Tooth developmental anomalies in severe combined immunodeficiency disease and juvenile myelomonocytic leukemia: common clinical features and treatment outcomes

Abstract

Background Human Severe Combined Immunodeficiency (SCID) is a prenatal disorder of T lymphocyte development that depends on the expression of numerous genes. Juvenile myelomonocytic leukemia (JMML), previously known as juvenile chronic myeloid leukemia (JCML), is a rare, myelodysplastic/myeloproliferative disease typically presenting in early childhood.

Case Reports Two cases are described of immunodeficiency disorders, both treated with chemotherapeutic drugs (Busulfan plus cyclophosphamide) before bone marrow transplantation. After treatment, these two different cases showed several similar oral lesions: microdontia, root alterations, numerous tooth ageneses, incomplete calcification, enamel hypoplasia, premature apexification and hypodontia. Both subjects underwent dental and orthodontic treatment. The first phase comprised orthopaedic treatment using a removable appliance (Interim-G®) followed by rapid palatal expansion; in the second phase patients underwent tooth extraction and were treated using fixed appliances for 19 and 26 months, respectively (mean 2 years) to obtain final alignment and maximum intercuspation. In the third and final phase, reconstruction of malformed teeth was completed, and implant-supported prostheses were applied.

Conclusion The difficulties of managing and treating these diseases are discussed, with particular focus on tooth anomalies and malocclusion disorders. Collaboration between dentist and paediatrician in dealing with patients with a variety of oral lesions and tooth anomalies is important in order to prevent any other possible tooth lesions and ensure correct jaw development.

Keywords Juvenile Myelomonocytic Leukemia; Severe Combined Immunodeficiency; Tooth agenesis; Tooth anomalies.

Introduction

Severe Combined Immunodeficiency Disease (SCID) may be considered to be a primary immunodeficiency, usually being based on genetic alterations; it is characterised by an altered count and function of lymphocytes T and B. Children with this disease show defective growth and are repeatedly infected by bacteria, viruses and other opportunistic pathogens. Genetic alterations that can cause SCID have been described, and may be summarized as:

- defects of the lymphocyte receptors;
- defects of the intracellular signaling molecules;
- defects of the transcription enzymes;
- defects of the enzymes of purine metabolism, such as adenosine deaminase (ADA) and purine nucleoside phosphorylase (PNP).

The incidence of SCID is between 1/50000 and 1/75000 live births [Fischer et al., 1997]. Without bone-marrow transplantation, patients die during the first year of life [Friedrich, 1996]; they generally acquire infections during the first three months, with rash or erythema on the legs where the diaper ends, due to candida or monilia. Even if growth and bone development may progress normally during the first three months, after that period an alteration of normal growth patterns is seen.

Some of these children present a measles-like skin rash immediately after birth, due to the transplacental diffusion of lymphocytes from the mother to the newborn baby, which may cause a graft-versus-host reaction (GFHR). If the patient becomes infected by herpes virus, adenovirus...
or cytomegalovirus, death may supervene within a few days. Diagnosis of severe combined immunodeficiency disease should be considered, and must be treated as a severe emergency; this disorder may lead very rapidly to the patient’s death, although the infant can be treated by restoring a correct immune system through bone-marrow transplantation [Atkinson et al., 2000; Szczawinska-Poplonyk et al., 2009]. Infants affected by SCID typically have severe lymphopenia (lymphocytes <1000 per µl).

Oral manifestations currently reported in the literature include oral infections due to candida, herpes infections, recurrent ulcers of the oral mucosa and tongue, and necrotising gengivitis [Jaffe, 1991; Antoine, 2003; Hoffmann 2009].

Chronic Myeloid Leukaemia (CML) is a bone-marrow stem-cell deficiency characterised by severe accumulation of granulocytes of differing degrees of maturation, mainly in the bone marrow, but also in the extra-marrow area, as well as in the blood, spleen and liver. From the genetic standpoint, in 95% of patients the presence of the Philadelphia chromosome has been demonstrated (1969); this is derived from the translocation of genes ABL and BCR, located on chromosomes 9 and 22, and leads to the leukemic differentiation of other normal stem cells [Hoffmann, 2009]. This is caused by an alteration of stem-cell DNA and may be clinically expressed in adult patients as well as in children: it is much common in adults, with a predilection for the male gender 3:2 at age 40-50.

