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Case Report

Congenital anomalies with pancytopenia: the vital role of physical examination in the diagnosis

Harshith Siddappaswamy[1], Arumugam R.[2], Sudeep Gaddam[3]*, Dhaarani Jayaraman[3], Niranjani Maniurmila[2], Julius Xavier Scott[3]

[1]Sri. Ramachandra Institute of Higher Education and Research, Chennai, Tamil Nadu, India
[2]Department of Pediatrics, Sri. Ramachandra Institute of Higher Education and Research, Chennai, Tamil Nadu, India
[3]Department of Pediatric Hematology and Oncology, Sri. Ramachandra Institute of Higher Education and Research, Chennai, Tamil Nadu, India

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***Correspondence:**
Dr. Sudeep Gaddam,
E-mail: sudeepgaddam2@gmail.com

ABSTRACT

Fanconi anemia is a rare autosomal recessive inherited disorder impacting the interstrand cross-link DNA repair pathway, leading to systemic and hematologic manifestations as well as an increased susceptibility to malignancies. Diagnosing FA involves a comprehensive approach, combining physical examinations, clinical investigations, and genetic analysis. In this report, we present the case of an 11-year-old girl with FA who exhibited notable physical characteristics such as short stature, microcephaly, hyperpigmentation, and bifid thumbs in both hands, coupled with the hematologic complication of pancytopenia. The challenge often lies in the delay of identifying physical findings, given the variable and subtle nature of these anomalies. Although genetic analysis confirms the diagnosis, the child had regular visits to pediatrician elsewhere for immunization, congenital anomalies, hyperpigmentation, short stature and received blood transfusions, this delay in recognizing physical manifestations underscores the need for heightened awareness among healthcare professionals to ensure an early diagnosis.

Keywords: Fanconi anemia, Physical examination, Pancytopenia, Bifid thumb, Hyperpigmentation

INTRODUCTION

Fanconi anemia (FA) is a rare genetic disorder impacting the interstrand cross-link DNA repair pathway, characterized by variable congenital anomalies, progressive bone marrow failure, and high predisposition to acute leukemia and other malignancies particularly in the head and neck as well as the urogenital region.[1,2] Diagnosing FA involves a comprehensive approach, combining physical examinations, clinical investigations, and genetic analysis.[3,4] As pediatricians are the first contact for children with any issue and every visit should be used as an opportunity to examine in detail to suspect related disorders. The challenge often lies in the delay of identifying physical findings by pediatricians, given the variable and subtle nature of these anomalies. Early diagnosis helps to improve the prognosis and quality of life of the patient. In our case report we describe missed opportunities for early diagnosis of FA in a 11-year-old girl who had regular checkups with the pediatrician and received blood transfusions despite the presence of congenital anomalies, physical findings with pancytopenia.

CASE REPORT

A 11-year-old girl presented for evaluation of progressive pallor. She was the third born child of a consanguineously married couple. There was no history of bleeding manifestations or recurrent infections.

Although she had congenital anomalies, microcephaly and hyperpigmentation, no evaluation was done prior to this presentation. Her two older siblings were normal. She has required packed red cell transfusion thrice prior and was not evaluated for FA. Physical examination of the patient revealed pallor, microcephaly, short stature, low set ears, triangular facies with hyperpigmentation (Figure 1A) and bifid thumb in both hands (Figure 1B).

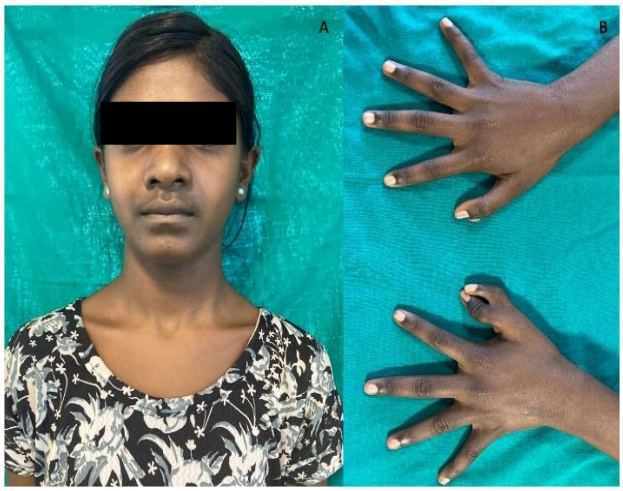

Figure 1: A) Microcephaly, and triangular facies with hyperpigmentation, B) Bifid thumb in both hands.

