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Orthognathic surgery in a patient with Diamond Blackfan Anemia

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ABSTRACT

Diamond Blackfan Anemia (DBA) is a rare, congenital, hypoplastic anemic syndrome, which frequently presents with accompanying facial and bodily anomalies that require corrective surgery. We describe a 19-year-old girl with DBA, who presented at our department of Oral and Maxillofacial Surgery with a class II malocclusion and an anterior open bite. The treating orthodontist referred her for a combined orthodontic-orthognathic treatment plan. DBA is an uncommon hematologic disorder, which is mostly heritable in an autosomal dominant fashion with variable penetrance. Not all etiological factors can be entirely explained. Patients with this disease often experience severe hematological anomalies and physical abnormalities and the condition might require multiple transfusions and corticoid therapy. Both congenital aberrations and potential treatments can complicate surgery. Therefore, several considerations should be taken into account. Orthognathic surgery in patients with DBA can be performed safely, when the patients are hematologically stable, and when DBA-associated organ impairment is limited. Under these conditions, these patients can be treated with the same surgical and pharmacological procedures as those applied in healthy individuals.

Introduction

Diamond Blackfan anemia (DBA) is a rare, congenital, hypoplastic anemia that was first described by the American pediatricians Diamond and Blackfan, in 1938 [1]. DBA is estimated to occur in 1 out of 100,000 to 200,000 live births [2], and it typically presents within the first year of life, although presentation in adulthood has also been described [3]. The inheritance pattern is mostly autosomal dominant, with a variable penetrance. Some genes are inherited in an X-linked pattern, which can explain the heterogeneous character of the disorder [4]. In addition to the hematological complications, patients often have facial anomalies, which require orthognathic surgery. Here, we describe a patient with severe hematological and maxillofacial abnormalities.

Presentation of case

A 19-year-old girl was referred to the department of Oral and Maxillofacial Surgery by a treating orthodontist. She presented with vertical maxillary hyperplasia and protrusion of the upper lip, which resulted in a gummy smile. She displayed an Angle class II malocclusion with an anterior open bite and eversion of the lower incisors (Fig. 1). A further clinical examination showed normal

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sensitivity in the teeth and radiography showed pulp stones in elements 36 and 46 (shown on the panoramic radiograph, Fig. 2). The patient had no history or clinical signs of a disorder in the temporo-mandibular joint.

Overall, we noted that the size of the patient's head was disproportional to the body, with frontal bossing, and a flat nasal bridge (Fig. 3). A computed tomography of the skull showed that the cranial bones were substantially wider than normal, which could indicate extramedullary hematopoiesis (Fig. 2).

The patient's medical history included congenital dyserythropoietic anemia. As a child, she had had multiple blood transfusions, until a splenectomy was performed, at age 8 years. A cholecystectomy was performed one year later. The patient was scheduled for routine follow-ups with her general practitioner and hematologist. Excess iron storage throughout the body was treated with iron chelation therapy, which showed good effects.

Due to her splenectomy, she received amoxicillin 250 mg twice daily. Her platelet count was elevated, to values above 1000×10^9/L (normal values: 150–400 $\times 10^9$/L). This condition could be attributed to post-splenectomy thrombocytosis, which was treated with 80 mg aspirin daily. The patient was also followed up regularly for a minor cardiac dilatation, due to chronic anemia, without hemodynamic repercussions. She had a history of poor wound healing. However, four impacted wisdom teeth were removed 6 months earlier, and recovery was uneventful.

Up to the moment of presentation at our institute, the patient had no diagnosis of a possible genetic disorder. However, due to the unusual combination of her hematological condition and the intra-oral and extra-oral clinical observations, we set up a collaboration with the Department of Human Genetics at our institute, to identify the genetic anomaly. This specific array of symptoms pointed towards a possible diagnosis of Diamond Blackfan anemia. A microarray analysis showed a 404-kb duplication in genes *GABRA6*, *GLRXP3*, and *GABRA1*, located in chromosomal region 5q34.

To improve the occlusion, aesthetics, and oral function, a combined orthodontic-orthognathic treatment plan was proposed. The patient was cleared for surgery after a hematological workup. No contra-indications were found for surgery or for the postoperative use of antibiotics, nonsteroidal anti-inflammatory drugs, or other analgesics. First, extraction of elements 14 and 24 and placement of bone anchors in the upper jaw would allow the orthodontist to retrude the upper front teeth and perform presurgical orthodontic decompensation. Next, a bimaxillary osteotomy is to be performed to correct dentoskeletal discrepancies. Finally, orthodontic finishing is needed to establish the final occlusion.

