Endocrine Phenotype of Children and Adults With Fanconi Anemia

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Background. Features of Fanconi anemia (FA) are well known, including bone marrow failure, congenital anomalies such as radial anomalies, renal and ear anomalies, tracheo-osophageal fistula, imperforate anus, and elevated risk for cancer. We sought to further characterize the endocrine phenotype in children and adults with FA. Procedure. Clinically indicated endocrine evaluation data from 120 persons with FA, including 78 children (43 female) and 42 young adults (who had achieved adult height, 19 female), were entered in an institutional review board-approved database. Data were analyzed according to gender, birth weight, FA complementation group, and whether or not the patient had completed linear growth or had undergone hematopoietic cell transplant, using Wilcoxon Rank Sum or Chi-square, as appropriate. Results. Overall, 60% of children and 58% of adults with FA had short stature, 68% of children and 30% of adults had glucose intolerance, 61% of children and 37% of adults had mild hypothyroidism, and 40% of adults had evidence of hypogonadism (not possible to fully assess in children). In general, bone mineral density (BMD) was normal in adults, while BMD in children was normal when results were adjusted for bone size/thickness using height age. Conclusions. We have evaluated in detail children and adults with FA for their growth and endocrine function. Overall, 79% of children and adults with FA had one or more endocrine abnormality. Pediatr Blood Cancer © 2012 Wiley Periodicals, Inc.

Key words: bone marrow failure; Fanconi anemia; glucose intolerance; hypogonadism; hypothyroidism; short stature

INTRODUCTION

Features of Fanconi anemia (FA) are well known, including bone marrow failure and congenital anomalies such as radial anomalies, renal and ear anomalies, tracheo-osophageal fistula, and imperforate anus. Patients have a genetic mutation affecting the protein complex controlling DNA repair, leading to chromosomal fragility and sensitivity to oxidative injury [1–3]. Risk for cancer is elevated in FA, especially acute myeloid leukemia and later oropharyngeal and genital squamous cell carcinomas [4–5]. Many patients undergo hematopoietic cell transplant (HCT) [6,7].

Along with the above characteristics, short stature is a common feature of FA. Reports describe a few cases of diabetes mellitus [8] or growth hormone deficiency (GHD) [9–12]. Of 54 FA patients with endocrine evaluations, 47 were pediatric (2–16 years) and only seven were over 16 years [13]. Another study evaluated 45 FA patients, only 17 with age >18 years [14]. These two studies reported that 81% and 73% FA patients, respectively, had at least one endocrine deficit. The studies emphasized GH abnormalities, insulin resistance, and low BMD [13,14].

We characterized the endocrine function of a series of children and young adults evaluated clinically as a part of their routine comprehensive care for FA, confirming prior investigators’ findings of frequent endocrine abnormalities in FA. We found the most common abnormalities are blunted first phase insulin release, mild primary hypothyroidism, and male gonadal dysfunction.

METHODS

Patients attending the FA Comprehensive Care Clinic of Cincinnati Children’s Hospital Medical Center (CCHMC) were also assessed for clinical and laboratory endocrine evaluation. The population included 78 children (43 females), median age 7.0 years (range 0.3–15.9 years), including 17 who had undergone HCT; and 42 adults (adult height had been reached) (19 females), median age 19.0 years (range 13.5–31 years), including 24 after HCT. Patients were considered to be biologically “adult” if they had progressed through puberty, had fused skeletal epiphyses and were no longer growing taller, or were age 18 years or older. Those 18 years or older included 26 patients (14 females). (The youngest patient at adult maturation had bone maturation of 16 years at chronological age 13.5 years, had shown no height increase in 12 months, and had menses for 4 years.) Assessment for gene mutation was performed in 88 (Table I).

Parents and patients ≥18 years provided consent (children ≥11 years, assent) to participate in an institutional review board-approved database. Data were analyzed using SAS® version 9.2 (SAS Institute, Cary, NC) according to gender, birth weight [small for gestational age (SGA) versus appropriate for gestational age (AGA)], FA complementation group, completion of linear growth (child vs. adult), and HCT status (without HCT vs. after HCT). Wilcoxon Rank Sum test was used when comparing continuous variables between groups; Chi-square test was used for categorical comparisons. In order to assess association between demographic variables and individual endocrine outcomes, a multiple logistic regression approach was used to examine the associations simultaneously. The reason for this approach was varying degrees of missing values. However, it was felt that associations in different subgroups should be examined. Specifically, 36 were not tested for complementation group, and SGA status was unavailable for 52. The approach was to include all defining demographics first: complementation group (FANC A vs. other), gender, transplant status (without HCT vs. after HCT), maturity status (child vs. adult), and SGA status (SGA vs. AGA). The second model did not include complementation group; the third model also did not include SGA status. A P-value <0.05 was considered statistically significant.

