Case Series

Oral and Dental Findings in Children With Fanconi Anemia

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Abstract: ***Purpose:*** *The purpose of this study was to investigate the oral and dental findings in children with Fanconi anemia (FA).* ***Methods:*** *The study included 26 FA patients who came to the hospital (Hacettepe University Faculty of Medicine, Pediatric Hematology Unit) from the central region of Anatolia (17 [65%] male, 9 [35%] female; mean age=10.0±5.2 years (range=2-18; median=9 years]). Oral and radiological examinations and salivary collection were performed at the Department of Pediatric Dentistry of Hacettepe University Faculty of Dentistry.* ***Results:*** *Among 26 FA children: (a) 16 (62%) had never visited a dentist; (b) 6 (23%) had visited a dentist once; and (c) 4 (15%) had visited a dentist regularly. Furthermore: (a) only 5 children (19%) brushed their teeth regularly; (b) 7 (27%) had never brushed their teeth previously; and (c) the other 14 (54%) had brushed their teeth rarely. The prevalence of dental caries was 35% in this study's patients. Gingival examination revealed that 9 (35%) children had gingivitis and the other 17 (65%) had normal gingival health status. Examination of the oral cavity revealed that: (a) 3 children (12%) had a coated tongue; and (b) 1 (4%) had papillary atrophy. No leukoplakia or other precancerous lesion was detected in this patient group. Salivary flow rate was less than 0.7 ml/minute in 56% of the patients. No patients had a salivary pH less than 5. Salivary buffering capacity of less than 5, however, was detected in 5 patients (33%). Radiological evaluation revealed that the most common congenital dental abnormalities were: (1) microdontia (44%); (2) congenitally missing teeth (26%); (3) transposition (9%); and (4) supernumerary teeth (4%).* ***Conclusion:*** *These results demonstrate that poor oral hygiene, dental decay, gingivitis, and congenital dental abnormalities—including generalized microdontia, supernumerary teeth, transposition, and congenitally missing teeth—are common oral and dental findings in this group of Turkish children with Fanconi anemia. (Pediatr Dent 2007;29:248-52)*

KEYWORDS: ORAL FINDING, DENTAL FINDING, FANCONI APLASTIC ANEMIA, CHILDREN

Fanconi anemia (FA) is an autosomal and X chromosomal recessive DNA instability syndrome characterized by: (1) progressive bone marrow failure; (2) multiple congenital abnormalities; and (3) a predisposition to cancer.[1,2] Twelve complementation groups have been identified (A, B, C, D1, D2, E, F, G, I, J, L, and M), and the genes responsible for 11 groups have been cloned. FA-A is the most common complementation group, accounting for approximately 65% of all affected individuals.[3]

Most FA patients have many physical abnormalities, including: (1) short stature; (2) abnormal thumbs; (3) microcephaly; (4) cafe au lait; (5) hypopigmented and hyperpigmented spots; and (6) a characteristic physical appearance. Oral and dental findings in FA have been rarely reported in the literature.[4-8] The following have been previously reported in FA patients as oral findings: (1) generalized microdontia; (2) supernumerary teeth; (3) congenitally missing teeth; (4) periodontitis; and (5) gingivitis.

Oral and dental injuries constitute a source of infection and facilitate development of infections in this patient group. Additionally, the risk of squamous cell carcinoma is increased in the mucosal linings from the oral cavity to the anus, especially after the second decade.[9,10]

Recognizing oral and dental findings in FA is very important to maintain oral health status in these patients. Therefore, the purpose of this study was to evaluate the oral and dental findings in children with Fanconi anemia.

Methods

This study involved 26 FA children who were diagnosed and followed in the Pediatric Hematology Unit of the Hacettepe University Faculty of Medicine, Ankara, Turkey, between January 2004 and January 2006. Diagnosis of FA was confirmed by a study of chromosomal breakage induced by diepoxybutane (DEB) in peripheral blood lymphocytes in all of the children. Physical examinations and hematological evaluations—including complete blood count, fetal hemoglobin measurement, and bone marrow aspiration (when

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necessary)—were performed in all children diagnosed with FA. The study was performed after ethical approval was obtained from the local ethics committee of Hacettepe University Faculty of Medicine and Dentistry, and written consent was granted from each patient and/or their parents or legal guardians.