Discussion

DBA is a congenital, pure red-cell aplasia that displays genetic and clinical heterogeneity. The DBA diagnosis is based on clinical and laboratory diagnostic criteria (Table 1). Moreover, a large number of patients that fall outside these criteria might be diagnosed with a 'non-classical' DBA [5]. DBA is associated with an elevated risk of congenital malformations and a predisposition to cancers, such as acute myeloid leukemia and osteosarcoma [6]. Current treatment options consist of corticosteroid therapy, blood transfusions, and hematopoietic stem cell transplantation [7].

The exact pathophysiology of DBA remains unknown, but it is acknowledged that an intrinsic dysfunction in erythroid progenitor cells causes them to be more sensitive to apoptosis, which subsequently leads to disturbed hematopoiesis [5]. The dysfunction is caused by mutations in ribosomal genes that result in a haploinsufficiency of the encoded ribosomal proteins (RPs) [7]. Currently, DBA has been associated with mutations in 19 RP genes and three non-RP genes [8]. Although a microarray analysis could not provide an explanation for the hematological and maxillofacial anomalies in our patient, we could not exclude the possibility of Diamond Blackfan anemia. In approximately 30–40% of patients with DBA, no clear genetic anomaly can be diagnosed. Furthermore, as described by Takuya et al. [9], the number of novel candidate genes involved in bone marrow failure syndromes continues to grow. Although DBA is mostly inherited in an autosomal dominant manner, it has shown variable penetrance and expressivity, in both the hematological and physical manifestations [7]. This genetic heterogeneity of the disorder makes the diagnosis extremely challenging.

More than 50% of patients with DBA have physical abnormalities, including craniofacial anomalies, short stature, and malformations of the upper limbs, thumbs, genitourinary system, and heart [4,5]. Specific craniofacial anomalies occur in 50% of patients [5]. The oral and dental findings reported in the literature include severe gingivitis, multiple caries, impacted third molars, poor healing at extracted tooth sites, and pulp stones [10]. In the present case study, the existing anemia and the typical physical anomalies in the patient strongly suggested a diagnosis of Diamond Blackfan anemia. However, primary genetic screening was negative; consequently, further examination with whole exome sequencing is necessary.

When planning surgery, several considerations should be taken into account. The presence of craniofacial anomalies in DBA can

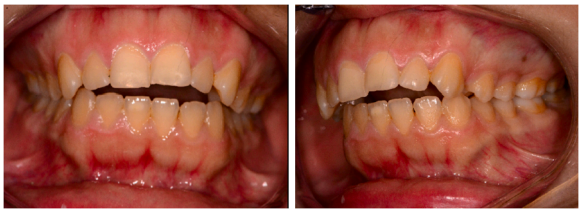

Fig. 1. Clinical photograph of patient's teeth. The (*left panel*) anterior and (*right panel*) left anterolateral views show the Angle class II malocclusion with an anterior open bite and an overjet of 8 mm.

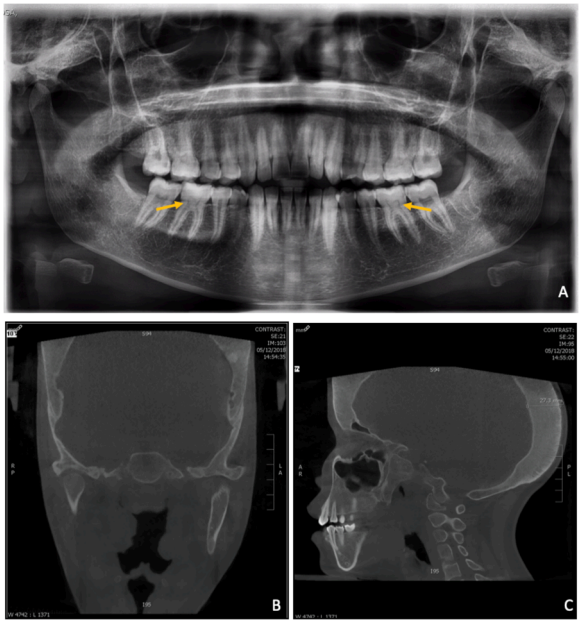

Fig. 2. Panoramic radiograph of the patient's jaws. (A) Note the presence of pulp stones in element 36 and 46. (B) Cranial computed tomography, coronal view. Note that the width of the cranial bones exceeds the normal range by nearly 3 cm. (C) Cranial computed tomography, sagittal view.