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Conflict of interest: Nothing to declare.

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### TABLE I. Clinical Characteristics in the Combined Group of Children and Adults With Fanconi Anemia by Gender, According to Complementation Group

<table>
<thead>
<tr>
<th>Gender</th>
<th><strong>N</strong></th>
<th><strong>CA (years)</strong></th>
<th><strong>HCT (%)</strong></th>
<th><strong>SGA (%)</strong></th>
<th><strong>MPH for gender (cm)</strong></th>
<th><strong>HT SD (Z-score)</strong></th>
<th><strong>BMI SD (Z-score)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Male</strong></td>
<td>82</td>
<td>15.8 [7.8, 20.3] (3.5–23)</td>
<td>45% (14)</td>
<td>6% (1)</td>
<td>178 [178, 182] (168–191)</td>
<td>-2.2 to -8.1</td>
<td>-1.4 to -2.6</td>
</tr>
<tr>
<td><strong>Female</strong></td>
<td>70</td>
<td>6.9 [3.9, 10.5] (1.3–7.8)</td>
<td>42% (5)</td>
<td>5% (1)</td>
<td>180 [179, 182] (166–184)</td>
<td>-2.1 to -8.1</td>
<td>-1.4 to -2.0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>152</td>
<td>12.3 [8.0, 20.3] (3.5–23)</td>
<td>46% (14)</td>
<td>6% (1)</td>
<td>179 [178, 182] (166–184)</td>
<td>-2.2 to -8.1</td>
<td>-1.4 to -2.6</td>
</tr>
</tbody>
</table>

Values noted are median [25th, 75th percentile]. Other: in males includes four with FANCC, four with FANCD2, one with FANCL, and four with non-A, B, C, G, E (number in sub-group). Other: in females includes four with FANCC, four with FANCD2, one with FANCL, and four with non-A, B, C, G, E (percent of subgroup). MPH (mid-parental height). Ht SD (standard deviation units from the mean for height for age and gender). BMI SD (standard deviation units from the mean for body mass index for age and gender).

Details of HCT treatment were available in 29 of 39 evaluated after HCT. Seven of the remaining ten were transplanted at outside institutions, while charts of the remaining three were not available. All but four of the 29 patients received total body irradiation at low dose (400–450 cGy, with one at 300 cGy). Chemo-immunotherapy included ATG and cytotoxic, with fludarabine added in half of the patients. Three of four with no total body irradiation received busulfan additionally.

Medical history, weight, height by stadiometer, pubertal staging, and blood tests were included in the database. Endocrine evaluation was performed in patients at time of stable health and, in the small number of patients receiving transplants, was at least a month after any transfusion.

Glucose homeostasis was evaluated using fasting/postprandial glucose, glycosylated hemoglobin (HgbA1c), and fructosamine. Postprandial glucose was considered high if any of 30, 60, or 120-minute values were >140 mg/dl. Postprandial insulin was considered high if any values were >100 mcU/ml. Thyroid function was evaluated using thyroxine (T4), free T4 (FT4), thyrotropin (TSH), and TSH surge if FT4 was low without TSH elevation [15,16]. Thyroid function was considered low if TSH was >3.5 mIU/L, FT4 <1.0 ng/dl, or TSH surge showed <50% rise. Stimulated growth hormone (GH) was low if <5 ng/ml [17]. Insulin-like growth factor 1 (IGF-I) and IGF binding protein 3 (IGFBP3) were measured. Overnight GH sampling (every 20 minutes) was performed in 20 children with results compared to age- and pubertal stage-adjusted normal data [18]. Puberty was assessed by Tanner staging and luteinizing hormone (LH), follicle-stimulating hormone (FSH), and estradiol (E2) or testosterone (T). FSH was considered suggestive of primary hypogonadism if >18 mIU/ml. ACTH-stimulated cortisol was considered low if <18 mcg/dl [19]. Radiograph of left hand/wrist assessed bone maturation. Bone mineral density (BMD) was assessed by Dual X-ray Absorptiometry (DXA), compared to age/gender/race norms and (in children) adjusted for height age [20,21].

