FEATURE

A Review of Fanconi Anemia for the Practicing Pediatrician

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Abstract

Early recognition of a patient who might have Fancomi anemia by the general pediatrician and referral to a tertiary care center with a dedicated cancer risk program is critical for early diagnosis. Genetic testing and close multidisciplinary surveillance is required for patients with this syndrome and their families because of its multisystem involvement and propensity for early-onset bone marrow failure and leukemic transformation. This article reviews the clinical symptoms and signs, radiologic findings, and screening guidelines of FA for the general pediatrician. **[*Pediatr Ann*. 2015;44(10):444-445,448,450,452.]**

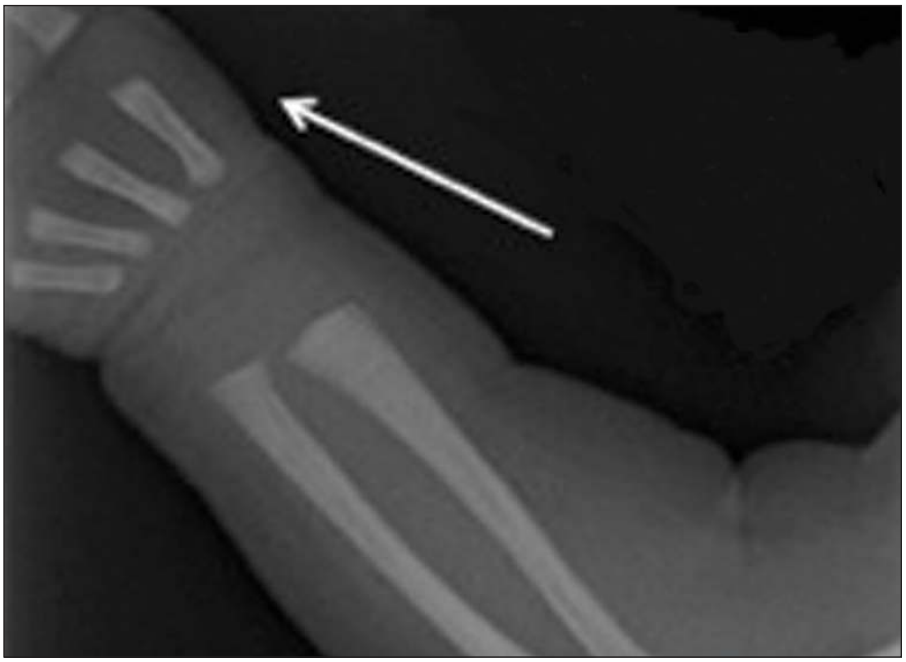

Figure 1. Radiograph of right upper extremity revealed an absent right thumb.

An infant born at 35 weeks gestation presented to the neonatology intensive care unit with an absent right thumb with no radial anomaly, café-au-lait spots, and early systolic grade III/VI heart murmur upon evaluation of her congenital and physical abnormalities.

Complete blood count (CBC) was within normal limits. A radiograph of the right upper extremity was obtained and confirmed four metacarpal bones without radial abnormality (**Figure 1**). An echocardiogram demonstrated a small midmuscular ventricular septal defect and patent foramen ovale. Renal ultrasound was normal.

In conjunction with the clinical and radiographic findings, a diagnosis of Fanconi anemia (FA) was made after diepoxybutane testing demonstrated high chromosomal breakage, and genetic testing revealed two frameshift mutations in the *PALB2/FANCN* gene.

CLINICAL COURSE

The patient was referred to the University of Chicago Pediatric Familial

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Cancer Clinic for the coordination of a multidisciplinary approach and the initiation of cancer-risk surveillance. A screening protocol was initiated that included a CBC every 3 to 4 months and yearly bone marrow evaluation. Multiple subspecialists were involved in her care. Our patient was found to have developmental dysplasia of the hip (**Figure 2**) at a routine clinic visit and subsequently had an orthopedic surgical intervention.

The patient did not return for follow-up visits for 6 months. Upon representation at age 14 months, our patient was found to have severe failure to thrive (FTT) (Z score = -5.76). She improved with assistance from speech therapists and nutritionists, but ultimately required a gastrostomy tube for caloric intake. Brainstem auditory-evoked response was obtained due to failed newborn hearing screen and was normal.

