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Fanconi Anaemia: A Case Report in Nigeria

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Abstract: *Fanconi Anaemia (FA) is an inherited autosomal recessive disease which is characterized by multiple physical abnormalities (especially the fore arm and thumb), bone marrow failure, and a higher than normal risk of cancer.*
A 3[1/2]year old male child presented with a congenital absence of the thumb with associated flexure deformity of the middle and ring finger. On examination he was neither pale nor icteric. The right forearm was short and bowed. There was no skin pigmentation echocardiography revealed small subaortic ventricular septal defect. Radiograph of the right upper limb showed shortening and bowing of the ulna with absence of radius and thumb. There was medial curving of the phalanx of the middle and ring finger
Keywords: *Fanconi Anaemia, absent radius and thumb, ventricular septal defect.*

I. Introduction

Fanconi Anaemia (FA) is a congenital anomaly most frequently associated with skeletal defect involving the thumb and the radius, skin pigmentation, congenital heart defect especially ventricular septal defects (VSD) and malformation of the genitourinary tract [(1,2,3)]. Other anomalies that may associate with it include microcephalus, hydrocephalus, small or abnormally shaped eyes, malformed ribs, spine and hip [(1, 2, 3, 4, 5)].

Guido Fanconi (GF) in 1927 was the first Scientist to report three brothers with macrocytosis, pancytopenia, and physical abnormalities and subsequent cases were diagnosed because of combination of aplastic anemia [(6)]. As such this disease was named after GF [(6, 7)].

FA accounts for 25% of Aplastic Anaemia seen at referral centers and approximately 25% of FA patients are not presented with major birth defects [(6)].Reports show that the frequency of FA is more in Ashkenazi Jews in Israel [8], and Afrikaners in South Africa than in USA [(9)], in sub-Sahara blacks and Spanish gypsies than in other populations of the world [(10, 11)].

Parents might not know that they are carriers because FA is caused by a recessive gene [(4, 6)]. FA is a rare genetic disease due to defect in a cluster of protein required for DAN repair [(12)]. It is therefore necessary to look out for anaemia, immune problems, digestive disorders and leukaemia in the family history [(4, 14)].

The visible symptoms in FA individuals may present at birth or may start manifesting between the ages of 2 and 15 years [(4)]. Anaemia usually manifest between the age of 17 months to 22 years [(14)], and the patient usually present with tiredness, weakness, dizziness, increased need of sleep, headache, pale skin colour, irritability, cardiac symptoms and difficulty in breathing [(1)]. The prognosis is usually fatal within 5 years after the onset of the anaemia [(14)]. Minor injury may lead to excessive bruising and may result in spontaneous bleeding [(14)] from the mucous membrane especially those of the nose and gums [(1)].

FA patients develop bone marrow failure which will affect both the red blood cells and the white blood cells [(3, 15)]. They also develop cancer like acute myeloid leukaemia (AML) and myelodys plastic syndrome between the age of 5 to 15 years [(1, 15)]. When they reach adulthood they have a high risk of getting wide range of cancer like mouth and bone cancer [(3)] and tumor of the liver [(16)].

About 75% of the cases have skin pigmentation which is usually seen in the neck, axilla, trunk and groin [(14)].FA individuals usually have developmental problems of low birth weight, smaller than normal head size and height, delay growth, intellectual disability and poor appetite [(4)]. However, it is strongly suggestive of FA when there is hypoplastic or absent of the radius with hypoplastic or absent of the thumb [(5,14)].

FA individuals have a median life span of 29 years but some may live up to 50 years.Stating the clinical features of FA, one can easily rule it out by screening, investigating and following up cases that were formerly ignored or overlooked.

II. Case Report

A 3[1/2]year old male child presented with congenital absence of the right thumb with associated flexure deformity of the right middle and ring fingers was examined.

On examination, he was neither pale nor icteric. The heart rate was $100/^{Min}$; blood pressure was $120/85^{mmhg}$ with normal purse. The palms were rather smooth with faint palmer and finger creases. The right thumb was absent and the right little and ring fingers were curved medially. The right forearm was short and bowed. There was no skin pigmentation.

The chest radiograph showed normal heart size, situs solitus and laevocardia. Echocardiography revealed small sub aortic ventricular septal defect. Radiograph of the right upper limb showed shorting and bowing of the ulna with absence of the radius and first finger (thumb), figure 1. There was medial curving of the phalanges of the middle and ring fingers. The middle phalanx of the 5^{th} finger was hypoplastic. Only two carpal bones were noted which is for a child of 2 years indicating retardation of the bone maturation. There was no other skeletal abnormality detected. The full blood count was normal.

