



A Perspective of Fanconi Anemia and Its Association with Skeletal Anomalies in Northwestern Iran

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Received 2018 March 28; Revised 2018 April 08; Accepted 2018 April 09.

Abstract

Background: Fanconi anemia is the most common hereditary aplastic anemia characterized by progressive bone marrow deficiency, congenital anomalies, and an increased risk for leukemia. Skeletal deformity is one of the primary manifestations before diagnosis and hematological disorder.

Methods: This study presents a perspective of Fanconi anemia at its concomitant skeletal anomalies at a sub-national level in northwestern Iran. Between 2000 and 2017, all records were collected in 3 provinces of northwest Iran.

Results: Overall, 64 patients (38 female (59.4%) and 26 male (40.6%)) with Fanconi anemia in 3 provinces of northwestern of Iran were identified. The mean age at the time of diagnosis was 6.6 ± 4.8 years. Thirty-seven (57.8%) patients had skeletal deformity in their upper or lower limbs. The 3 most common anomalies, included microcephaly in 29 (45.3%), short stature in 27 (42.2%), and thumb anomalies in 22 (34.2%) patients. The association of the thumb anomalies with microcephaly and short stature was a significant association between them (Chi-square test, p value 0.03; Odds Ratio 3.1 in 95% confidence interval 1.07 to 9.2). Fourteen (21.9%) patients among the 37 patients with skeletal deformities sustained surgeries before the diagnosis of the disease.

Conclusions: A combination of the thumb anomalies and microcephaly should alert the physician to investigate further for a probable existence of Fanconi anemia.

Keywords: Congenital Anomalies, Fanconi Anemia, Microcephaly, Short Stature, Thumb Anomalies, Skeletal Anomalies

1. Background

Fanconi anemia is the most common hereditary aplastic anemia characterized by progressive bone marrow deficiency, congenital anomalies, and an increased risk for leukemia and malignant solid tumors (1, 2). Fanconi anemia is inherited by autosomal recessive pattern with an incidence of approximately 3 per 1 million people. According to various genetic studies up to now, the mutation has been found to be effective in at least 8 genes (1, 2). Congenital anomalies in patients with Fanconi anemia can affect various organs and systems, including skeletal involvement, eye, auditory, renal and urogenital tract, and central nervous system; however, anomalies may be variable in different regions in terms of typing or severity (2).

Skeletal involvement is a common and apparent concomitant of Fanconi anemia (3). Based on an epidemio-

logical study, older patients have an ever-increasing risk for development of solid tumors, with at least 5% reported to have liver tumors (male: female ratio, 2:1) (1). However, there are a few comprehensive studies about the skeletal anomalies in Fanconi anemia (1-8). The aim of this brief report was to present a perspective of Fanconi anemia and its association with skeletal anomalies in northwestern Iran.

2. Methods

In a descriptive-analytic study in northwestern Iran, the recorded cases of Fanconi anemia between 2000 and 2017 in 3 university centers in the northwest of Iran, including West and East Azarbaijan and Ardabil provinces, were included in the study. Data included demographic characteristics (gender, age, and consanguineous parents),

skeletal anomalies, history of bone marrow transplantation (BMT), and history of surgery to correct the deformities, and the overall mortality and survival rates during the study period were recorded and analyzed.

Diagnosis of Fanconi anemia was made clinically (apparent anomalies) along with laboratory findings by the expert pediatric hematologists. Fanconi aplastic anemia is characterized by absolute neutrophil counts of less than 1000 μL , hemoglobin less than 10 g/dL, and platelet count less than 100000 μL in peripheral blood. In Fanconi anemia, bone marrow aspiration and biopsy is hypoplastic.

Statistical analysis was done using the SPSS 16 statistical package (IBM, New York, USA). The data is shown as Mean \pm SD with 95% confidence interval. The relative risk and Chi - square or Fisher's exact tests were employed. p values of less than 0.05 were considered significant.

3. Results

Sixty - four patients with Fanconi anemia in 3 provinces of northwestern Iran were identified. There were 38 female (59.4%) and 26 male (40.6%) patients. The mean age at the time of diagnosis was 6.6 ± 4.8 years. The mean age of patients at the time of the current study was 10.28 ± 6.4 years. The parents of 31 (48.4%) out of the 64 patients were consanguineous relatives. Nineteen (29.7%) patients underwent bone marrow transplant (BMT); however, 3 of them were died at the time of the current study.

Thirty - seven (57.8%) patients had skeletal deformity in their upper or lower limbs while 27 (42.2%) patients had no apparent skeletal deformity. The most common anomaly was microcephaly, which was observed in 29 (45.3%) patients. Twenty - seven (42.2%) patients had short stature and 22 (34.2%) patients had different thumb anomalies. Table 1 demonstrates the anomalies and their frequencies in the upper limbs. Fourteen patients with thumb anomalies had microcephalies, which had a statistically significant association (Chi - square test, p value: 0.03; Odds Ratio: 3.1 in 95% confidence interval 1.07 - 9.2). Twelve patients with the thumb anomalies had also short stature, which was statistically significant (Fisher's exact test, p value: 0.04; Odds ratio: 2.1, 95% confidence interval 0.4 to 3.4) in the lower extremities, syndactyly was present in one case (1.6%), and 2 patients (3.1%) had club feet.