Body mass index (BMI, kilograms/meters²) was expressed in standard deviations from mean for age and gender (BMIz). Clinically significant BMIz-scores were selected: that is, BMIz >1.5 SD was considered significantly thin, while BMIz >2 SD signified overweight. Height was expressed in SD from mean for age/gender (HtSD). For adults >18 years of age, height was compared to age 18 years. Clinically significant height BMIz-scores were selected: that is, HtSD <−1.8 SD (3rd percentile) was considered significantly short.

### RESULTS

#### Children

Birth information was available in 59 of 78. Of the 59, 75% were born full-term and 25% at 36–37 weeks gestation; 51% were born at SGA weight or length (Tables I and II). Parental heights were available in 60 of 78 and were similar to the general population (Table I). Median HtSD (−2.0 SD) was shorter than expected in both males (−4.6 to +1.3 SD) and females (−5.3 to +1.8 SD) (Fig. 1). Of males, 57% without HCT, 71% after HCT, had heights <−1.8 SD (Table III). Of females, 65% without HCT, 44% after HCT, had heights <−1.8 SD. Median BMIz was normal at −0.2 SD (males −3.3 to +5.0 SD, females −2.6 to +6.0 SD) (Fig. 2). However, 33% (8 males, 15 females) were thin; 11% (4 males, 4 females) were overweight.
Small stature was associated with abnormal hormone testing in 33 (3 with GH deficiency, 30 with mild hypothyroidism). Overnight GH sampling in 20 was normal (mean, number of pulses, mean peak amplitude) compared to age- and pubertal stage-matched normal data [18]. Peak stimulated GH tested in 32 was low (<5 ng/dl) in two without HCT and in one after HCT (Table III). In addition, GH screening (IGF-I, IGFBP3) were <−2 SD in seven others growing normally.

Thyroid levels were tested in 70, abnormal in 61% (Table III). TSH was mildly elevated in 48% without HCT (3.1–7.1 mIU/L), 53% after HCT (3.1–10.2 mIU/L). FT4 was low (<1.0 ng/dl, minimum 0.7 ng/dl) in 21% without HCT, 20% after HCT. TSH surge tested in 27 (with FT4 in lowest third of normal) was low in five (19%), suggesting central hypothyroidism. ACTH-stimulated cortisol was low in only one of 42 tested.

Fasting glucose and insulin tested normal in 54. One additional child had type 1 diabetes (family history of type 1 diabetes). However, postprandial glucose was elevated in 68% of 47 tested (Table III). HgbA1c was unexpectedly low (median 4.0%) compared to postprandial glucose (median 177 mg/dl) without HCT. In contrast, HgbA1c after HCT (median 5.0%) was more consistent with postprandial glucose (mean 144 mg/dl). Fructosamine was normal in all 32 tested (range 179–259 mmol/L), despite elevated postprandial glucose levels. Postprandial glucose was elevated >140 mg/dl in 71% without HCT, 58% after HCT. At time of peak glucose, paired insulin levels were also elevated in 23% without HCT, 42% after HCT. Fasting insulin was only high in one, 38.5 mcU/ml (otherwise range 2–25 mcU/ml, inconsistent with insulin resistance). Islet cell antibodies were negative in all 19 tested. Lipid panels were performed in 24; total cholesterol was >200 mg/dl in four (one after HCT).

Males had relatively small gonads, both for age and compared to testosterone concentrations. Without HCT, 12 of 61 were at pubertal age: six clinically/biochemically in puberty, four not yet in puberty (status not available in two). None had pubertal delay. After HCT, 12 of 17 were at pubertal age: eight clinically biochemically in puberty, three not yet in puberty. One female had gonadal failure with elevated FSH. Three of those in puberty also had FSH elevation (Table III), suggesting partial gonadal impairment. BMD was assessed in 22 without HCT. BMD Z-score was <-2.0 SD in one, after adjustment for height. Height-adjusted BMD assessed in seven after HCT was also normal (Table III).