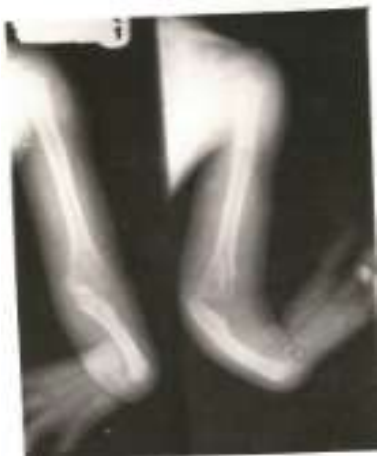

Figure 1: Radiograph of the right upper limb showing shortening and bowing of the ulna with absence of radius and thumb and only two carpel bones.

III. Discussion

Skeletal characteristic deformities in diagnosing FA are hypoplastic or absent of the radius with hypoplastic or absent of the thumb [5, 17].In this case report, there was absent radius and thumb. Occasionally the ulna may be short or bowed; the middle phalanx of the 5^{th} finger may be hypoplastic and the carpal bones absent or hypoplastic [17].There was shortening and bowing of ulna with hypoplastic of the carpal bones and middle phalanx of the 5^{th} finger in this case report. In severe cases of FA, both the right and the left radius and thumb (bilateral) may be affected [5].

It is necessary to differentiate FA from "thrombocytopenia with absent radius" (TAR) syndrome. In FA, the absence of radius is always associated with hypoplastic or absent of the thumb but in "thrombocytopenia with absent radius" (TAR) syndrome, in spite of the absent radius, all the fingers and both thumbs are always present [5, 18].Symptoms of FA in adults who are diagnosed later in life are delayed onset of period, fertility issues, frequent miscarriages, smaller than normal genital and early menopause in women. Men could have smaller than normal genitals and fertility issues [3].

All these deformities and abnormalities in FA individuals is due to inability of the chromosomes within their cells to repair deoxyribonucleic acid (DNA) damage or the repair of the damaged DNA may be very slow [1].

When the process of DNA replication is blocked due to DNA damage, FA pathway will be activated. FA pathway response to a type of DNA damage known as inter-strand cross links abbreviated as CLS .When two DNA building blocks (nucleotides) on opposite strands of DNA attach abnormally, preventing DNA replication, ICLS will occur [19].

FA is associated with 8 proteins (i) Fanconi Anaemia Complementation Group A. (FANCA). (ii) Fanconi Anaemia Complementation Group B (FANCB). (iii) Fanconi Anaemia Complementation Group C (FANCC), (iv) Fanconi Anaemia Complementation Group E (FANCE), (v) Fanconi Anaemia Complementation Group F (FANCF), (vi) Fanconi Anaemia Complementation Group G (FANCG), (vii) Fanconi Anaemia Complementation Group L (FANCL) and (viii) Fanconi Anaemia Complementation Group M (FANCM), which are grouped together to form a complex known as Fanconi Anaenia core complex (FA core complex), [19]. The FA core complex will stop functioning if there are mutations in any of the genes associated with it [19]. This will lead to ineffective repair of DNA damage thereby resulting in the building up of ICLS. The ICLS stall DNA replication will lead to either uncontrolled cell growth because of lack of DNA repair processes or leads to abnormal cell death because new DNA molecules could not be made [19].

Fast dividing cell are affected most, like cell of the developing fetus and bone marrow cell [19].The physical characteristic abnormalities seen in FA and decrease in blood cells are due to the death of these cell. Acute myeloid leukaemia or other cancers develop when there is uncontrolled cell growth and errors in DNA are built up [19].

The following chemical: formaldehyde, tobacco smoke, herbicides, paint thinner and gasoline increase the risk of the breakage of chromosome in individuals with FA [1].These chemicals should be avoided in any family where there is a trace of FA.

Various types of investigations can be carried out for genetic diagnosis of FA. One is chromosome breakage test where the skin cell or blood of the individual is mixed with a chemical and the analysis of the cell chromosomes examined under the microscope. If there is distinctive breakage of the chromosomes it means that the individual has FA [4].

The second test is flow cytometry_(cytometric flow analysis), where the individual skin cell is combined with the chemical. If the cell reacts with the chemical it means the individual is likely to have FA [4].

Another test is mutation screening_whereby a skin cell sample of the individual is used to search for any defects in the fifteen known genes associated with FA [4].

IV. Conclusion

With the knowledge of the clinical feature of FA stated above, more awareness of its existence in our environment could be created by screening and following up suspected individuals and families who could be carries.

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