

# Frequency of Hypothyroidism in Fanconi Anemia

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## Abstract

**Background:** Fanconi anemia (FA) is a rare, autosomal recessive (AR) and multifactorial disorder. A high prevalence of FA observed in Iran is perhaps due to the high rate of consanguineous marriages. This study investigates the extent of short stature in patients with FA, the frequency of hypothyroidism in FA and the correlation between height and hypothyroidism.

**Methods:** Eighteen patients with FA referred to the Pediatrics Clinic of Nemazee Hospital were selected based on specific congenital and malformational symptoms and bone marrow results. These patients were evaluated for weight, height, bone age, clinical goiter and thyroid function tests.

**Results:** Eleven out of 18 patients (61%) had overt or compensated hypothyroidism. Short stature was found in 89% of patients with a mean height more than two standard deviation (SD) below the mean height for that age. There was no significant correlation between short stature and overt or compensated hypothyroidism. The mean height standard deviation score (SDS) of patients with normal thyroid function was also more than two SD deviation below the normal mean, revealing that short stature is an inherent feature of FA. In seven cases with goiter, only three had hypothyroidism. The mean±SD weight SDS was  $-1.03\pm 0.99$ . The mean±SD bone age was  $12\pm 4.5$  yr.

**Conclusion:** According to the results of this study, our patients had a considerable prevalence of hypothyroidism and short stature was a common feature of FA. It is recommended that thyroid function test is necessary in these patients.

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**Keywords** • Fanconi anemia • short stature • hypothyroidism • goiter

## Introduction

**F**anconi anemia (FA) is an autosomal recessive disorder with variable penetrance and genetic heterogeneity.<sup>1</sup> Affected individuals may be offspring of consanguineous marriages in approximately all patients.<sup>1,2</sup> FA is a multisystem disease associated with excess chromosomal breakage and is characterized by a wide variety of clinical manifestations, pancytopenia, congenital anomalies and predisposition to malignancy.<sup>1-3</sup> The physical anomalies most commonly associated with FA are short stature and bone abnormalities, but some patients lack malformations.<sup>4-6</sup> Endocrinopathies are a common feature of FA, including glucose intolerance, growth

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hormone insufficiency and hypothyroidism.<sup>7</sup> In fact, short stature as the common feature of FA may be exaggerated by superimposed endocrinopathies.<sup>7</sup> We have studied a group FA patients to assess the frequency of hypothyroidism and short stature.

### Patients and Methods

Eighteen patients with FA were studied during two years of follow-up in Pediatric Clinic of Nemazee Hospital affiliated to the Shiraz University of Medical Sciences. Medical history was obtained and complete physical examination including height, weight, head circumference, thyroid size was done. Bone ages were assessed using the methods of Greulich and Pyle.<sup>8</sup> Standing height was measured using a Harpenden stadiometer. Thyrotropin (Thyroid-stimulating hormone, TSH), T<sub>4</sub>, T<sub>3</sub> and T<sub>3</sub>-resin uptake were measured by immunoradiometric assay (IRMA) with standard commercial kit (Kavoshiar, Iran) and T<sub>4</sub> by Radioimmune Assay (RIA; Kavoshiar, Iran), T<sub>3</sub> by RIA assay and T<sub>3</sub>-resin uptake by RIA assay (Kavoshiar, Iran), respectively.

Primary hypothyroidism was diagnosed if T<sub>4</sub> was less than 4.5 µg/dl (NL 4.5–12µg/dl) and TSH more than 3.8 µu/ml (NL 3.3–3.8 µU/ml). Secondary hypothyroidism was diagnosed if T<sub>4</sub> was less than 4.5 µg/dl and TSH was below or close to normal range. Compensated hypothyroidism was diagnosed if T<sub>4</sub> was normal and TSH was slightly elevated.<sup>9</sup>

Diagnostic criteria for FA consisted of bone marrow results. Most patients demonstrated clinical manifestations of FA, such as hematologic abnormalities and/or congenital anomalies characteristic of FA. In addition to bone marrow results and hematologic findings, all patients had at least one of the following criteria including, microcephaly, hyperpigmentation and skeletal anomalies. It was not possible to do a genetic study to confirm FA with DNA-cross-linking agents' sensitivity and diepoxybutane test. For all patients kidney sonography was recommended to detect the unusual renal abnormalities.

#### Statistical analysis

Data are presented as mean±SD and Student's t-test were used to compare the means.

### Results

Ten patients (55%) were male and the rest (45%) were female. The mean±SD age of the onset of pancytopenia in patients with FA was 8.22±2.98 yrs and mean±SD age at assessment was 12.7±4.9 yr with the age range of 5

to 24 yrs. Nine patients (50%) had positive family history, within their families. There was a tendency for hematologic disorders to occur at about the same age. Four patients did not use any drugs, ten were on combination of androgen and prednisolone therapy and four were receiving only prednisolone. None of them had been frequently transfused. Five patients had abnormal kidney, but surprisingly with no signs, such as horseshoe kidney, ectopic kidney, enlarged kidney or nephrocalcinosis.