### Adults

Although 26 were 18 years or older, 42 patients were physically adult. Birth information was available in 11 of 42. Three were born at SGA weight or length (Tables I and II). Parental heights were available in 11 of 42 and were similar to general population. Median HtSD was reduced in adults: 15 of 22 males (68%), 8 of 18 females (44%), had heights <−1.8 SD (males −4.4 to +0.5 SD, females −3.4 to +0.4 SD) (Fig. 1). Median BMIDSD was within normal limits at −0.95 SD (males −2.8 to +2.0 SD, females −2.7 to +3.2 SD) (Fig. 2). However, ten males (six after HCT), five females (three after HCT), were thin (38%); one female was overweight.

Small stature was associated with abnormal hormone testing in 30% of short adults (one with GHD, six with mild hypothyroidism). Overnight GH sampling was not performed in adults. Peak stimulated GH was tested in five without HCT, four after HCT, with low result (<5 ng/dl) in one without HCT, one after HCT (Table III).

Thyroid levels were tested in 27 of 42, abnormal in 37% (Table III). TSH was mildly elevated in 17% without HCT (3.1–6.7 mIU/L), 29% after HCT (3.1–4.1 mIU/L). FT4 was low in 25% without HCT, 38% after HCT. TSH surge was normal in all nine tested. ACTH-stimulated cortisol was normal in all but one of 13 tested.

### Table II. Height and Body Mass Index for Age and Gender According to Birth Weight and Hematopoietic Cell Transplant Status in Persons With Fanconi Anemia

<table>
<thead>
<tr>
<th>Birth weight</th>
<th>Transplant status</th>
<th>Ht SD (Z-score)</th>
<th>BMI SD (Z-score)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGA</td>
<td>No HCT (N=24)</td>
<td>−2.9 [−3.8, −2.1], (−5.3 to 0)*</td>
<td>−1.8 [−2.0, +0.7], (−3.3 to +2.2)</td>
</tr>
<tr>
<td></td>
<td>HCT (N=9)</td>
<td>−1.6 [−2.7, −0.3], (−3.3 to −0.3)</td>
<td>−0.8 [−1.9, +1.0], (−2.6 to +2.0)</td>
</tr>
<tr>
<td></td>
<td>All SGA (N=33)</td>
<td>−2.6 [−3.5, −2.0], (−5.3 to 0)</td>
<td>−1.3 [−2.0, +0.8], (−3.3 to +2.2)</td>
</tr>
<tr>
<td>AGA</td>
<td>No HCT (N=27)</td>
<td>−1.9 [−2.7, −0.9], (−4.0 to +1.3)</td>
<td>0.0 [−1.8, +0.9], (−2.0 to +6.0)</td>
</tr>
<tr>
<td></td>
<td>HCT (N=8)</td>
<td>−2.2 [−2.6, −1.7], (−3.3 to −0.2)</td>
<td>−0.8 [−1.5, −0.4], (−2.0 to +5.0)</td>
</tr>
<tr>
<td></td>
<td>All AGA (N=35)</td>
<td>−2.0 [−2.7, −1.0], (−4.0 to +1.3)</td>
<td>−0.5 [−1.8, +0.7], (−2.1 to +6.0)</td>
</tr>
</tbody>
</table>

*Values noted are Median [25th, 75th percentile] (range); Abbreviations include N (number in sub-group), HCT (hematopoietic cell transplant), Ht SD [standard deviation units (Z-score) from the mean for height for age and gender], and BMI SD [standard deviation units (Z-score) from the mean for body mass index for age and gender], SGA (history of small for gestational age), and AGA (history of appropriate for gestational age birth weight).
Fasting glucose, insulin, and HgbA1c were normal in all 18 tested. One other had insulin-dependent diabetes after pancreatitis following HCT. Postprandial glucose was elevated > 140 mg/dl in the 30% of 20 tested (Table III). Islet cell antibodies were negative in five tested. Lipid panels were performed in 16, with cholesterol elevated in three.

Several had achieved adult height early, related to androgens used to stimulate bone marrow function. Males tended to have small gonads compared to their testosterone concentrations. All had testosterone or estradiol in adult range (including those on sex steroid replacement or oral contraceptive pills). Three females without HCT were on OCP (one with premature menopause); two additional females and two males had FSH elevation (suggesting gonadal impairment) (Table III). Two females after HCT were on OCP (one with FSH elevation), and five males had FSH elevation. BMD was assessed in seven without HCT, low in one (Z-score < 2 SD, HtSD < 2.4). One of eight after HCT had low BMD (Z-score < 1.8 SD, HtSD < 1.8). Adult BMD was not adjusted for height.