CML may account for 15-20% of known cases of adult leukemia and 4% of childhood leukemias; its incidence increases with age (1 case in 1,000,000 among children aged <10 years; 1:100,000 adults aged < 40 years; 1:10,000 adults aged < 80 years) [Hasle et al., 2003]. It may be considered to have three main stages [Millot et al., 2003]:

1) the chronic stage (lasting 3-5 years), or first phase, characterised by a stable clinical aspect, with few if any symptoms (e.g. abdominal pain, pallor, tiredness, weight loss, anorexia, nocturnal sweating);
2) the accelerated phase (lasting weeks or months), an intermediate phase during which there is a worsening of clinical values (splenomegaly, arthralgia, asthenia, fever) and blood chemistry values (leucocytosis with immature granulocytes and a very marked increase in the number of basophilis and eosinophilis, low levels of leukocytic alkaline phosphatase, high blood/serum levels of uricemia, LDH, vitamin B12 and histamine);
3) the blastic stage (if therapy fails, this stage lasts no more than a few months); the last phase, characterised by pain at the spleen (infarction), lymphadenopathy, hemorrhage, fever, arthralgia, myalgia with characteristics of acute leukemia.

At onset, CML may be entirely asymptomatic: most patients only notice a slow but progressive decline in their general health, associated with skin pallor, fatigue, breathlessness at the slightest effort, heavy feeling at the left flank. Clinically, the most frequent finding is enlarged spleen, which may cause a sensation of abdominal tension and early satiety after meals; at the oral cavity it manifests with lymphadenopathy, pain at the larynx, mouth ulcer, bleeding and hypertrophy of the gums [Nikoui and Lalonde, 1996; Hou et al., 1997; Cousin,1997].

Diagnosis of CML is frequently achieved by chance during the chronic phase of the disease (85% of cases), during routine medical checkups (e.g. ECM) and/or investigations for other diseases. Depending on the severity and prognosis of CML, therapy may include allogenic bone marrow transplant and/or of stem cells from a HLA compatible donor (curative if performed at an early phase of the disease), chemotherapy, antineoplastic immunosuppressive drugs (e.g. busulfan, hydroxy-urea, INF-α, imatinib), irradiation of the spleen, and splenectomy [Goldmann and Melo, 2003; Ding et al., 2010].

The juvenile form (JCML/JMML) in particular is a rare neoplasm, without the acquired chromosome anomaly typical of the adult form (Philadelphia chromosome). It is characterised by irritability, lympho-adenomegaly, hemorrhage, skin reactions (erythema, desquamation) hepato-splenomegaly, bronchospasm, dyspnea, with peaks of incidence below two years of age, and prevalence in male infants (ratio 2-3:1) [Hasle et al., 2003].

This paper describes two cases with similar anomalies in dental development in patients who had been treated for systemic diseases with chemotherapy agents and bone marrow transplantation.

Case reports

Two patients were referred to the Department of Orthodontics, University of Milan, complaining of malocclusion, difficulty in chewing and speech. One patient had juvenile myelomonocytic leukemia (JMML) and the other had severe combined immunodeficiency disease (SCID). Both had been treated with chemotherapy agents and bone marrow transplantation (BMT).

Case 1

A 7 years-old boy with a medical history of SCID, TB, and with genetic alteration identified on the Artemis locus, mutation exon I, T85C->116T; exon V, C381G -> S119X and polymorphism on nucleoside 681, exon 8. At the age of 7 months he had been treated with bone marrow transplantation from a non-related donor; the other had severe combined immunodeficiency disease (SCID). Both had been treated with chemotherapy agents and bone marrow transplantation (BMT).

The chemotherapy treatment before bone-marrow transplantation entailed the administration of busulfan for the first four days followed by cyclophosphamide for the next four days. At the time of referral there was a typical delay in his skeletal development, with persistent infection of the upper airways, presence of skin nevi, and...
non severe alteration of the left ventricle. He responded well to all therapies and suffered no allergic episodes.