Oral and radiological examinations and salivary collection were performed at the Department of Pediatric Dentistry at the Hacettepe University Faculty of Dentistry. The patients were examined by a pediatric dentist under standard dental lighting using plain mouth mirrors and ball-ended periodontal probe. The dental assessment included clinical examination of teeth for dental decay and the gingival tissues for oral hygiene. The surfaces of all erupted teeth were assessed using the dmft/DMFT-dmfs/DMFS (decayed, missing or filled teeth/surfaces; lowercase letters for primary teeth, uppercase for permanent teeth) indices.[11]

Oral hygiene was assessed with 2 standard epidemiological indices: (1) the gingival index (GI); and (2) the plaque index (PI).[12] Erupting permanent teeth and exfoliating primary teeth were excluded from the evaluation. The GI was scored as follows:

a. 1=normal gingiva, no inflammation; discoloration or bleeding;
b. 2=mild inflammation, slight color change, mild alteration of gingival surface, no bleeding on pressure;
c. 3=moderate inflammation, erythema and swelling, bleeding on pressure; and
d. 4=severe inflammation, erythema and swelling, tendency to spontaneous bleeding, perhaps ulceration.

The PI was scored as follows:

a. 0=no plaque;
b. 1=tooth appears clean, but plaque may be removed from its gingival third with a probe;
c. 2=moderate accumulation of plaque deposits visible to the naked eye; and
d. 3=heavy accumulation of soft material filling the niche between the gingival margin and tooth surface.

Using techniques described in a previous study by Krasse,[13] saliva was collected and evaluated regarding: (1) salivary flow rate; (2) salivary pH; (3) buffering capacity; and (4) salivary *Streptococcus mutans* (*S mutans*) levels. Stimulated and unstimulated whole saliva was collected from each child.[14] The individuals were instructed not to eat for at least 2 hours before collection. A stimulated saliva sample was collected by asking the children to chew a standard piece of paraffin wax, and the collection was started after chewing for 30 seconds. Salivary flow rate was assessed as the amount of saliva per minute after a 5-minute collection period.[14] Buffering capacity of saliva was evaluated using an Orion Model 720 A (Orion Research Inc, Boston, Mass) according to the procedures described in earlier studies.[13] Unstimulated saliva samples (20µl) were:

1. collected from each child;
2. placed into microcentrifuge tubes containing 180µl of nutrient broth (Difco Laboratories, Detroit, Mich); and
3. transported to the microbiology laboratory for culturing within 1 hour.

The test tubes containing the saliva samples were dispersed in a vortex mixer for 30 seconds and serially diluted. From these serial dilutions, 0.1 ml was transferred and inoculated on Mitis Salivarius agar (Difco Laboratories, Detroit, Mich) supplemented with 0.2 U/ml bacitracin (Sigma Chemical Co, St Louis, Mo) and 1% potassium tellurite. The agar plates were incubated in air with 5% to 10% CO_2 at 37°C for 72 hours. *S mutans* ATCC 25175 was used as a reference strain. After the incubation period, 3 colonies were recovered from each plate. Species identification was based on:

1. gram staining;
2. presence of catalase enzyme;
3. biochemical properties (acid production from mannitol, sorbitol, melibiose, raffinose, starch, inulin, and dextrin);
4. hydrolysis of arginine;
5. esculin; and
6. Voges-Proskauer.

The colonies of *S mutans* were counted as CFU/ml and determined as $\log^{10}$ ([cfu+1]/ml) of saliva.

Additionally, orthopantomographic radiographs were taken for evaluation of congenital dental abnormalities. Three of 26 patients were uncooperative, and radiological evaluation could not be performed. Furthermore, some complicated procedures could not be managed in many younger patients.

SPSS software for Windows version 12.0 (SPSS, Inc, Chicago, Ill) was used to evaluate the data. Spearman's correlation test was used to compare the: (1) dmfs; (2) dmft; (3) DMFS; (4) DMFT; (5) GI; (6) PI; and (7) salivary parameters.

Results

This study included 26 patients (17 [65%] male, 9 [35%] female; mean age=10.0±5.2 years [range=2-18; median=9 years]) with the diagnosis of FA. The median follow-up duration was 5 years (range=1-13 years), and 19 children (73%) received only oxymetholone treatment during the follow-up period. Oxymetholone treatment was used in FA patients to: (1) increase erythropoietin production; (2) stimulate erythroid stem cells; and (3) increase hemoglobin levels.[1]

Among the 26 FA children: (a) 16 (62%) had never visited a dentist; (b) 6 (23%) had visited a dentist once; and (c)

4 (15%) had visited a dentist regularly. Furthermore: (a) only 5 children (19%) brushed their teeth regularly; (b) 7 (27%) had never brushed their teeth previously; and (c) the other 14 (54%) brushed their teeth rarely. The prevalence of dental caries was 35% (9/26) in this patient group. The dmft and dmfs indices were 0 (normal) in 50% (11/22), whereas the DMFS and DMFT indices were 0 (normal) in 37% (7/19) of the patients. Gingival examination revealed that:

a. 9 children (9/26, 35%) had gingivitis; and
b. the other 17 children (17/26, 65%) had normal gingival health status.