Other Analyses

Analysis by complementation group compared FANCA to all other complementation groups (Table I). In general, persons with FANCA were evaluated at older age (median 15.4 years) than were persons in other groups (median 8.8 years).

Persons born SGA (N = 33, median birth weight 2.02 kg, range 1.5–2.6 kg, at 36–45 weeks) were compared to those born AGA (N = 35, median birth weight 2.87 kg, range 1.8–3.6 kg, at 31–42 weeks) (Table II). SGA group was more likely to have congenital anomalies (54%) than AGA group (17%). At time of endocrine evaluation, those born SGA without later HCT were shorter (median HSD = 10.2 cm, range 6.2–15.2 cm) than those born AGA, regardless of transplant status. Those born SGA who later underwent HCT had growth and length consistent with catch-up growth (median HSD = 7.3 cm, range 6.9–8.2 cm).

TABLE III. Proportion of Fanconi Anemia Patients With Abnormal Endocrine Status According to Age, Gender, and Hematopoietic Cell Transplant Status

<table>
<thead>
<tr>
<th>Age group</th>
<th>Gender, HCT status</th>
<th>N</th>
<th>Low thyroid (TSH &gt; 3, FT4 &lt; 1.0), % (N)</th>
<th>Low GH (FSH &gt; 18), % (N)</th>
<th>High postprandial glucose (&gt;140), % (N)</th>
<th>Short height (Z-score &lt; 1.8 SD), % (N)</th>
<th>Low bone mineral (Z-score &lt; 2 SD), % (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children</td>
<td>All</td>
<td>78</td>
<td>61% (70)b</td>
<td>12% (9)</td>
<td>68% (47)</td>
<td>60% (70)</td>
<td>3% (29)</td>
</tr>
<tr>
<td></td>
<td>Female no HCT</td>
<td>34</td>
<td>64 (28)</td>
<td>13 (8)</td>
<td>78 (18)</td>
<td>65 (31)</td>
<td>7 (15)</td>
</tr>
<tr>
<td></td>
<td>Male no HCT</td>
<td>27</td>
<td>62 (25)</td>
<td>10 (8)</td>
<td>65 (17)</td>
<td>57 (23)</td>
<td>0 (7)</td>
</tr>
<tr>
<td></td>
<td>Total no HCT</td>
<td>61</td>
<td>60 (53)</td>
<td>12 (12)</td>
<td>71 (55)</td>
<td>61 (54)</td>
<td>5 (22)</td>
</tr>
<tr>
<td></td>
<td>Female HCT</td>
<td>9</td>
<td>89 (9)</td>
<td>25 (4)</td>
<td>50 (6)</td>
<td>44 (9)</td>
<td>0 (5)</td>
</tr>
<tr>
<td></td>
<td>Male HCT</td>
<td>8</td>
<td>38 (8)</td>
<td>25 (4)</td>
<td>67 (6)</td>
<td>71 (7)</td>
<td>0 (2)</td>
</tr>
<tr>
<td></td>
<td>Total HCT</td>
<td>17</td>
<td>65 (17)</td>
<td>25 (8)</td>
<td>58 (12)</td>
<td>56 (16)</td>
<td>0 (7)</td>
</tr>
<tr>
<td>Adults</td>
<td>All</td>
<td>42</td>
<td>37% (27)</td>
<td>40% (25)</td>
<td>58% (40)</td>
<td>13% (15)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Female no HCT</td>
<td>11</td>
<td>44 (9)</td>
<td>29 (7)</td>
<td>67 (6)</td>
<td>17 (6)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male no HCT</td>
<td>7</td>
<td>0 (0)</td>
<td>100 (1)</td>
<td>33 (3)</td>
<td>83 (6)</td>
<td>0 (1)</td>
</tr>
<tr>
<td></td>
<td>Total no HCT</td>
<td>18</td>
<td>31 (13)</td>
<td>20 (5)</td>
<td>56 (9)</td>
<td>56 (16)</td>
<td>14 (7)</td>
</tr>
<tr>
<td></td>
<td>Female HCT</td>
<td>8</td>
<td>17 (6)</td>
<td>17 (6)</td>
<td>0 (4)</td>
<td>50 (8)</td>
<td>25 (4)</td>
</tr>
<tr>
<td></td>
<td>Male HCT</td>
<td>16</td>
<td>62 (8)</td>
<td>62 (8)</td>
<td>14 (7)</td>
<td>62 (16)</td>
<td>0 (4)</td>
</tr>
<tr>
<td></td>
<td>Total HCT</td>
<td>24</td>
<td>43 (14)</td>
<td>25 (4)</td>
<td>9 (11)</td>
<td>58 (24)</td>
<td>12 (8)</td>
</tr>
</tbody>
</table>