On examination, her height was less than third percentile and head circumference was less than -3SD as per IAP and WHO growth chart respectively. Her complete blood cell count revealed $2.5x10^9$/l WBCs, platelets of $31x10^9$/l, and haemoglobin 74 g/l with macrocytosis. Bone marrow examination showed hypocellular marrow with marked reduction in trilineage hematopoiesis. Her ultrasonogram of abdomen and echocardiography were normal. She was evaluated elsewhere with multiple endocrine evaluations for growth failure and parameters were normal. With classical phenotypic features and anemia requiring transfusions, Fanconi anemia was considered. Peripheral blood chromosomal breakage test with mitomycin C (MMC) revealed increased chromosomal breaks compared to control with triradials and tetraradials, suggestive of Fanconi anemia. Her bone marrow aspirate karyotyping showed complex karyotyping. She underwent haplo-identical bone marrow transplant with her brother as the donor. The patient is doing well one year post bone marrow transplant.

DISCUSSION

Despite the numerous advancements in modern medical technologies and the increasing array of laboratory investigations, the core foundations of a physician's daily practice continue to hinge upon the invaluable tools of history-taking and physical examination. In navigating the current era, where patient confidence in healthcare providers is on the decline and COVID-19 has brought in hybrid virtual models for teaching where importance of good bedside clinical skills is also important.[5] FA patients present with variable congenital abnormalities, progressive bone marrow failure which may manifest as pancytopenia and high predisposition to developing malignancies later in life. 75% of all FA patients present with physical anomalies which may include short stature, low birth weight and microcephaly.[6] The identification of these findings during the physical examination in the regular pediatric consultations could have enhanced the timeliness of diagnosis, thereby potentially influencing the overall quality of care. Cutaneous findings include generalized hyperpigmentation, café au lait macules and hypopigmentation. Skeletal anomalies of the upper limb are more common than those of the lower limb with thumb, radii, and hand malformations having the highest incidence rate. Thumb anomalies include absent, long, proximally placed, hypoplastic, bifid, duplicated and triphalangeal. Notable facial features include triangular face shape, micrognathia, and mid face hypoplasia.[7] Endocrinological disorders include growth hormone deficiency, hypothyroidism and glucose-insulin abnormalities.[8] Kidney abnormalities including horseshoe, ectopic, pelvic, hypoplastic, dysplastic, or absent kidney is seen in 20% of FA patients.[7] Reduced fertility is noted in both males and females with males presenting micropenis, cryptorchidism, hypospadias, oligospermia and azoospermia. Females present relatively smaller ovaries, malposition of uterus, and bicornuate uterus.[9,10]

FA patients have a 500-fold increased risk of developing acute myelogenous leukemia during their life span.[11] 28% of patients developed solid tumors by age 40 commonly occurring in the anogenital region, and the head and neck.[12] They also have a higher risk of developing cancer associated with human papillomavirus.[13] Due to the affected DNA repair pathway, FA patients are extremely sensitive to chemotherapy and radiotherapy. The early diagnosis of FA is important to avoid poor hematologic outcome and to screen for any future malignancies and complications. In our case, a classic presentation including bifid thumb, hyperpigmentation, short stature, microcephaly, and anemia lead to the diagnosis of FA. This is confirmed by peripheral blood chromosomal breakage test which showed a higher incidence of chromosomal breakage compared to control. By performing bone marrow transplant we can treat the hematologic condition. Following diagnosis, regular multidisciplinary follow up is required to improve life expectancy and general quality of life. Hyperpigmentation is also an important physical examination finding in megaloblastic anemia which is often overlooked.[14] Triphalangeal thumb is seen in a number of conditions including but not limited to AASE syndrome, Holt-Oram Syndrome, PRCA (pure red cell aplasia), and Diamond-Blackfan anemia.[15] The clinical examination findings of hyperpigmentation and thumb anomalies is an important association to form with FA which can help in the early diagnosis of the disease.

CONCLUSION

Early diagnosis of FA is facilitated by a thorough head to toe physical examination. Physical examination findings such as hyperpigmentation, upper limb anomalies, microcephaly, etc. to name a few combined with hematological findings such as pancytopenia help a clinician form an association with FA. This case underscores the delicate balance between embracing technological progress and ensuring that traditional clinical skills remain at the forefront of medical practice, particularly in cases where early recognition can significantly impact patient outcomes.

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