Periodontitis and alveolar bone resorption were not detected in this patient group. Examination of the oral cavity revealed that: (a) 3 children (3/26, 12%) had coated tongue; and (b) 1 child (1/26, 4%) had papillary atrophy. No leukoplakia or other precancerous lesions were detected in this patient group. The clinical data regarding dmft, dmfs, DMFT, DMFS, and gingival and plaque indices of the children are presented in Table 1.

Salivary flow rate was less than 0.7 ml/minute (xerostomia range) in 56% (9/16) of the patients. None of the patients had a salivary pH less than 5. A salivary buffering capacity of pH less than 5, however, was detected in 5 patients (5/15, 33%). Also shown in Table 1 are: (1) salivary flow rate; (2) salivary pH; (3) salivary buffering capacity; and (4) *S mutans* levels.

A correlation between PI and GI was detected (r=0.74; $P<.001$) in this patient group. There was also a correlation between salivary buffering capacity and DMFT index (r=0.79; $P=.002$) and between salivary buffering capacity and DMFS index (r=0.73; $P=.004$).

Radiological evaluation of the children revealed that the most common congenital dental abnormalities were: (1) generalized microdontia (10/23, 44%); (2) congenitally missing teeth (6/23, 26%); and (3) transposition (2/23, 9%). Distribution of congenital dental abnormalities and of abnormal teeth is presented in Table 2. According to the radiological evaluation, maxillary lateral incisor was the most common missing tooth and upper primary canine was the most common transpositioned tooth among this study's patients. Moreover, 2 supernumerary teeth were observed in 1 child (1/23, 4%).

Table 1. THE CLINICAL AND LABORATORY PARAMETERS OF A GROUP OF 26 TURKISH CHILDREN WITH FANCONI ANEMIA*

PARAMETERS	N	MEAN±(SD)	MEDIAN AND RANGE
Age (ys)	26	10.04±5.2	9.0 (2.0-23.0)
Follow-up duration (ys)	26	5.76±3.6	5.0 (1.0-13.0)
Dmft	22	2.23±2.6	0.5 (0-8.0)
Dmfs	22	3.59±5.3	0.5 (0-21.0)
DMFT	19	2.53±3.5	2.0 (0-14.0)
DMFS	19	4.53±8.8	2.0 (0-39.0)
Plaque index (PI)	26	1.17±0.5	1.1 (0.45-2.22)
Gingival index (GI)	26	1.63±0.6	1.6 (0.35-2.89)
Salivary flow rate (ml/min)	16	0.83±0.9	0.6 (0-3.8)
Salivary pH	15	7.52±0.3	7.6 (6.7-7.9)
Salivary buffering capacity (pH)	15	5.68±1.0	5.6 (4.22-7.25
Streptococcus mutans (MS) level (CFU/ml)	16	$8.6x10^6$± $17.1x10^6$	$0.5x10^6$ ($0.3-52 x10^6$)
Log_{10}MS ([cfu+1] per ml)	16	6.08±0.8	5.7 (5.4-7.7)

Discussion

Fanconi anemia is an autosomal and X chromosomal recessive disease associated with: (1) chromosomal breakage; (2) pancytopenia; (3) congenital physical abnormalities; and (4) increased risk of malignancy.[1] There are few reports of the oral and dental manifestations in FA.[3-7] In this study, the authors evaluated the oral and dental findings in FA children.

Generalized microdontia was the most common (44%) dental abnormality among FA children in the present study. The other dental abnormalities were: (1) supernumerary teeth (4%); (2) transposition (9%); and (3) congenitally missing teeth (26%).

Joho and Marechaux reported an FA patient who had generalized

microdontia and macroglossia.[15] Similarly, 10 of 23 (44%) children had generalized microdontia in the present study. Microcephaly and short stature are common congenital abnormalities in FA children. The authors observed that microdontia is also common among FA children, which may result from the microcephaly.

