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ORIGINAL ARTICLE

Fanconi's anemia: clinical and radiographic oral manifestations

MR de Araujo, M de Oliveira Ribas, ACGA Koubik, T Mattioli, AAS de Lima, BHS França

Department of Stomatology and Surgery of Pontifícia, Universidade Católica do Paraná, Paraná, Brazil

BACKGROUND: Fanconi's anemia (FA) is a rare autosomal recessive disorder characterized by progressive bone marrow failure, congenital abnormalities, and predisposition to malignancies. There are 11 genetic subtypes characterized by complementation groups – FA- A, B, C, D1, D2, E, F, G, I, J, and L.
OBJECTIVE: To evaluate and describe clinical, oral and radiographic manifestations of patients with FA.
METHODS: A quantitative analysis of clinical manifestations, oral lesions and panoramic radiographs was performed in 33 patients.
RESULTS: Clinical manifestations included melanin skin pigmentation, skin vascular and ocular anomalies. Melanin pigmentation on oral mucosa, traumatic lesions, gingival bleeding, dental biofilm and gingival alterations were the main oral manifestations that were found. Oral and clinical manifestations were not dependent on patient's sex. No significant statistical difference between females and males was detected. Dental anomalies were not remarkable either at clinical or at radiographic examinations. Although several dental anomalies were observed in patients with FA, the correlation between this disease was not established from this study. Panoramic radiographs showed agenesis, taurodontism, radicular anomalies such as dilaceration, tapering, and foreshortening.
CONCLUSION: This study suggests that gingival alterations are associated with defective oral hygiene but not with hematologic conditions. It also helps elucidate oral manifestations of FA. These patients are living longer and need special dental care.
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Keywords: oral; manifestation; mouth; radiography; Fanconi's anemia

Correspondence: MR de Araujo, MSC, Rua Aviador Mário Fundagem Nogueira 3-09 apartamento 604, Jardim América, Bauru, São Paulo, Brazil. Tel: +55 14 3226 3906, Fax: +55 41 3357 8179, E-mail: melissararaujo@hotmail.com (or) melissararaujo@gmail.com
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Introduction

Fanconi's anemia (FA) is a rare autosomal recessive disorder characterized by multiple congenital abnormalities, bone marrow failure, and susceptibility to malignancies (D'Andrea and Grompe, 1997), especially leukemia, solid tumors such as liver tumors and squamous cell carcinoma of mucous areas (Kutler *et al*, 2003).

Patients with FA are hypersensitive to DNA cross-linking agents such as diepoxybutane (DEB) and mytomicin C (Alter, 2002). The diagnosis of FA is based on spontaneous chromosomal breakage on DEB presence. The DEB test is highly sensitive and specific to FA (D'Andrea and Grompe, 1997). To date, 11 distinct subtypes of FA have been identified, described as complementation groups A, B, C, D_1, D_2, E, F, G, L, I, and J, all of which, except for group B, have been mapped to specific gene products (Nisbet-Brown, 2004). The specific role of mutations in the FA genes in the pathogenesis of birth defects, bone marrow failure, or oncogenesis is not clear yet (Alter, 2002).

Magdalena *et al* (2005) standardized a precise screening test using polymerase chain reaction assay for a specific mutation (3788-3790del in exon 38 of the gene FANCA) in Brazilian FA patients. These authors detected the mutation in 30% of the 80 patients studied, showing a high frequency of the FANCA 3788-3790del mutation in Brazilian FA patients.

The clinical manifestations of FA may be related either to congenital abnormalities or to later hematologic disturbances (Kerviller *et al*, 2000). The clinical course of FA usually begins during the first decade of life. The hematologic complications are progressively higher pancytopenia, anemia, thrombocytopenia, leukopenia, macrocytosis, and fetal-like erythropoiesis (D'Andrea and Grompe, 1997; Pasquini and Zanis Neto, 2001). Physical anomalies are frequent, such as altered skin pigmentation and/or cafe-au-lait spots, short stature, thumb and radial anomalies, structural renal defects, microcephaly, and development delay (Alter, 2002). Skin pigmentations are caused by melanin deposition, mainly consisting of cafe-au-lait

spots and hypo- or hyperpigmented areas (Kerviller *et al*, 2000).

