FANCONI PANCYTOPENIA SYNDROME: REPORT OF A CASE IN GHANA

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Summary

A fatal case of Fanconi Pancytopenia Syndrome in a young Ghanaian girl is presented. At her initial presentation growth failure was her chief complaint though other physical stigmata were present from birth. Pancytopenia subsequently developed. The diagnosis warrants consideration in all children presenting with growth failure, pancytopenia or skeletal abnormalities particularly of the hands and forearm.

Key Words: Pancytopenia growth failure

INTRODUCTION

The Fanconi pancytopenia syndrome was first described in three brothers in 1927.[1] Since then over 160 cases have been reported.[2] The syndrome is characterized by chronic pancytopenia with or without several definite congenital abnormalities (predominantly limb defects) in which there is evidence of a constitutional origin. There has been no success in defining the underlying mechanisms for the bone marrow failure and the associated anomalies. A single early defect in the embryo may be responsible for all the latter manifestations as evidence by the fact that the organ systems frequently involved undergo embryonic differentiation at a similar time, i.e. twenty-fifth to thirty-fourth day of foetal life.[3] Most patients are born relatively small and tend to have recurrent respiratory infections. Bleeding, pallor and systemic infections secondary to marrow failure appear between five and ten years. Survival seldom lasted more than two years following the diagnosis of marrow failure until the recent introduction of a combination therapy of testosterone and hydrocortisone analogues.[4] A single case of this syndrome was recently seen in a Ghanaian girl, the first to be reported in Ghana. This case is being reported because of the need to consider the syndrome among the differential diagnoses in children presenting with growth failure or marrow failure especially when associated with congenital abnormalities.

CASE REPORT

MD, a Ghanaian girl, was first seen at the children's out patient department of the Korle Bu Teaching Hospital, Accra on April 5, 1979 aged 3 years with the sole complaint of being small for her age. She had weighed 2.60kg at birth to a 38 year old mother after an apparently uncomplicated term pregnancy. She was the third of four siblings and the smallest at birth. Both parents and the three siblings were healthy and had no congenital abnormalities. She was described as an active healthy girl with normal developmental milestones, including speech and psychosocial development. Her initial examination revealed an alert smallish child with a weight of 10.0kg, height of 85cm and head circumference

of 46cm (all measurements being below the third percentile for age). Her facies was rather odd, with small eyes, mouth and nose. Both her ear lobes were malformed with tapering at the top. She had a rather hyperpigmented skin, especially when compared to that of both parents and the other sliblings who were light-skinned. She had three cafe-au-lait spots (1cm in diameter) on the trunk. Her thumbs were malformed; hypoplastic and abnormally placed with limited active abduction, adduction and flexion. No abnormality was detected in the clinical examination of the cardio-respiratory, renal and central nervous systems.

Her peripheral blood showed a haemoglobin of 10.6gm/dl and PCV of 37%. The smear showed microcytosis and mild hypochromia of red blood cells; the white cells were 6 400/ mm^3 (lymphocytes 60%, neutrophils 33%, monocytes 6% and eosinophils 1%). Leucocyte morphology was normal and platelets were assessed as adequate in the film. Her blood group was O Rh-Positive and the sickling test was negative. X'ray of the chest and long bones of the forearm and wrist were normal. In the hands there was hypoplasia of both first metacarpals, all three phalanges of the thumbs and the middle and terminal phalanges of both little fingers. Her bone age was assessed at 1.5 years.

She was lost to follow-up until April 14, 1982 when she presented at age 6 years with a three week history of persistent fever and vomiting. Her physical examination showed no focus of infection or evidence of intestinal obstruction. Her physical measurements then were weight 13.0kg, height 102cm, head circumference 47cm (all measurements persisting below the third percentile for age). The abnormal features noted three years earlier were still present but her skin pigmentation was darker than before. She had marked pallor of the mucous membranes unaccompanied by jaundice, lymphadenopathy or evidence of bleeding. The haemoglobin was 2.1gm/dl, PCV 0.7%, RBC count 0.6 million/mm^3. The smear showed marked pancytopenia without primitive cells; the white cells numbered 1 600/mm^3, of which 87% were lymphocytes, 10% neutrophils and 3% monocytes. Platelets were scanty (the platelet count being 46 000/mm^3). Her sickling test was negative and haemoglobin electrophoresis AA. Her serum-iron was 100 ug/dl. Her blood film was negative for malaria and other parasites. Bone marrow aspirate was of normal consistency. Marrow smears showed markedly depressed erythropoiesis and granulopoiesis with an M:E ratio of 1.2:1. Lymphocytes formed 77% of all nucleated cells; plasma cells 2%; while megakaryocytes were significantly absent. The smear was consistent with the dianosis of pancytopenia secondary to marrow failure. Radiographs of the chest and long bones showed no new abnormality. Cultures of blood, urine and cerebro-spinal fluid were sterile, the Mantoux test negative and urinalysis normal. She was tranfused with fresh whole blood (30ml/kg) on two occasions, and treated with chloroquine and parenteral antibiotics with resolution of the fever and vomiting within four days. Following her recovery her renal system was investigated for possible involvement. Results included normal urinalysis; serum creatinine of 86.5 µmol/l and cretinine clearance of 72ml/min/1.73m^2.