At age 17 months, our patient was found to have global developmental delay. Upon formal developmental assessment, she was diagnosed with central hypotonia with motor delay, mild developmental delay, and moderate communicative delay, although these were difficult to quantify in the setting of FTT.

Due to her high risk for bone marrow failure and risk of developing leukemia and solid tumors, a CBC, bone marrow biopsy, and brain magnetic resonance imaging (MRI) scan were obtained. Brain MRI revealed a nonenhancing expansile medullary mass with cranial extension into the pons (**Figure 3**). This subsequently was found to be an infiltrating astrocytoma on stereotactic brain biopsy.

Bone marrow biopsy revealed high-grade myelodysplastic syndrome, and the decision was made to proceed with stem cell transplant (SCT), which is the current standard of care. At a routine clinic visit for SCT preparation, a CBC test revealed hyperleukocytosis, white blood cell count of 107.6 k/mcL, thrombocytopenia, and platelets of 11 k/mcL. She was started on hydroxyurea for hyperleukocytosis and responded well. She underwent matched, unrelated-donor SCT. Her posttransplant course was complicated by severe mucositis, respiratory failure, transformation of myelodysplastic syndrome into acute myeloid leukemia, and septic shock. After multiple weeks of high-level intensive care and further deterioration, our patient was transitioned to full comfort care and subsequently died.

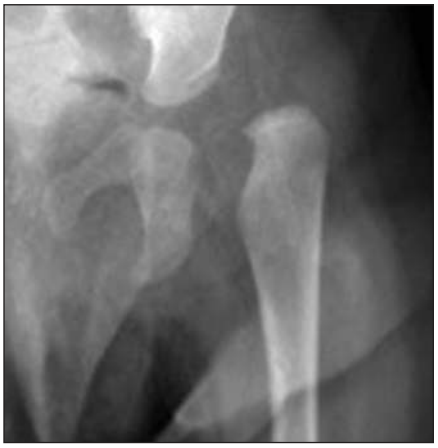

Figure 2. Radiograph of left lower extremity revealed hip dysplasia.

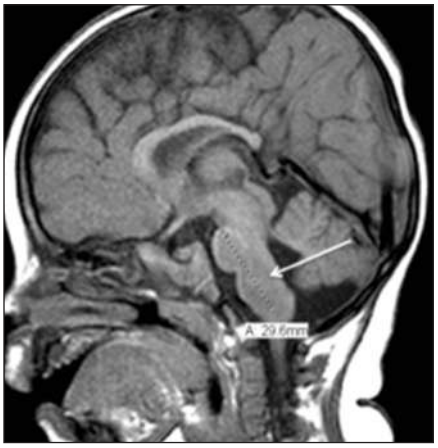

Figure 3. Magnetic resonance imaging scan of the brain revealed astroctyoma.

DISCUSSION

FA is an autosomal recessive condition that was first reported by Swiss pediatrician Guido Fanconi,[1] who described three brothers with aplastic anemia and associated developmental defects.[2] Since then, much has been learned about FA, including specific DNA mutations and the risk of malignancy. The prevalence of FA is 1 to 5 cases per 1 million people, with a heterozygous carrier frequency of about 1 per 300 people; however, carrier rates are much more common in people of Ashkenazi Jewish ethnicity.[3]

Early diagnosis is critical in FA due to the multiorgan involvement and need for subspecialty care. Typical findings of FA include skin hyperpigmentation and café-au-lait spots, short stature, and abnormal thumbs and radii; however, many other anomalies can be seen (**Table 1**). It should be noted that at least 25% of those affected have few or no abnormal features.[4] It is important to consider a differential diagnosis that includes other bone marrow failure syndromes, as well as other syndromes with radial anomalies or café-au-lait spots, when considering FA as a potential diagnosis. If FA is suspected, the patient should have a diepoxybutane or mytomycin C test (a screening test that can confirm FA), followed by mutation analysis to determine the specific type (as occurred with our patient at the time of diagnosis) in conjunction with genetic counseling at a tertiary care center.[5] It is known that patients with many birth defects, including radial, cardiopulmonary, renal, hearing, and developmental delay, are more likely to have early-onset bone marrow failure and the highest risks for leukemia and solid tumors, making early diagnosis crucial.[6]

GENETICS

There are at least 16 genes that are known to cause FA.[7] An individual

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TABLE 1.

