickle-cell trait, ordinarily of no particular importance, may assume clinical significance in relation to other disease states." However, Vandepitte *et al.* (1953) could not confirm this association in Africans in the Belgian Congo.

Edington and Lehmann (1955) question the accepted view that the sickle-cell trait is a benign congenital anomaly and refer to the finding of haematuria due to pathological

lesions in the kidneys in such cases. In their case of sickle-cell trait death was due to haemolytic crisis and septicaemia associated with the expulsion of a hydatidiform mole in a 23-year-old woman. Post-mortem histology revealed the characteristic findings of a sickle-cell crisis. They considered that "the terminal crisis was probably initiated by the septicaemic condition and was directly responsible for death."

In the case referred to by Griffiths (1955) a sickle-cell crisis occurred in a case of sickle-cell trait during pregnancy. In a personal communication Griffiths confirms that "gross intravascular haemolysis" was present and that other possible causes of haemolysis were not demonstrable.

In our case a haemolytic anaemia developed in a patient with sickle-cell trait during an infection. This anaemia was probably precipitated by the intercurrent disease—sarcoidosis or (atypical) tuberculosis. It is significant, however, that changes in red-cell morphology in the first blood film suggested the need for a sickling test. It is appreciated that both sarcoidosis and miliary tuberculosis *per se* can (rarely) be associated with a haemolytic anaemia. Nevertheless in view of the findings of Edington and Lehmann (1955) and Griffiths (1955) it seems reasonable to suggest that the red cells in cases of sickle-cell trait may be more susceptible to haemolytic mechanisms during intercurrent infections or pregnancy. If this assumption is correct other similar cases should soon be reported.

It is, of course, possible that this man was a heterozygote for the thalassaemia gene and that he was symptomless until under increased stress sickle-cell thalassaemia disease became manifest. We consider this possibility as virtually excluded—though of course only a family study could give a decisive answer—for the following reasons: foetal haemoglobin was absent, the adult haemoglobin was present in a considerably greater proportion than the sickle-cell haemoglobin, and the fragility was only slightly decreased, being of the same order as seen by us in two other cases of sickle-cell trait. There are few references to accurate osmotic fragility tests in cases of sickle-cell trait. Chernoff (1955) states that the osmotic fragility is normal in sickle-cell trait and "somewhat decreased" in sickle-cell anaemia. We have since found a low normal fragility (0.400%) and a decreased fragility (0.382% NaCl) respectively in two further cases of asymptomatic sickle-cell trait. These cases had no anaemia and were discovered only on routine sickling tests. Electrophoretic and foetal haemoglobin studies showed them to be apparently simple S-trait cases. It appears that more observations on the osmotic fragility test in sickle-cell trait cases should be made. In any case, it would appear that we can no longer accept the view that the sickle-cell trait is a harmless anomaly unassociated with anaemia or morphological changes in the red blood cells under all conditions.

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The National Association for Mental Health has established a public information committee under the chairmanship of LORD FEVERSHAM. Its objects are to acquaint the public with the possibility of preventive measures against mental illness, the need for education in principles of mental hygiene, and "the great need to stimulate and support programmes of research in the mental health field." The committee includes psychiatrists, educationalists, and others.