Over the next few months she needed repeated transfusion of fresh whole blood initially fortnightly but later at reduced intervals. Two months after the diagnosis of marrow failure she started

bleeding from her gums and developed recurrent superficial skin infections. On December 4, 1982 she was re-admitted with a week's history of persistent pyrexia above 38 °C. Her physical examination was negative except for severe pallor, few bruises on the legs, a perianal abscess and an open boil on the left labium major. Her haemoglobin was 4.4gm/dl, WBC 1 300/mm^3, platelets 28 000/mm^3, and ESR 68mm (Westegren) in the first hour. Urine examination showed moderate microscopic haematuria and proteinuria 3+ but culture was sterile. Blood cultures repeatedly grew klebsiella species sensitive to gentamicin. A swab from the labial boil yielded staphylococcus aureus sensitive to cloxacillin. In spite of appropriate antibiotic treatment and blood transfusions her general condition deteriorated steadily until she died on January 5, 1983. Autopsy revealed further internal abnormalities: a hypoplastic bi-lobed spleen and left hypoplastic kidney.

Discussion

Though the disease is often familial, inherited as a recessive trait,[5] it may also occur sporadically possibly due to a gene mutation.[6] Great variation exists in the presentation of the syndrome in reported cases in the literature. Table 1 lists the congenital anomalies more commonly associated with the syndrome and their relative frequencies[2]. Marrow failure, is a prerequisite for the diagnosis of the syndrome. Although the more obvious defects are usually noticeable soon after birth the effects of marrow failure do not usually manifest until after 6 years of age. Rarely, it may manifest earlier or be delayed till adulthood.[7,8] When our patient was first seen at age 3 years she had most of the features of the syndrome but with a normal peripheral blood picture. The possibility of the syndrome was considered but her default from follow-up prevented us from determining when

Table I

Reported Features of Fanconi Pancytopenia Syndrome and their Relative Frequencies

1. Pancytopenia (marrow failure at mean age of onset of 6 - 8 years)	—	100%
2. Defects of thumb (and occasionally radius)	—	78%
3. Small stature with or without prenatal onset	—	56%
4. Relatively small cranium	—	43%
5. Small penis and testes and/or cryptorchidism in males	—	44%
6. Pigmentation of skin	—	Frequent
7. Splenic hypoplasia at autopsy	—	,,
8. Mental deficiency	—	Occasionally
9. Renal Anomaly	—	,,
10. Anomaly of auricles and deafness	—	,,
11. Cardiac defects	—	,,
12. Eye defects	—	,,

Table II

Comparison of Congenital Abnormalities

Reported Cases	Patient M.D.
1. Pancytopenia (mean onset age 6-8 years)	Pancytopenia absent at 3 years. but present at 6 years age.
2. Defect of thumbs	Present
3. Small stature	"
4. Small cranium	"
5. Hyperpigmentation of skin	"
6. Splenic hypoplasia at autopsy	"
7. Mental retardation	Absent
8. Renal Anomaly at autopsy	Present
9. Anomaly of auricles	"
10. Cardiac defects	Absent
11. Eye defects	"

marrow failure actually started. When seen at age 6 years she already had well established pancytopenia, dying only nine months after the documentation of marrow failure.

Our patient's main congenital abnormalities are contrasted with the reported anomalies of the syndrome in Table II. It is remarkable that the main initial complaint of the child was growth failure (in both weight gain and linear growth), a presentation present in only 56% of reported cases. Intrauterine growth retardation, chromosomal defects and various syndromes are associated with growth failure in early life. A careful physical examination is usually necessary for the characteristic clues leading to the diagnosis of chromosomal aberrations or syndromes. Fanconi pancytopenia syndrome needs consideration in the differential diagnosis of all cases of growth failure and congenital abnormalities, with or without marrow failure. Close relatives of patients suspicious for the syndrome also need investigation because of the abnormally high incidence of leukemia among such relative [9]. We were unfortunetely unable to assess the apparently beneficial effects of testosterone and hydrocortisone analogues on the failing marrow in our patient.

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