Orthopantamography at 6 years revealed many tooth ageneses (Fig. 1) and the absence of the following teeth: 18, 15, 14, 12, 24, 25, 28, 34, 35, 38, 44, 45, 48. Intraoral examination revealed poor oral hygiene, hypertonic lips, normotrophic face, and hypertonic facial muscles.

In accordance with the paediatrician, the patient entered an oral hygiene programme to improve his periodontal health, with fluoride prophylaxis and subsequent orthodontic treatment.

The orthodontic diagnosis was of biretrusion and deficit of both maxilla and mandible, and was treated with a one-piece orthodontic appliance constructed with 1 cm raised bite and upper and lower shields, in addition to extraction of maxillary V teeth and maxillary IV teeth. The subsequent OPG showed tooth 14 to be mesio-inclined (Fig. 2). The permanent canines were anomalous in shape, with microdontia and conoid aspect (Fig. 3). The roots of the permanent teeth, particularly of the first molars, showed altered development and appeared short. A fixed appliance was then bonded onto the first upper left molar, with a traction arm to the upper left canine, for extrusion of the second upper left premolar. A space maintenance device was applied until completion of growth, when an implant-supported prosthesis could be constructed. Malformed teeth were restored with composite.

**Case 2**

A 14-year-old boy had undergone bone-marrow transplantation and splenectomy for juvenile myelomonocytic leukaemia (JMML). The chemotherapy treatment before bone-marrow transplantation entailed Busulfan plus cyclophosphamide and Melphalan. He reported compensated arterial hypertension. The OPG revealed the absence of teeth 12, 15, 18, 22, 25, 27, 28, 35, 38, 45, 47 and 48, with 13, 14, while tooth 23 was impacted (Fig. 4). The clinical examination showed the presence of 55, 53, 52, 62, 63, 65, 75 and 85, with microdontia and conoid shape of teeth 34 and 44 (Fig. 5).

The orthodontic treatment was started and it consisted of rapid palatal expansion with bands on the first molars and traction arms to extrude the impacted teeth. A removable appliance (Interim-G®) was then fitted. Surgical extrusion of the upper canines and of the first upper right premolar was recently performed. The case was re-evaluated after two year’s use of the...
orthodontic appliance, the correct vertical dimension was restored and on completion of this treatment, an implant-supported rehabilitation and the reconstructed of the malformed teeth was planned.

**Orthodontic treatment**

The treatment was performed in 2 phases. The first phase consisted of orthopaedic treatment with a removable appliance (Interim-G®); this was followed by rapid palatal expansion with the device attached to the maxillary first molars, and activated once or twice per day. Each activation was 0.2 mm and the maximum expansion possible was 10 mm. Expansion was terminated when the first molars were in normal occlusion and when there was sufficient space for the impacted teeth (on average 20 days). The appliance was stabilised and kept in place as retention for at least 7 months (average 12 months).

In the second phase of the treatment, the permanent dentition was completed and both patients were treated using fixed appliances for a mean period of 2 years (19 to 26 months) to obtain final alignment and maximal intercuspation. Due to the mechanics of fixed orthodontic treatment, some movements are extrusive and can alter the vertical dimension. However, this alteration of the vertical dimension coincides with vertical facial development in growing individuals; such alterations usually occur as a consequence of the craniofacial growth process.

In the second case described here, surgical extrusion of the upper canines and of the first upper right premolar had been performed; the patient was re-evaluated after two year’s use of the orthodontic appliance, at which time the correct vertical dimension was restored and deciduous teeth were extracted.

The vertical dimension was assessed in both cases, by measuring the SN–GoGn angle on lateral cephalograms taken before treatment. The vertical dimension was considered to be normal if the angle was between 30 and 36 degrees, low if the angle was less than 30 degrees, and high if the angle was more than 36 degrees. In both cases the new mandibular and maxillary position improved the facial profile and corrected the malocclusion. On completion of the orthopedic treatment, the malformed teeth were reconstructed and implant-supported rehabilitation was applied; patients were monitored monthly throughout treatment.

**Results and discussion**

Immunodeficiency diseases, human SCID and JMML are very often accompanied by oral diseases, that include periodontitis, persistent candidiasis, and herpetic infections, as well as prolonged or unusual dental infections lympho-adenopathy, mouth ulcer, bleeding and gingival hypertrophy. For these reasons, they must be monitored monthly throughout treatment.

