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Fanconi's Anemia: A Review and Dental Considerations in Pediatric Patients

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Abstract **Review Article**

Fanconi's anemia (FA) is an autosomal recessive disorder associated with many systemic problems. A thorough diagnosis of FA in dental clinical practice is important because this disease can compromise the growth and development of the entire stomatognathic system. However, the literature shows that each case has its own peculiarities, which hinder the diagnosis of FA. The present article presents manifestations of FA together with the management of pediatric dental problems associated with FA.

Keywords: Fanconi's Anemia, Oral Manifestations, Dental Management.

INTRODUCTION

Fanconi's anemia (FA) is an autosomal recessive disorder associated with a very high frequency of bone marrow failure, leukemia, and squamous cell carcinoma. A fanconis anemia patient will show many other manifestations which includes severe bith defects, chromosomal instability and defected DNA repair. Fanconi's anemia (FA) is a rare disease with an approximate prevalence of 1:350,000 births, affecting males twofold more than females [1- 3]. FA can cause blood disorders (due to progressive bone marrow failure), bone marrow fibrosis, leukopenia and thrombocytopenia, as well as multiple congenital abnormalities, development disorders and an increased predisposition to malignant tumors [4, 5]. Approximately one third of affected individuals exhibit no congenital signs of the disease; diagnosis in such cases is generally determined after the first decade of life, when development abnormalities become apparent [2-6]. Most of these patients show birth defects that can involve any system of the body with little or no predilection or probability. Approximately one fourth of the patients are born with structural renal malformation associated with dermal hyperpigmentations. Some patients are born with cardiac defects- most commonly ventricular septal defects (VSD), bone marrow failiure usually begins at 7 year of age with a range usually from 3- 12 years. A thorough diagnosis of FA in the dental clinical practice is important because this disease can compromise the growth and development of the entire stomatognathic system. However, the literature shows that each case has its own peculiarities which make it difficult to follow a standardized diagnostic protocol for oral manifestations associated with FA.

Biological Signaling of Fanconis Anemia

FA is defined by its cellular hypersensitivity to DNA cross-linking agent such as diepoxybutane (DEB) and mitomycin (MML). Presence of mutations in one of the different genes can bring about the emergence of the disease. FA is divided to 8 complementary groups (A, B, C, D1, D2, E, F, G), with each group having in common the cellular hypersensitivity to cross-linking agent. In the International Fanconi Anemia Registry (IFAR) complementation group A (65%), C (15%) and G (10%) are the most common [7]. The FA genes (genes that have been found to be mutated in FA patients) are called FANC, the most frequent being FANCA, FANCC, FANCG, and FANCD2. Except for the very rare FANCB, which is located on the X chromosome, all other FANC genes are autosomic and the disease is recessive (Table No.1). There are typically several clinical stages in FA that are related to age. At birth and early childhood, only physical signs are present and

range from discreet to extensive. To date, 15 FA genes have been identified. Products of the FA genes function in a common DNA repair signalling pathway, which closely cooperates with other DNA repair proteins for resolving DNA interstrand cross-links (ICLs) during replication. The protein products of eight genes form a complex which permits ubiquitination of the FANCD2 protein, which in turn interacts with downstream FA gene products in the FA/BRCA DNA repair pathway.

Importance of Early Diagnosis

Early diagnosis of FA permits the exclusion of other diseases and precludes inappropriate management of hematologic disease (aplastic anemia [AA], myelodysplastic syndrome [MDS], acute myeloid leukemia [AML]), and permits appropriate consideration of remadies like hematopoitic growth factors, stem cell transplant or supportive care.If diagnosis of FA is known, surgical care for orthodontic reasons, renal anomalies are optimized. So to avoid development of significant cytopenias surgeries must be accelarated. Physicians can offer targeted cancer surveillance and early aggressive surgery for solid tumors. Experts can discuss realistic prognoses. Genetic counseling is imperative, because of the 25% risk of FA in each subsequent pregnancy.

DIAGNOSIS

It is crucial for family counseling and treatment centers to identify patients with FA. Physical abnormalities may be subtle (Table No.2). Many FA patients during their first and second decades of life develop BMF, and for the majority of patients, the suspicion of FA will only be made after the onset of pancytopenia. In some patients, the underlying diagnosis of FA is not known until MDS/AML occurs. Increases of fetal hemoglobin, serum alpha- fetoprotein, and macrocytosis are commonly noted in FA, but their absence does not rule out the disease (although not specific for FA, they may help to distinguish an inherited from an acquired BMF). A significant, and probably underestimated, number of patients do not develop overt BMF but still have an increased risk of malignancies [8]. Fanconi's anemia is under- diagnosed probably because of lack of knowledge about the signs and symptoms of the disease. Blood diepoxy butane analysis to detect chromosomal breakage and tendency of rearrangement can distinguish between Fanconi's anemia and diseases with similar presentations. Before birth analysis can be done by analyzing chorionic villus samples, performed in the tenth to twelfth week of gestation or by amniocentesis, performed in the fifteenth to seventeenth week of gestation, as normally appearing siblings also can either be a carrier or can be affected by the condition, siblings of patients with Fanconi's anemia should also receive the chromosome breakage test.