Fourteen (21.9%) patients among the 37 patients with skeletal deformities sustained surgeries before the diagnosis of the disease. For the remaining 27 patients with diagnosed Fanconi anemia, surgical intervention was not offered or the parents declined any operation because of the complexity of the procedure and questionable survival of the patients.

Table 1. Frequency of Skeletal Deformities in 37 out of 64 Patients with Fanconi Anemia in Northwestern Iran

Deformity	Number (Frequency)
Microcephaly	29 (45.3%)
Short stature	27 (42.2%)
Thumb aplasia	5 (7.8%)
Polydactyly	12 (18.8%)
Floating thumb	2 (3.1%)
Syndactyly	3 (4.7%)
Hyperlaxity in thumb	6 (9.4%)
Hypoplastic thumb	6 (9.4%)
Radial ray deficiency	3 (4.7%)
Total	37 (100%)

There was no record about developing malignancies in the patients. At the time of this study, 16 (25%) out of 64 patients died in the cohort.

4. Discussion

Congenital malformations in these patients could affect various organs and systems, including skeletal involvement, eye involvement, auditory, renal and urinary tract, genital and central nervous system (2). Based on genetic variations, diversity of skeletal involvement has been reported in different societies in patients with Fanconi anemia. Knowing these skeletal anomalies is helpful in early diagnosis by physicians. This study presents a perspective of Fanconi anemia and its concomitant skeletal anomalies at a sub - national level in northwestern Iran. In the current study, the mean age at the time of diagnosis was 6.6 ± 4.8 years, which is in accordance with other international studies, according to which the average age of diagnosis was between 5 and 10 years old with the mean age of 7 years old (1, 2).

The occurrences of the skeletal anomalies in Fanconi anemia were variable from 30% to 71% (1-8). In Tischkomitz et al.'s study, 71% of patients with Fanconi anemia had skeletal deformity and 63% presented a short stature (3). In the current study, the skeletal anomalies were found in 37 (57.8%) patients.

In the current study, 14 (21.9%) patients out of 37 patients with skeletal deformities had surgeries before the diagnosis of the disease. Orthopedic surgeons have a unique opportunity for early diagnosis of Fanconi anemia since the patients usually refer early for reconstructive surgeries on their apparent skeletal anomalies. The first stigmata of an underlying Fanconi anemia might be decreased platelet

count. Although the surgery may be performed safely before the hematologic manifestations occurs, early diagnosis of a fatal disease is important to enable the parents to identify appropriate bone marrow donor, to avoid inappropriate treatments, and to perform genetic consulting for their probable next pregnancies. Meanwhile, as indicated in the current study, diagnosis of Fanconi anemia may affect the surgeons' decisions to perform a complex and complicated surgery (1, 6, 7).

Although the incidence of Fanconi anemia in the children with the thumb anomaly is low, the current study as well as others showed that the majority of Fanconi anemia patients have thumb and radius anomalies. In the current study, as well as other studies, the thumb anomalies had statistically significant association with microcephaly and short stature (1, 6, 7). Therefore, combination of these anomalies could alert the physician to investigate further for probable existence of Fanconi anemia. Al - Qattan et al. reported the relationship between Fanconi anemia with skeletal deformity, especially thumb deformities. They suggested further investigation of blood analysis in children with skeletal deformity (8).

Leukemia has been reported in 10% of Fanconi anemia patients with mean age of 14. In addition, malignant tumors have been reported in 10% of Fanconi anemia patients with mean age of 16; however, in the current study as well as another study from Iran, no malignancy was seen. This may be because of the relative lower age (mean 10.28 ± 6.4) of the patients (5).

The current study had several limitations. First, conventional diagnosis of Fanconi anemia was established based on chromosomal breakage analysis and coexistence of aplastic anemia; however, during the current study, diagnosis was made clinically and by laboratory findings. Second, some data were collected retrospectively and there might be flaws in records of the patients. Third, Fanconi anemia is a rare disease and the number of the patients was low thus most of the collected data had to be presented with descriptive analysis rather than analytic analysis. It is hoped that the current study increases awareness of Fanconi anemia and its associate skeletal anomalies, which will lead to better surgical planning, hematologic, and genetic care.

4.1. Conclusion

A combination of thumb anomalies with microcephaly should alert the physician to investigate the presence of Fanconi anemia. Thumb anomalies in children have a high correlation with problems of other internal organs and blood disorder. Therefore, accurate examination is very important before the surgical intervention.

Acknowledgments

This study was registered at Urmia University of Medical Sciences, deputy of research, as a dissertation thesis with record number 1395 - 01 - 63-2328. The authors express their gratitude to Clinical Research Development Unit of Imam Khomeini Hospital, Urmia University of Medical Sciences.

Footnotes

Conflict of Interest: There is no conflict of interest to be reported.

Ethical Issues: The study was confirmed by the Ethics Committee of Urmia University of Medical Sciences.

Funding/Support: This study was financially supported by Urmia University of Medical sciences.

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