Tooth anomalies are generally reported in patients after long-term chemotherapy [Welbury et al., 1984; Rosenberg et al., 1987; Maguire et al., 1987; Macleod et al., 1987; Pajari et al., 1995; Millot et al., 2003; Pedersen et al., 2012], and in patients who have undergone BMT, after total body irradiation [Dahlhof et al.1988]. Only a few cases of tooth alterations after SCID treated with BMT have been reported, all were after long chemotherapy treatment [Cole et al., 2000; Vaughan et al., 2005; Maciel et al., 2009]. The tooth anomalies observed in our two patients were very similar, and in our opinion the cause of these alterations is not correlated with the underlying disease (SCID – leukemia) but rather with the treatment they have undergone. In view of the high toxicity of chemotherapy agents, their action on cell lines with rapid turnover, and the low separation potential of tissues like tooth and dentine, it may be hypothesised that such treatment is the main cause of tooth developmental anomalies. This hypothesis is supported by the fact that both patients had been
treated with the same chemotherapeutic drugs (Busulphan plus cyclophosphamide), and that both developed the same tooth anomalies.

Development of the permanent teeth begins with the crown (first molar) in the last few weeks of intra-uterine growth, and is completed with root formation at age 17-18 years. It is likely that chemotherapy treatment prior to bone marrow transplantation, in the early months after birth, could generate tooth developmental anomalies like those observed in these two cases.

It is widely reported that oncologic paediatric patients treated with long cycles of chemotherapy (6-30 months) develop a series of tooth alterations that include incomplete calcification, enamel hypoplasia, altered root formation, premature apicification, microdontia, and hypodontia. The two cases reported here show that, even after a short period of chemotherapy, clinical evidence comparable with many of these anomalies (microdontia, root alterations, hypodontia) may be found. Both cases were given dental and orthodontic treatment; mycoses, herpetic and periodontal disease were treated, and malocclusion was corrected.

The patients were treated initially with orthopaedic treatment with a removable appliance, followed by rapid palatal expansion with a device attached to the maxillary first molars and activated once or twice per day. Fixed orthodontic treatment followed as the permanent dentition was completed, for a mean period of 2 years (19 to 26 months) to obtain final alignment and maximal interdigitation. In both cases the new mandibular and maxillary position improves the facial profile, corrects the malocclusion and allows the teeth to function normally. The final phase will comprise implant-supported rehabilitation and reconstruction of malformed teeth.

In agreement with the paediatricians, our cases entered the following treatment program: preventive dental care, including oral hygiene instruction, nutritional counseling, and fluoride gel applications to maintain oral health. Collection of all data concerning current medical history, recent hospitalisations, infections and medications. Before complicated dental procedures can be undertaken, a complete blood cell count with white cell differential and platelet count is necessary. Additional antibiotic prophylaxis is often warranted before invasive dental treatment, since bacteremias from dental procedures could be fatal to these patients. Since many patients are maintained on continuous antibiotic therapy, which permits the growth of penicillin-resistant oral organisms, prophylaxis with another class of antibiotics may be necessary. Consultation with infectious disease specialists can help dental clinicians choose alternative antibiotics. Viral, fungal, and bacterial cultures are thus often needed to establish the causative agent of oral infections, ulcerations, and lesions, and to help ascertain the appropriate treatment. It is essential that the dentist consults regularly with the pediatrician managing the immunodeficient patient.

Conclusion

Oral lesions frequently accompany immunodeficiency diseases, and teeth anomalies may be iatrogenic. They thus demand particular awareness directed toward diagnosis of an underlying disease of the immune system, and care in deciding the therapy. It may thus be appropriate a cooperation effort between dentists and paediatricians dealing with patients exhibiting complex oral lesions an adequate follow-up, in order to prevent any other possible tooth anomalies and ensure correct development of the jaws.

References

- Cole BOI, Welbery RR, Bond E, Aburn M. Dental manifestations in severe combined immunodeficiency following bone marrow transplantation. Bone Marrow Transplant 2005;25:1007-1009.