Treatment falls into four categories: androgen therapy, synthetic growth factor, bone marrow transplantation, and gene therapy. The androgenic agents stimulate erythropoiesis and make the hematopoietic stem cells more responsive to differentiation (Kutler *et al*, 2003). Synthetic growth factors are glycoproteins that stimulate the production of cells that are vital parts of the blood system; they are granulocyte-macrophage colony stimulating factor, granulocyte colony stimulating factor, and erythropoietin (D'Andrea and Grompe, 1997; Kutler *et al*, 2003). Bone marrow transplantation is an effective therapy for FA and the only therapeutic modality able to bring hematologic cure (Gluckman *et al*, 1995). Gene therapy studies the introduction of healthy genes into the patient's body at the right cellular location (Dos Santos *et al*, 1994).

Oral manifestations

There are a few reports about oral manifestations of FA.

Schofield and Abbot (1978) described a case of a woman with microcephaly, extreme gingival inflammation and recession.

Joho and Marechaux (1979) described a case of a woman with macroglossia and generalized microdontia with enamel hypoplasia, which may be caused by FA.

Schofield and Worth (1980) reported a case of a lady with severe generalized periodontitis, gingival inflammation and recession associated with bad hematologic condition. The patient also had ulceration on her tongue diagnosed as an invasive squamous cell carcinoma.

Opinya *et al* (1988) presented a case of a 24-year-old male patient with black hyperpigmentation on the oral mucosa and palate, generalized gingival inflammation, bleeding on probing and poor oral hygiene. The right third molar showed a crown deformed and smaller than the normal size.

Lau *et al* (1988) reported a case of a boy with hypoplasia, large enamel opacities, and hypodontia.

Morizaki *et al* (1989) described a case of a boy with retarded development of permanent dentition by 3 or 4 years. All teeth were normal in size and shape.

Nowzari *et al* (2001) described a case of a 11-year-old boy with severe gingivitis and periodontitis characterized by pain, redness, bleeding, and loss of periodontal attachment around the teeth.

Yalman *et al* (2001) evaluated 16 children undergoing bone marrow transplantation for aplastic anemia (AA) and found significantly higher scores for plaque and gingival index, probing depth and bleeding on probing in non-transplanted children compared with bone marrow transplanted children. This oral condition was associated with poor oral hygiene procedures during the period of intense immunosuppression.

Brennan *et al* (2001) evaluated the prevalence and risks of oral complications in AA and showed 27% of the patients with oral petechiae. These were the most common intra-oral finding in patients with AA. However, there was no difference between platelet counts of the AA patients with or without petechial hemorrhages. Minor trauma from deglutition and mastication may have contributed to oral mucosal petechiae.

Patients and methods

This study consisted of 33 patients with FA aged 2–28 years, who were diagnosed and followed up at the Hematology Department of the Clinical Federal University Hospital of Paraná. Patients were diagnosed based on the presence of congenital malformations known to be associated with FA and hematologic manifestations. An accurate diagnosis was made by DEB test. None of the patients had received bone marrow transplantation. Fifteen patients were male and 18 were female. Before oral examination patients or their parents were asked to sign an informed consent form.

A dentist examined all the patients clinically, and panoramic radiographs were taken. Oral examination was performed following Castro's (2000) protocol of normality, which describes normal aspects of the mouth. Parameters of normality of oral health were no signs of alterations on oral tissues or lesions on oral mucosa. Gingivitis was evaluated by oral examination of the gingiva and aspects of normality were also considered, such as no signs of inflammation, no spontaneous bleeding, no bleeding on probing, and no gingival enlargement. Gingival tissues should have gingival stippling. Periodontitis was considered whenever teeth mobility, gingival recession, or loss of periodontal attachment on probing were detected. On oral examination the presence of oral biofilm was evaluated and characterized with a plaque index. For the plaque index the following scale was considered: zero (absence of plaque), 1 (plaque visualized after probing on gingival margin), 2 (plaque clinically visible), and 3 (abundant plaque) (Lindhe, 1997). During the plaque index measurement the absence of plaque was considered when the index was zero and the presence of plaque when the indices were 1, 2 or 3.