Congenital Malformations in Patients with Fanconi Anemia

Organ System	Malformation
Skin	Café-au-lait spots, hyperpigmentation, and hypopigmentation
Growth	Intrauterine growth retardation, short stature, endocrine abnormalities
Eyes	Microophthalmia, short or almond-shaped palpebral fissures, ptosis, epicanthal folds, hypertelorism and hypotelorism, strabismus, cataracts
Thumb and radius	Thenar hypoplasia, absence or hypoplasia of radius and/or thumb, bifid thumb, digitalized thumb/abnormal thumb placement
Skeletal system, other	Dysplastic or absent ulna, micrognathia, frontal bossing, spina bifida, Klippel-Feil, verterbral anomalies, absent clavicles, Sprengel's deformity, Perthes disease, congenital hip dysplasia, scoliosis, rib abnormalities, clubfoot, sacral agenesis, leg length discrepancy, kyphosis, humeral abnormality, brachydactyly, arachnodactyly, craniosynostosis
Kidney and urinary tract	Ectopic, horseshoe, rotated, hypoplastic or absent, dysplastic, hydronephrosis, hydroureter, urethral stenosis, reflux
Ears	Deafness (usually conductive), abnormal or absent pinna, prominent ears, abnormally positioned ears (low set), small or absent ear canals, absent tympanic membrane, microtia, fused ossicles
Genital	Males: micropenis, penile/scrotal fusion, undescended or atrophic or absent testes, hypospadias, chordee, phimosis, azoospermia Females: bicornate uterus, aplasia or hypoplasia of vagina and uterus, atresia of vagina, hypoplastic uterus, hypoplastic/absent ovary, hypoplastic/fused labia
Cardiopulmonary	Patent ductus ateriosis, ventricular septal defect, pulmonic or aortic stenosis, coarctation of aorta, double aortic arch, cardiomyopathy, tetralogy of Fallot, pulmonary atresia
Gastrointestinal	Esophageal atresia, duodenal atresia, anal atresia, tracheoesophageal fistula, annular pancreas, intestinal malrotation, duodenal web, biliary atresia
Central nervous system (CNS)	Microcephaly, hydrocephalus, Bell's palsy, CNS arterial malformations, abnormal pituitary, absent septum pellucidum/corpus callosum, hyperreflexia, neural tube defection, Arnold-Chiari malformation, Moyamoya, single ventricle

Reprinted with permission from Auerbach.[12]

with FA has two mutations in one of these genes, with one mutation inherited from each parent. Our patient had two mutations in the *PALB2/FANCN* gene pair, meaning that each of her parents is an obligate carrier of the *PALB2/FANCN* gene (**Figure 4**). PALB2/FANCN, which is a partner and localizer of *BRCA2*, is a protein that is involved in the maintenance of double strand break repair. Genotype-phenotype correlations have been described for the numerous genes that can cause FA, with some genes being associated with higher risk for malignancy than others. Patients with FA due to biallelic *PALB2/FANCN* mutations have a much higher predisposition for the development of hematologic malignancies and solid tumors (medulloblastoma, astrocytoma, Wilms tumor) in early childhood, comparable to the risk associated with the presence of biallelic *BRCA2/FANCD1* mutations (up to 97% probability of malignancy by age 5.2 years).[8]

Correspondingly, individuals with monoallelic *PALB2/FANCN* mutations, such as each of our patient's parents, have similar risks for developing cancer as those with heterozygous *BRCA2/FANCD1* mutations. Therefore, these people are at an increased risk for developing breast cancer, as well as other malignancies, including pancreatic and ovarian cancer, and should undergo genetic consultation to discuss recurrence risk and cancer screening for family members.[8]

MULTIORGAN INVOLVEMENT

Hematology and oncology are the most discussed complications of FA in the literature. Most FA patients develop bone marrow failure culminating in pancytopenia, with a median age at presentation of 7 years.[9] Our patient had normal blood counts at birth, which is expected in patients with FA. It is important to note that