Hand x-rays, for bone age and for obscure congenital bone deformities showed thumb abnormalities (grossly abnormal thumb) in four patients and parallel correlation between bone age and chronological age in the rest. Short stature was a very common finding in these patients (89%) with mean height more than two SDs below the normal mean height for age and sex. The mean±SD height standard deviation score (SDS) for all patients was (-2.4±1.7). The mean±SD height SDS for males was -2.09±1.8 and for females -2.9±1.6 which were not significantly different. Eight patients (44%) had a height more than two SDs below the normal mean height and five patients (28%) had a height more than three SDs below the normal mean height (considered as severe short stature). Seven patients with normal thyroid function tests had a mean±SD height SDS -2.1±0.7. There was no significant correlation between short stature and hypothyroidism. Weight SDS (-1.03±0.99) was below normal. Anthropometric patient data are summarized in Table 1.

**Table 1:** Anthropometry of Fanconi anemia patients

Number of patients	18
Mean±SD Age (yr)	12.7±4.9
Height ± SDS	-2.4±1.7
Bone age (yr)	12±4.5
Weight ± SDS	-1.03±0.99

SDS= standard deviation score

As shown in Table 2, seven patients (39%) had goiter mostly grade Ib according to the physical examination of their thyroid gland using WHO grading. The level of T<sub>3</sub> in all patients was within normal range (150±12 ng/dl). Seven patients (39%) had normal thyroid function test and 11 patients (61%) had hypothyroidism with the characteristics of: six patients (33%) having compensated hypothyroidism, two (11%) secondary hypothyroidism, and three (17%) primary hypothyroidism respectively.

### Discussion

Fanconi anemia is a genetically heterogenous disorder of unknown pathophysiology and multisystem involvement especially bone anomaly

**Table 2:** Characteristics of FA patients

Factor(s)	n (%)
Gender	
Male	10 (55)
Female	8 (45)
Ht 1 - 2 SDs < mean	3 (17)
Short stature	
Ht between 2-3 SDs < mean	8 (44)
Ht > 3 SDs < mean	5 (28)
Ht above the mean	2 (11)
Goiter	7 (39)
Compensated hypothyroidism	6 (33)
Secondary hypothyroidism	2 (11)
Primary hypothyroidism	3 (17)

Ht= Height, SD= Standard Deviation

and endocrine dysfunction.<sup>1,2,7</sup> In our study, the mean height SDS at assessment for all the patients studied was  $-2.4 \pm 1.7$  which is significantly below normal. Five patients (28%) had a height more than 3 SDs below the mean (i.e., severe short stature). Therefore, short stature is common and the severity of short stature varies widely. Short stature is an inherent feature of FA. Chronic disease could contribute to growth retardation. Dupuis Girod et al documented decreased growth hormone (GH) secretion in children with FA.<sup>10</sup> Participants with FA have greatly elevated levels of a type 1 collagen marker that does not respond normally to GH, paradoxically decreasing the response to GH. In the face of poor growth, this suggests that these individuals undergo futile biosynthesis of collagen.<sup>7</sup>

There was no correlation between short stature and hypothyroidism. Short stature in FA can not be explained based on endocrinopathy alone.<sup>7</sup> Seven cases with normal thyroid function tests had a mean height SDS  $-2.1 \pm 0.7$ , demonstrating that a significant degree of short stature is typical and inherent picture of FA. Weight SDS ( $-1.03 \pm 0.99$ ) was below normal but significantly better than the height SDS ( $-2.4 \pm 1.7$ ), indicating that insufficient caloric intake is not enough to explain the height deficit.

Wajnrajch et al, showed that 81% of their FA patients, in general, had endocrine abnormalities, in which only 36% had overt or compensated hypothyroidism,<sup>7</sup> whereas, hypothyroidism was observed in 61% of our patients and it seems that hypothyroidism is a common feature of FA in our population. Moreover, they reported that 25% of their patients had compensated hypothyroidism while 4 patients had low thyroxin value with normal TSH levels. These findings could be secondary to pituitary/hypothalamic dysfunction, to reduced thyroid hormone binding, or to sick-euthyroid syndrome, a condition thought to be an adaptation to the catabolic state.<sup>7,11</sup>

Wajnrajch et al, also showed that the actual height SDS for their patients, however, was  $-2.35 \pm 0.28$ , indicating that the patients lost an average of 2.46 SDs as compared with their expected target height.<sup>7</sup> The improvement from

the actual height SDS to the predicted height SDS is explained by the patient's delayed skeletal maturity. The mean delay in bone age from the chronological age was 0.98 yrs. Our results are not in accordance with the results of Wajnrajch et al,<sup>7</sup> because most of our patients suffered from poor drug consumption, irregular follow up and were of low economic classes.

The high frequency of hypothyroidism can be explained on several basis such as central and peripheral hypothyroidism, discrepancy between peripheral thyroid hormone concentrations and the central sensing or feedback mechanisms, and/or TSH molecule with decreased bioactivity. We should pay attention to these mechanisms and that their risk in order to be able to prevent or postpone their complications.

## Conclusion

Hypothyroidism should be considered as a common finding in Fanconi anemia. Therefore, endocrine evaluation of these patients is suggested to prevent complications and to improve the overall quality of life.

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