In a study conducted by Acikgoz et al, they found supernumerary teeth in 1 patient (N=1/15) and congenitally missing teeth in another (N=1/15), but they found no microdontia in their study group of 15 FA children.[4] In this study group—in addition to the supernumerary teeth that were observed in 1 child (4%)—congenitally missing teeth were also observed in 6 (26%) children. To the best of the authors' knowledge, the transposition, which was observed in 2 of this study's patients (9%), had not been described previously in FA patients.

A high proportion of FA patients had major characteristic congenital abnormalities such as those involving: (1) thumbs and radii; (2) kidneys; (3) head; (4) eyes; and (5) ears. Multiple congenital abnormalities of various systems—including cardiopulmonary, gastrointestinal, and genitourinary systems—are well recognized and have been described earlier in FA children.[1] In addition to these congenital abnormalities, it should be remembered that supernumerary teeth, congenitally missing teeth, transposition, and generalized microdontia are the common congenital dental abnormalities that may be observed in FA children.

The risk of squamous cell carcinoma is increased in FA patients and may be located from the oral cavity to the anus. Stem cell transplantation (SCT), the only curative treatment for FA, is suggested to increase the risk of developing solid tumors, particularly in the oral cavity. The survival in FA patients who underwent SCT was longer than that of the nontransplanted FA patients. The longer survival time and conditioning regimens, including radiotherapy, result in increased risk of developing solid tumors in transplanted FA patients.[16,17] In another study, cytogenetic characteristics of oral squamous cell carcinoma in FA were studied and it was suggested that FA genes support a caretaker function in the protection against oral carcinogenesis. In FA patients, the absence of support by FA genes and increased sensitivity to environmental DNA cross-linkers cause increased susceptibility for oral squamous cell carcinoma.[18]

In a study reported from the authors' center, 1 (26-year-old male) of the 52 FA patients developed squamous cell carcinoma of the gingiva.[2] In this study's series, no squamous cell carcinoma or even precancerous lesion was detected in any of the patients. The risk of malignancy, especially of squamous cell carcinoma, is increased in older FA patients. It was reported that more than 80% of the tumors developed in FA patients when they were at least 20 years of age. The median age of this study group was 9 years, which is too early for development of squamous cell carcinoma. Dentists should be aware of the risk of later development of squamous cell carcinoma, however, and they should follow up with FA patients in this respect.

FA children are more susceptible to infections than healthy children. Natural killer (NK) cell numbers and function have been reported to be decreased in some FA patients. Defective NK function and low numbers of NK cells, as well as neutropenia, may lead to their increased susceptibility to infection.[1,19] In the present study: (1) gingivitis was detected in 9 children (35%); (2) coated tongue was detected in 3 children (12%); and (3) papillary atrophy was detected in 1 child (4%). A salivary flow rate of less than 0.7 ml/minute (detected in 56%) and a salivary buffering capacity of less than 5 (detected in 33%) were contributory factors for developing infections. Since most of this study's patients (81%) did not brush their teeth regularly, poor oral hygiene may also have been an additional factor in the development of infections.

Some potential limitations of the present study are: (1) relatively small sample size; and (2) geographic distribution of this study's patients. The observations and results obtained from the present study, however, should be studied in larger series of FA patients for general conclusion.

Regular dental care in the mul-

Table 2. DISTRIBUTION OF CONGENITAL DENTAL ABNORMALITIES AND ABNORMAL TEETH ACCORDING TO RADIOLOGICAL EVALUATION OF THIS GROUP OF TURKISH CHILDREN WITH FANCONI ANEMIA

CASE NO.	HYPODONTIA (TOOTH NO.)	TRANSPOSITION (TOOTH NO.)
1	2, 15, 18, 29, 31	–
2	2, 4, 7, 10, 13, 15, 18, 20, 29	–
5	7, 10	C, H
7	7	–
10	2, 15	–
15	–	H
24	7, 10, 25	–

tidisciplinary management of FA should be performed by an experienced dental team during the follow-up period in this patient group. This may:

1. improve life quality;
2. decrease the infection rate; and
3. provide early detection and treatment of precancerous lesions and squamous cell carcinoma in FA patients.

Conclusions

Based on this study's results, the following conclusions can be made:

1. Poor oral hygiene, dental decay, gingivitis, and con genital dental abnormalities—including generalized microdontia, supernumerary teeth, transposition, and congenitally missing teeth—are common oral and dental findings in this group of Turkish children with Fanconi anemia (FA).
2. Dentists should be aware of the common oral and dental findings in FA children and of the risk for later development of squamous cell carcinoma.

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