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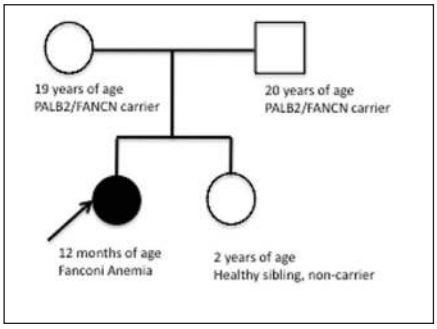

Figure 4. Pedigree of the affected family.

normal blood counts at birth do not eliminate FA as a possible diagnosis. As abnormalities present, thorough hematologic testing is warranted because patients are at high risk of developing myelodysplastic syndrome and acute myelogenous leukemia, both of which were ultimately present in our patient. Patients should be screened with a CBC biannually at a minimum, along with an annual bone marrow aspiration.[4] Furthermore, as described here, our patient was found to have an astrocytoma on routine MRI screening. Although this is somewhat of an anomaly, the literature shows brain tumors, as well as other solid tumors, have been present in pediatric patients with FA.[10]

Radial and thumb abnormalities are the most common skeletal abnormality associated with FA (as seen in our patient). Up to 35% of patients have a thumb abnormality, with another 7% having absent or hypoplastic radii. In addition (as with our patient), 5% of patients with FA have lower extremity anomalies, with congenital hip dislocation being a prominent abnormality of the lower extremity.[6] Although radiation exposure due to imaging is necessary throughout a patient's lifetime, it is important to minimize radiation due to the increased sensitivity to radiation. All physicians involved in caring for patients with FA should work closely with a pediatric radiologist to help reduce exposure when imaging studies are necessary.[4]

Congenital heart disease is present in 6% of patients with FA.[6] Because our patient had an audible murmur on examination, an echocardiogram was necessary for further evaluation. Given that cost constraints make universal screening for congenital heart disease in FA patients with echocardiogram not possible, the literature supports screening for those with clinical evidence of desaturation or undergoing advanced therapeutic options, such as stem cell transplant, in which an echocardiogram is warranted.[11]

Hearing loss was a concern of our patient's parents, but our patient's auditory brain stem response was normal. Hearing problems are a relatively common finding in patients with FA. In 2009, Auerbach[12] reported 126 of 1,075 (11%) patients with FA had hearing loss. Furthermore, there is an increased risk for head and neck cancers in patients with FA, and concerning symptoms should therefore prompt referral to an otolaryngologist.[13]

As shown by our patient's severe FTT, gastrointestinal testing and management is essential for optimizing and maximizing a patient's growth and development. Approximately 7% of FA patients have gastrointestinal symptoms, which range from poor oral intake to duodenal atresia or other gastrointestinal abnormalities. A pediatric gastroenterologist is an active and essential member of the care team of a patient with FA.[14]

Developmental delay or intellectual disability occurs in 10% of the FA population.[6] Unfortunately, in this case the diagnosis of developmental delay lagged because the patient was brought in for follow-up too late. Timely diagnosis is critical so that an intervention referral is completed early in life to assess developmental delay.

It is noted that short stature may be present in more than 50% of patients with FA.[4] It is recommended to assess for short stature, thyroid disease, and osteoporosis, as endocrine disorders are sometimes present in patients with FA.[15] Furthermore, although our patient did not have a renal disorder, 20% of patients do with their disease and should be assessed with an ultrasound, serum electrolytes, blood urea nitrogen, and creatinine.[6]

Resources for patients, families, and pediatricians are available through the International Fanconi Anemia Registry[16] and Fanconi Anemia Research Fund.[17] These organizations provide excellent reviews and recommendations for the general population and the general pediatrician.

CONCLUSION

As can be seen from our patient with multiorgan involvement, FA is a heterogeneous condition that can present with a variety of congenital defects. Although the main causes of morbidity and mortality are oncologic, FA requires a multidisciplinary approach in managing patients. Furthermore, a high index of suspicion should be present, because patients with FA often initially present to general pediatricians or other subspecialists. Early detection and diagnosis is essential to optimize multidisciplinary subspecialty care, as screening of each organ system is essential to optimize the patient's quality of life.

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