Panoramic radiographs were taken with SIEMENS ORTHOPHOS (CD®) (Siemens, Benshein, Germany) following the manufacturer's instructions by the same radiologist.

Data collection included a review of medical charts (which were filled out by the physician responsible for the bone marrow transplantation service) and taking notes of given medication, hematologic condition records and platelet count. Physical manifestations of FA such as skeletal abnormalities and skin pigmentations were evaluated. The medical charts include patient's identification (address and age of the patient, name of parents, city, date of birth, skin color), anamnesis, medical history (medication taken), physical examination, hematologic conditions, and a description of general medical status of the patient.

Results

Skeletal anomalies were present in 57.57% (19) of the patients. Among these, the most frequent were hand

and/or radial anomalies in 45.45% (15 patients), anomalies on thumbs in 12.12% (4 patients) and anomalies on feet in 3.03% (1 patient) of the cases (Figure 1).

Skin pigmentation was seen in 81.81% (27) of the patients, such as cafe-au-lait spots, hypo- and hyperpigmented areas. Petechiae and hematoma on skin were detected in 72.72% (24) of the patients. Anomalies on eyes such as epicanthal folds, strabismus, and hypertelorism were seen in 60.60% (20) of the patients. Only 3.03% (one) of the patients did not show any skin manifestation.

All anomalies were submitted to statistical analyses and did not show any relation to patient's sex ($P \leq 0.05$ – Fisher's test, chi-square test).

The main oral findings were: gingival bleeding in 48.48% (16) of the patients; melanin pigmentation on the tongue, floor of mouth and gingiva in 45.45% (15 patients); calculus or dental biofilm in 48.48% (16 patients) demonstrating poor oral hygiene; gingivitis or periodontitis in 36.36% (12 patients) (Figure 2); traumatic lesions (lesions like hematoma or purpura caused by trauma, not ulcerated in these patients) in 30.30% (10 patients); teeth color (Figure 3) and shape alterations in 12.12% (four patients) and 9.09% (three patients), respectively; recurrent aphthous ulcers in 9.09% (three patients). Other less prevalent lesions were furred tongue, dental trauma, and verruca vulgaris. Oral manifestations were not statistically dependent on patient's sex ($P \leq 0.05$ – Fisher test, chi-square test).

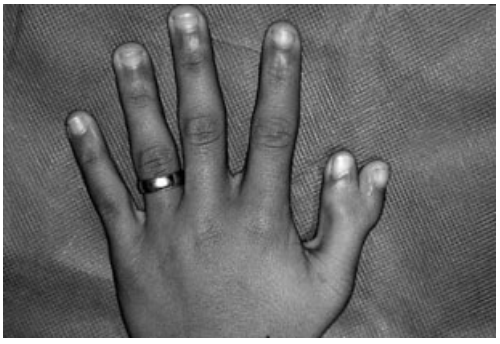


Figure 1 A bifid thumb of a 12-year-old girl with Fanconi's anemia

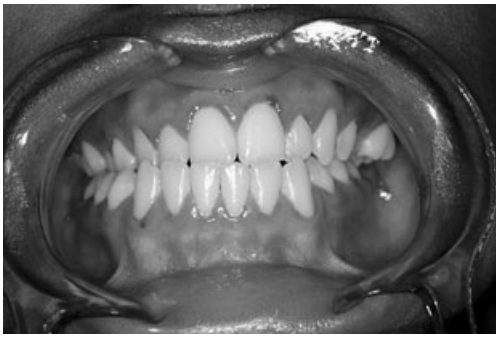


Figure 2 Gingival enlargement and bleeding points demonstrating inflammation on gingiva of a 13 year-old boy