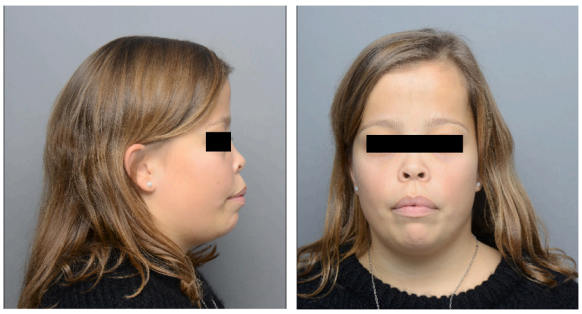

Fig. 3. Clinical photograph of the profile and anterior view of the patient. Note the atypical face with frontal bossing.

Table 1
Clinical diagnostic criteria of Diamond Blackfan anemia[a].

Diagnostic criteria
Age, less than 1 year
Macrocytic anemia with no other significant cytopenias
Reticulocytopenia
Normal marrow cellularity with a paucity of erythroid precursors
Supporting criteria
Major
Gene mutation described in "classical" DBA
Positive family history
Minor
Elevated erythrocyte adenosine deaminase activity
Congenital anomalies described in "classical" DBA
Elevated Fetal Hemoglobin
No evidence of another inherited bone marrow failure syndrome

[a] Modified with permission from Vlachos et al., 2008.

potentially lead to problematic endotracheal intubation, due to abnormal anatomy [11]. To ensure optimal airway management, the anesthesiologist must conduct a detailed examination of the airway and estimate the level of difficulty entailed in intubation. Indeed, a preoperative assessment of our patient revealed a high probability of difficult airway intubation. Moreover, in cases of severe

underlying anemia, it is often necessary to correct abnormal parameters preoperatively and perform red blood cell transfusions during surgery to improve patient outcomes. A transfusion threshold of 7 g/dL is recommended for most patients that are hemodynamically stable [12]. In the present case, our patient manifested only minor symptoms of anemia, because she had undergone a splenectomy, and she had a stable hemoglobin level of 8.2 g/dL. Only a limited amount of blood loss is anticipated in orthognathic surgery, therefore, it is unlikely that the patient will require a blood transfusion during or after surgery. DBA can also cause cardiac problems, due to congenital abnormalities, chronic anemia, or iron overload. Thus, a preoperative evaluation, including echocardiography, is suggested. Furthermore, in orthognathic surgery, local anesthesia with adrenaline is provided for hemostasis and postoperative pain relief. However, catecholamines in local anesthetics can lead to elevations in heart rate and systolic blood pressure. Nevertheless, no clinically significant adverse effects were observed, when anesthetics, with or without adrenaline, were given to patients with cardiovascular conditions [13]. Therefore, the use of vasoconstrictor agents in local anesthetics is considered safe in patients with controlled cardiovascular diseases. In addition, it can be useful to evaluate liver function with echography and laboratory analyses, because an iron overload, due to blood transfusion, can impair liver function [5]. In turn, impaired liver function can cause alterations in hemostasis and drug metabolism. In these cases, certain analgesics, antibiotics, and local anesthetics should be used with caution. Moreover, every individual patient should be evaluated for the use of nonsteroidal anti-inflammatory drugs, because they can increase the risks of gastrointestinal bleeding and gastritis [14]. Most amide local anesthetics, except for articaine and prilocaine, are primarily metabolized in the liver; thus, these drugs can cause toxic reactions at relatively low doses [15]. Our patient showed no signs of liver damage with an ultrasound examination and laboratory testing, therefore, there were no contra-indications against using these drugs.

Conclusion

Because DBA is a rare congenital condition of the bone marrow, the literature is limited on the pre- and perioperative measures that should be taken when performing orthognathic surgery. Patients with DBA often present with hematological and physical abnormalities that can impede surgery. Therefore, a profound preoperative assessment should be conducted, including a hematological checkup, airway examination, and evaluation of organ function. When patients with DBA are hematologically stable and DBA associated organ impairment is limited, orthognathic surgery can be performed safely.

Conflicts of interest

None.

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None.

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