*Bone mineral SD represents bone mineral density adjusted for age, gender, and race; abbreviations include HCT (hematopoietic cell transplant), TSH (thyrotropin, mIU/L), FT4 (free thyroxine, ng/dl), GH (overnight or stimulated peak growth hormone, ng/ml), FSH (follicle-stimulating hormone, mIU/ml), and SD (standard deviation units (Z-score) from the mean for age and gender). b Values noted are % (N), % signifies percent of those evaluated who tested abnormal and N signifies total number evaluated for this condition.

Fig. 2. Body mass index has a normal distribution in most of 120 children and young adults with Fanconi anemia, expressed in standard deviation units (Z-score) from the mean for age and gender.
Of interest, higher BMI was associated with taller height and with delayed diagnosis of FA. BMISD was correlated with HtSD ($r = 0.31, P = 0.001$). Short height (HtSD $<-1.8$ SD) was significantly associated with low BMI (BMISD $<-1.5$ SD), $P = 0.0001$. Without HCT, patients had similar HtSD ($P = 0.8$), occurrence of GHD ($P = 0.62$), and hypothyroidism ($P = 0.98$) compared to after HCT (Table III), but had greater occurrence of glucose intolerance ($P = 0.01$).

Examination of endocrine outcomes according to defining demographics [complementation status (FANCA versus other), gender, transplant status (without HCT vs. after HCT), maturity status (child vs. adult) and SGA status (SGA vs. AGA)] gave the following results. For low GH and short height, no demographic was statistically significant. For low thyroid only, maturity status was significant ($P = 0.02$): odds of low thyroid were increased in child vs. adult, OR = 3.09 (95% confidence interval 1.16, 8.13). For high postprandial glucose, odds were increased in child vs. adult, $P = 0.02$ [OR = 4.03 (95% CI 1.23, 13.3)]. Transplant status was of borderline statistical significance, $P = 0.06$ [odds of high postprandial glucose were reduced after HCT, OR = 0.33 (95% CI 0.11, 1.04)]. Low BMD was not analyzed due to small numbers; hypogonadism was not analyzed as gonadal status could not be assessed in most children.

Despite no growth-related endocrine abnormalities (low thyroid or GH), children still had relatively short stature (median HtSD $<-1.0$ SD), similar to adults ($-1.7$ SD, $P = 0.12$). However, children with growth-related endocrine abnormalities had shorter mean HtSD ($-2.2$ SD) than did those with normal function ($P = 0.01$). Likewise, adults with growth-related endocrine abnormalities had shorter mean HtSD ($-2.2$ SD) than did those with normal function. There was no significant difference in HtSD between overall group (all ages) without HCT (median $-2.2$ SD) and overall group after HCT (median $-2.1$ SD, $P = 0.73$).

When analysis included glucose abnormalities in addition to growth-related endocrine abnormalities, 79% of children (69% of adults) without HCT had at least one endocrine deficiency, 88% of children (79% of adults) after HCT.

Overall, 79% of all FA patients had at least one endocrine abnormality (thyroid, GH, glucose, gonadal, bone mineral). HtSD was shorter in those with endocrine abnormalities, median $-2.4$ SD [interquartile interval $-3.1$ to $-1.6$] (range $-5.3$, $1.8$), than in those with no endocrine abnormality, median $-1.0$ SD [$-1.3$, $-0.3$] ($-1.8$, $0.7$).