ORAL MANIFESTATIONS

The main FA - associated oral manifestations reported in the literature were gingivitis (41.5%), periodontitis (22.3%), rotated teeth (22.3%) and agenesis (20.2%). Tekcicek M *et al*., mentioned poor oral hygiene, dental decay, gingivitis and congenital dental abnormalities including microdontia, supernumerary teeth, transposition, and congenitally missing teeth: as some of the common oral and dental findings in this group [10]. The high predisposition to periodontal disease and gingivitis in patients with FA may be related to the frequent immune system deficiency, anemia and leucopenia in affected individuals. Moreover, FA treatment with immunosuppressant agents, such as corticosteroids, may further reduce the immunological defense leading to higher risk for periodontal disease [11]. A low number of platelets may also be associated with gingival bleeding and can be severe states of risk in conditions where platelet counts are very low [3]. However, in 33 patients with FA, Araújo *et al*., [12], found that deficient oral hygiene was the most common factor associated with periodontal disease and gingivitis, and no significant association of number of platelets was found with periodontal disease or gingivitis. Although several dental anomalies were observed in FA patients no correlation were ruled out from the above mentioned studies. Few abnormalities like taurodontism root anomalies and agenesis of dentition were observed radiographically. Beside dental alterations, FA causes congenital disorders, such as bifid thumbs, malformations of hands and arms, splotches on the skin, gastrointestinal disorders and genital anomalies [2- 13]. Developmental disorders may also occur, such as microcephaly and growth deficiency. The short stature of these patients is related to deficiency of growth hormone, which affects approximately 81% of FA individuals [14]. Koubik *et al*., [14], found that skeletal and dental age in patients with FA was lower than their chronological age. In patients with FA there is a high risk (11.7%) for development of oral squamous cell carcinoma [2- 15]. Öksüzoglu and Yalçın [16], found that [14], out of 40 FA cases with squamous cell carcinoma had lesions on the tongue. In the case reported here, there was no lesion indicative of squamous cell carcinoma or any other apparent lesions. Patients with FA have a short life expectancy, generally three decades, due to occurrence of severe health problems, such as multiple bone marrow failure, leukemia and tumor [14]. Transplantation is the definitive treatment when progressive bone marrow failure occurs, but the necessary procedures, such as chemotherapy, use of immunosuppressant agents and radiotherapy, predispose to further development of carcinomas, particularly in the head and neck region.

General Treatment Protocol and Dental Considerations

Classical systemic treatment protocols for FA falls into 4 categories: bone marrow transplantation, androgen therapy, synthetic growth factors, and gene therapy. A successful bone marrow transplant or umbilical cord blood infusion can correct problems related to anemia, neutropenia, thrombocytopenia, myelodysplasia, or leukemia; however, patients can still