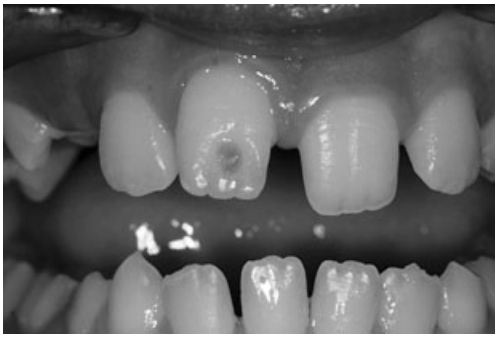


Figure 3 A brownish color and a creasy surface of right superior central incisor in a boy. The patient did not refer history of trauma and no other teeth showed this alteration

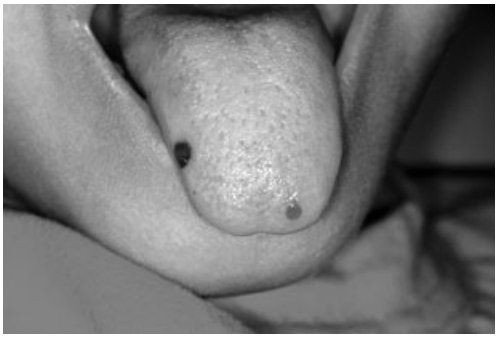
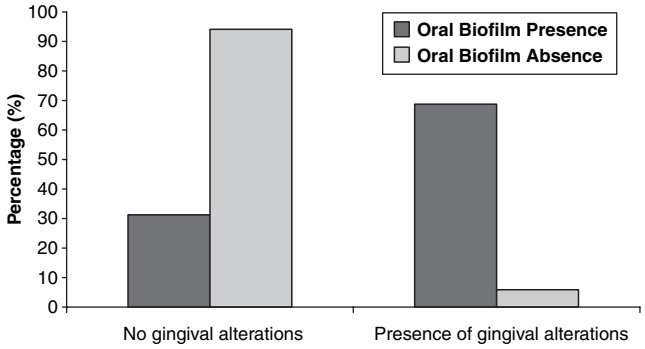


Figure 4 Purpura on the tongue of a 5-year-old girl with abnormal hematologic conditions observed after a trauma during chewing

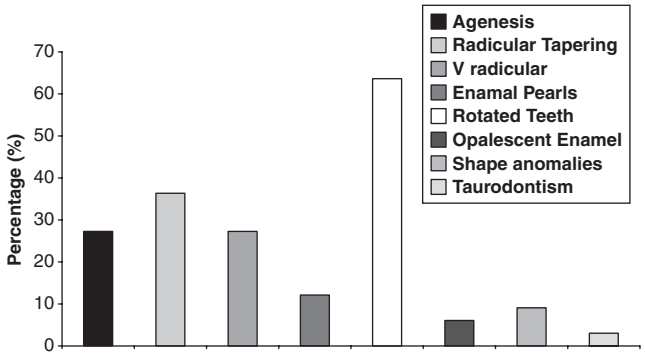
Oral, skin and skeletal anomalies were not interdependent (Fisher test – $P \leq 0.05$).

The platelet count refers to the day of oral examination. The median platelet counts of patients were analyzed using Kolmogorov–Smirnov test and the Mann–Whitney *U*-test ($P \leq 0.05$). The median platelet count in patients with oral traumatic lesions (Figure 4) was 22 900 mm^{-3} and when those lesions were not present the platelet count was 66 478 mm^{-3}, demonstrating significant statistical difference. The median platelet count when gingival bleeding was present was 50 437 mm^{-3} and when it was absent the platelet count was 55 941 mm^{-3}. After statistical analysis, platelet count was significantly lower in the presence of gingival bleeding. However, gingivitis and periodontitis were not associated with lower platelet count. The median platelet count in the presence of inflammations was 52 582 mm^{-3} and when it was absent this count was 53 666 mm^{-3}. The platelet count could not be statistically associated with gingivitis and periodontitis. Therefore, oral hygiene was also evaluated. Patients were examined for the presence or absence of oral biofilm. Fisher and chi-square tests showed that 68.75% of the patients demonstrated gingival inflammation when oral hygiene was poor. In addition, 94.12% (16 patients) of the patients with periodontal health did not show dental biofilm (Graph 1).