**DISCUSSION**

Overall, 60% of children with FA and 58% of FA patients who were physically adult had short stature, 68% of children and 30% of adults showed glucose intolerance, 61% of children and 37% of adults showed hypothyroidism, and 40% of adults had evidence of hypogonadism. BMD was normal in most adults (without height adjustment) and in children when the result was adjusted for bone size/thickness using height age. Overall 79% of patients with FA had one or more endocrine abnormality. This was a retrospective review of existing clinical data, so not every patient had every evaluation performed, and in some instances the number of results available was fairly small.

Previous reports [13,14] showed that FA patients have insulin resistance, GH deficiency, and low BMD. In contrast to prior reports, we found evidence for limited first phase insulin secretion, but rarely found insulin resistance [22]. Only a few of our patients had GHD. In addition, we found that BMD was frequently normal when adjusted for height and bone size [20]. Finally, we add to evidence for thyroid dysfunction in FA. In addition, we described endocrine function in a greater number of young adults with FA than described before.

Approximately 51% of FA children were born SGA. In contrast to general population, 73% of SGA children with FA persisted with height $<-1.8$ SD, while 59% of AGA children also had height $<-1.8$ SD. Glucose intolerance in FA occurred regardless of whether they were born SGA or AGA. There is a high incidence of impaired glucose tolerance, elevated insulin levels, and overt diabetes mellitus in FA [13,14,22,23]. Elevated insulin could suggest insulin resistance; however, normal fasting insulin levels are more consistent with beta cell dysfunction leading to sluggish initial insulin release [22,23]. In FA patients without HCT, HgbA1c did not identify glucose intolerance, theoretically related to faulty glycosylation or to high fetal hemoglobin in bone marrow failure. Similarly, fructosamine was not elevated when there was glucose intolerance. HgbA1c may have more utility after HCT, when hemoglobin A concentrations are more normal. Baseline tendency toward hyperglycemia and “sluggish” insulin secretion leads most FA patients to require insulin during illness, steroid therapy, or HCT, and may contribute to poor growth.

GHD in FA has been described in case reports [11–14,24]. Prior study proposed that persons with FA have a “hypoactive hypothalamus,” leading to “partial GHD” [13]. In their report, 13 FA patients underwent overnight GH sampling and were found to have low mean GH. However, we observed no utility of overnight GH sampling in FA patients when results were compared to age/gender/pubertal stage-matched results in normal children. We identified GHD in 12% of our whole group. GH and IGF-I were not as severely affected as height. Methods for diagnosing GHD have limitations and may yield false positive results [25,26]. In overnight studies of GH, there is significant overlap between results of normal children and results of children with GHD when utilizing appropriate reference ranges based on results in normal gender-matched children at similar stages of puberty [18,25].

FA patients have a lifelong cancer risk even if their bone marrow has been corrected by HCT. It is not known whether GH therapy increases these risks; thus GH therapy in FA should be reserved for non-ambiguous diagnosis of GHD [27]. If GH therapy is used in FA, doses should be titrated to achieve mid-normal IGF-I levels [28].

Thyroid levels are abnormal in many children with FA; thyroid therapy improves growth rate [29]. Our observations and prior research suggest that thyroid hormone treatment should be initiated in FA if TSH is $>3$ mIU/L at 0800 hours and/or FT4 is $<1.0$ ng/dL [16,29–31], particularly if stature is short.

Many males with FA at all ages have small testes for age and pubertal status, most likely reflecting reduced Sertoli cell mass and spermatogenesis. Chemotherapy and radiation therapy (given in preparation for HCT) may also result in gonadal failure. Delayed onset of puberty can occur in FA; pubertal progression should be assessed at least annually after age 11 years. Pubertal hormones (LH, FSH, estradiol, or testosterone) should be measured in adolescents (Table IV).

BMD appeared low when interpreted by age, but adjusted to normal when patients’ height was taken into account [20]. Since
DXA provides a two-dimensional measurement of BMD, bone size/height affects the test result. Adjustment for bone size discrepancy from normal has been found to lead to fewer false positives [21]. No particular method of size adjustment is perfect (height age, bone age, or other method) but applying some adjustment for bone size improves accuracy of DXA interpretation. We chose to adjust for height age in children, but not for adults. Theoretically, adjustment for height age in adults would compare biologically mature but short persons to normal children not yet exposed to sex steroids, introducing a new artifact into interpretation of DXA results.