suffer from problems related to other organs or systems [17]. The prognosis for transplant is best for young patients with uncomplicated aplastic anemia who are in otherwise good clinical condition [9- 17], Between 50% and 75% of patients respond to oxymetholone or other types of androgen therapy that entail artificial male hormones to stimulate production of one or more types of blood cells. Androgens prolong the lives of many patients but are not a cure and most patients eventually fail to respond to androgens [18]. In the recent years hematopoietic growth factors have been used to further stimulate the production of cells that are vital parts of the blood system. Although gene therapy is not yet a reality, gene therapists have been studying the introduction of the healthy gene into the patient's body at the right cellular location. In the future it may be possible to accomplish autologous transplantation of bone marrow that has been genetically corrected which imparts a better health and increase the life expectancy of a FA patient [19]. An awareness of the signs and symptoms of Fanconi's anemia is an important aspect of dental management of this constellation of conditions. Though several genes have been identified it is important for an effective genetic counseling beforehand that would benefit in the future treatment modalities. Neutropenia is a sign in this disorder, and its treatment leads to an increased susceptibility to infection; mucosal bleeding and bruises are seen due to thrombocytopenia. Sepsis and haemorrhage correspond with both the complications and is the main cause of death in these patients. The oral cavity is a common site of these complications. Hence early detection and treatment of oral lesions are mandatory. All standard haematological test should be carried out to rule out the blood-related diathesis before the introduction of any invasive procedure at the dental office. Patients with FA are more prone to get infections, so proper precautions should be taken to avoid any situation which would put them at risk of infection or bleeding. Dentists can postpone dental treatment procedures until the patient's white blood cell count rises to the normal level. Antibacterial mouthwash and oral antibiotics must be prescribed before dental procedures. Anti fibrinolytics may reduce the risk of unwanted bleeding during major dental treatments [20]. Since the bleeding tendencies are more in these patients before any invasive procedure or minor surgical procedure the level of thrombocytes should be assessed and should be maintained at optimum quantity to achieve proper haemostasis. If the desired levels of platelets are not achieved, a platelet replenish therapy has to be advocated well prior to the desired treatment procedures. In case of extractions or minor surgeries use of local haemostatic agents like BLOTOCLOT/ Gelfoam/ bone wax/ surgical will be beneficial in achieving complete haemostasis. Chronic periodontitis is a severe focal infection and considered a potential risk of systemic infection in patients with FA. Therefore, some clinicians advocate using antibiotic prophylaxis in periodontal treatments in order to reduce the risk of systemic infection. Management of periodontal problems are challenging in patients with FA as the bleeding tendency is more. A comprehensive clinical examination should be performed to determine the number of remaining teeth, probing depth for each tooth, level of the mucogingival junction and the width of keratinised gingiva. Full mouth radiographic evaluation is always beneficial to examine and evaluation of alveolar bone loss. Full mouth rehabilitation also includes the removal of dental caries which is initiated as atraumatic as possible. Tooth extractions are preferred to pulp therapies so as to effectively reduce the chance for infections to spread to more periapically which could cause more complications to immunosuppressive patients. Also the chance for reinfection and pain will cause more discomfort to the patient if effective pulp therapy is not carried out. The choice of restorative material could type IX GIC or composite restorative materials. Effective oral health measures include the caries risk assessment which includes the assessment of salivary quantity, quality, buffer capacity and plaque index. Based on the readings a proper oral hygiene protocol is implemented which will benefit the patient from exposure to new lesions or progression of the existing lesions. Oral rehabilitative treatment includes RPD s and crowns can be given with proper care and a special interest in oral hygiene measures. RPDs should be constructed in such a way that it should serve proper form and function as well as should cause minimum trauma to the oral mucosa. Hence it is mandatory to keep all the margins rounded off. Home and in-office oral hygiene measures also include fluoride therapy which can be performed using special trays at least once a day. The patient is instructed to place a sufficient amount of fluoride gel onto the trays for 5 minutes immediately following brushing and to continue this preventive method throughout. Home oral hygiene measures should include fluoridated toothpaste and fluoride mouth rinse which will serve as an effective barrier to protect the teeth as well as the gingival from harmful loads of bacterial plaque [20]. Objectives of periodontal treatment for a patient with FA are to prevent infection and manage the hemorrhage— bleeding exaggerated locally or systemically by infection or due to bone marrow depression. The clinician should evaluate a complete hematologic test at each recall visit in coordination with the patient's physician to ensure the complete blood picture.

CONCLUSION

Patients with FA require close follow-up of an interdisciplinary team, including an endocrinologist for the assessment and treatment of developmental disorders, a hematologist for the control of anemia and an oncologist for the diagnosis and treatment of tumors. This critical review of the literature reveals a heterogeneous pattern regarding the oral manifestations and treatment considerations of FA, which requires that the dentist has appropriate training and participates in the interdisciplinary team responsible for the diagnosis and treatment of these individuals.

Table 1: genes identified in Fanconi Anemia

CONDITION	GENES IDENTIFIED
Fanconi's anemia	FANCA, FANCB, FANCC, FANCD1/BRCA2, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCJ/BRIP1, FANCL, FANCM, FANCN/PALB2, FANCO/ RAD51C, and FANCP/SL

Table 2: Physical anomalies in Fanconi Anemia

Skin	**Generalized hyperpigmentation on the trunk, neck, intertriginous areas, cafe au lait spots**
Body	Microsomia: Short stature
Upper Limbs: Thumbs	Absent or hypoplastic, bifid, rudimentary, attached by a thread, triphalangeal
Lower Limbs Feet Legs	Toe syndactyly, abnormal toes. Congenital hip dislocation
Gonads Males Females	Hypogenitalia, undescended testes, hypospadias, micropenis Hypogenitalia, bicornuate uterus, abnormal menstrual cycles
Other skeletal Head and face	Microcephaly, micrognathia, Triangular
Neck	Sprengel, Klippel-Fiel
Spine	Spina bifida (thoracic, lumbar. cervical, occultsacral), Scoliosis, abnormal ribs, sacrococcygeal sinus
Eyes	Ectopic or pelvic, abnormal, horseshoe, hypoplastic
Ears	Deaf (usually conductive), abnormal shape, atresia, abnormal middle ear
Renal	Ectopic or pelvic, abnormal, horseshoe, hypoplastic
Gastrointestinal	High- arch palate, atresia (esophagus,duodenum, jejunum), imperforate anus, tracheo-esophageal fistula, Meckel diverticulum, umbilical hernia, hypoplastic uvula, abnormal biliary ducts, megacolon, abdominal diastasis, Budd- Chiari syndrome.
Cardiopulmonary	congenital heart defects
Hematology	AA(aplastic anemia), MDS (myelodysplasticsyndrome), AML(acute myeloid leukemia), single cytopenia/ macrocytic red cells
Solid Tumors	Head, neck, esophageal, and gynecological squamous cell carcinomas and liver tumors.

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