Panoramic radiographs were taken from each patient. The most frequent findings were: rotated permanent



Graph 1 Association between oral biofilm and gingival alterations



Graph 2 Panoramic radiographic findings in Fanconi's anemia

teeth in 63.64% (21 patients) of the panoramic radiographs, radicular tapering in 36.36% (12 patients), agenesis in 27.28% (nine patients), 'V' formation on root apex during radicular development in 27.28% (nine patients), enamel pearl in first molars in 12.12% (four patients), abnormal shape of the teeth in 9.09% (three patients), opalescent enamel in 6.06% (two patients), and taurodontism in 3.03% (one patient) of the panoramic radiographs (Graph 2).

Discussion

To date, conclusions over oral manifestations of FA have been based on case reports, and the prevalence data on oral manifestations have not yet been established. This study is more complete in the sense that a greater number of non-bone marrow transplanted patients were examined.

The male-to-female ratio in FA literature cases is about 1.2:1, even though equal numbers are expected in autosomal recessive disorders (Pasquini and Zanis Neto, 2001; Alter, 2002). Skeletal anomalies were seen in 57.57% and cafe-au-lait spots were noted in 81.81% of the patients. These findings are in close agreement to Alter's (2002) – skin pigmentation in more than 50%, and radii and thumb anomalies in 40% of the patients.

Dental anomalies were not frequent in this study; no cases of microdontia were identified, as Joho and Marechaux (1979) reported in a previous case suggesting that the cause could be FA. On oral examination, a brownish central superior incisor with a creasy surface was found only in one patient, who had no history of trauma (Figure 3). 9.1% of the patients showed anomaly on teeth anatomy on panoramic radiographs. Dental anomalies were not seen, contrary to Opinya *et al* (1988). Agenesis was detected by Joho and Marechaux (1979) and Lau *et al* (1988) on their report of cases. Dental anomalies were not frequent in this study except for root tapering, V-root formation, and agenesis.

On panoramic radiographs, radicular tapering, 'V' formation on root apex, and abnormal teeth shape were observed; nevertheless, permanent teeth germs were found to be normal in number and shape (Morizaki *et al*, 1989). Only two cases of enamel opalescence were noted, but no other anomaly, such as enamel hypoplasia, was described (Joho and Marechaux, 1979).

Gingival bleeding was another common manifestation associated with decreased platelet level seen in FA patients (Schofield and Worth, 1980). Gingivitis and periodontitis were seen in 36.36% of the patients. Nevertheless, they were not associated with lower platelet count because the median platelet count did not differ in the presence and absence of periodontal alterations, and they were related to poor oral hygiene (Schofield and Abbot, 1978; Schofield and Worth, 1980; Opinya *et al*, 1988; Brennan *et al*, 2001; Nowzari *et al*, 2001; Yalman *et al*, 2001). This study found the worst oral health status in a patient with mental retardation. Oral traumatic and petechial hemorrhage lesions were seen in 30.30% of the patients and they were associated with decreased platelet level (Schofield and Abbot, 1978). On the other hand, in AA patients, these manifestations were not associated with platelet level (Brennan *et al*, 2001).

This study elucidates oral manifestations of FA. This clinical and radiographic analysis shows that gingival inflammation is associated with poor oral hygiene, but not with hematologic conditions. However, oral traumatic lesion and petechial hemorrhage were more frequent in patients whose hematologic conditions were worse. Systemic control attention should be given to these patients, especially dental care and prevention from the beginning of the medical therapy. In addition, effective treatment protocols should be implemented.

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