In contrast to our findings, prior studies found that all but one of 13 adults with FA had osteopenia, compared to normal for gender and age [14]. Half of FA children had reduced BMD at one year after HCT, similar to effects in other children after HCT [32]. Of note, neither study adjusted BMD interpretation for height. Our results show more normal BMD than reported previously [14], perhaps because our young adults had shorter duration of hypogonadism, and only half of our adults with DXA results had undergone HCT.

Etiology of endocrinopathies in FA is complex. Hyperglycemia and hyperinsulinemia are related to pancreatic beta cell dysfunction. Hypothyroidism is accompanied by elevated TSH and appears to be primary hypothyroidism, although central hypothyroidism is present in a few FA patients. GH insufficiency is likely of hypothalamic origin. Hypogonadism in FA represents primary gonadal failure, related to HCT in some individuals. Thus, while there is not a single unifying cause for all endocrinopathies, some endocrine secretory cells may be damaged by excessive reactive oxygen species, related to underlying impairment of DNA repair mechanisms in FA [1–3,33,34].

The high frequency of endocrine abnormalities in FA underscores importance of endocrine assessment in the routine care of these patients. Nutritional and medical causes for poor growth should be identified at young age as possible. Children with deficient insulin production may have hyperglycemia and glucosuria, contributing to poor weight gain and slow linear growth. Healthy dietary intake should be encouraged, including sufficient calcium and vitamin D and avoidance of concentrated sweets, in order to normalize serum glucose and optimize growth and bone mineralization. Children with FA who have short stature or slow growth velocity should be referred for endocrine evaluation. Baseline and annual endocrine evaluation should be performed in every person with FA (Table IV). The endocrine clinical care team should include a dietician, pediatric endocrinologist, and reproductive endocrinologist or pediatric gynecologist. If an endocrine problem is identified, early intervention may lead to improved quality of life.

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REFERENCES


TABLE IV . Recommended Endocrine Screening in Fanconi Anemia (Adapted From Ref. [27])

<table>
<thead>
<tr>
<th>Annual screening</th>
<th>Other testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid hormone</td>
<td>Bone age X-ray every 2 years (if child is small, or puberty is early or late)</td>
</tr>
<tr>
<td>Height, weight, 0800 hour TSH, FT4</td>
<td>GH stimulation test, MRI of pituitary if peak GH &lt;10 ng/ml. Bone age X-ray every 2 years</td>
</tr>
<tr>
<td>Growth hormone</td>
<td>2 hour oral glucose tolerance test with insulin levels every 2 years, or if abnormal screening (yearly if OGTT not normal)</td>
</tr>
<tr>
<td>Height, weight, IGF-I (if &gt;age 4 years), IGFBP3 (if short stature or growth rate slow)</td>
<td></td>
</tr>
<tr>
<td>Glucose and insulin</td>
<td>Pubertal staging</td>
</tr>
<tr>
<td>One-hour postprandial paired glucose and insulin.</td>
<td>LH, FSH, estradiol or testosterone every 2 years after age 12 years</td>
</tr>
<tr>
<td>After HCT, HgbA1c may be useful</td>
<td>DXA every 5 years starting at age 14 years or one year after HCT. Repeat in one year if Z-score &lt;−1 SD for age and height age</td>
</tr>
<tr>
<td>Puberty, gonadal function</td>
<td>ACTH stimulation testing (low dose) in child age &lt;2 years</td>
</tr>
<tr>
<td>Pubertal staging</td>
<td></td>
</tr>
<tr>
<td>Bone mineral</td>
<td></td>
</tr>
<tr>
<td>Dietary calcium and vitamin D intake, 25OH-vitamin D</td>
<td></td>
</tr>
<tr>
<td>Cortisol</td>
<td>None</td>
</tr>
</tbody>
</table>

Abbreviations include TSH (thyrotropin), FT4 (free thyroxine), IGF-I (insulin-like growth factor), IGFBP3 (IGF binding protein 3), GH (growth hormone), MRI (magnetic resonance imaging), HCT (hematopoietic cell transplant), HgbA1c (glycosylated hemoglobin), LH (luteinizing hormone), FSH (follicle-stimulating hormone), 25OH-vitamin D (25-hydroxy-vitamin D level), DXA (dual X-ray absorptiometry), SD [standard deviation units (Z-score) from the mean], and ACTH (adrenocorticotropic hormone).


