Genetic Disorders and Bone Affecting the Craniofacial Skeleton

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Genetic disorders of bone that affect the craniofacial skeleton are individually rare; however, they have significant clinical relevance because of their overall frequency. These disorders include several that result in derangement of growth, development, and differentiation of the face and skull. The clinical severity differs greatly among individual patients, ranging from minor handicaps to death in the neonatal period. Traditionally these disorders have been divided into dysostoses (defined as malformation of individual bones or groups of bones) and osteochondrodysplasias (defined as disorders of chondro-osseous tissues) [1]. The complexity of these alterations has been known for some time. Although single entities have been described since the nineteenth century or the first part of the twentieth century, most entities we know currently have been delineated much more recently [2]. This progress has provided us with more insights into the genes that control normal skeletal development. To date, approximately 300 different types of skeletal disorders have been identified; however, only a few have a significant number of cases reported in the literature. For this reason and because of the limitations of time and space, we limit our discussion to the seven most common disorders in this group. For practical purposes we also leave out of this discussion the craniofacial disorders that involve skeletal physiognomy.

Fibrous dysplasia (McCune-Albright syndrome)

Fibrous dysplasia is an uncommon, noninherited genetic bone disorder of unknown origin. This condition is commonly found in children aged 3 to 15 years and can affect any bone of the musculoskeletal system (Fig. 1A–C). The genetic mutation is found on the guanine nucleotide binding protein gene (GNSA1) located on the 20q13.2 chromosome and can be categorized into three groups: (1) monostotic, which involves one bone, (2) polyostotic, which involves more than one bone, or (3) a form known as McCune-Albright syndrome, which involves the skin and endocrine system. An additional form is known as craniofacial dysplasia, which affects bones that are limited to the craniofacial complex [3–5]. Clinical symptoms include—but are not limited to—difficulty walking, pain, fractures, and bony disfigurement.

Fibrous dysplasia has been linked to multiple endocrine dysfunctions, including precocious puberty, hyperthyroidism, growth hormone excess, hyperprolactemia, and hypercortisolism. The most common clinical manifestation other than bone dysfunction is the presence of skin lesions known as café au lait spots, which are found in nearly 50% of the polyostotic cases. These skin lesions manifest secondarily to the excessive production of melanin in the basal skin layer.

Radiographic diagnosis is typically visualized using plain films. Severe cases that include the spine, cranial bases, and mid-face may require the use of CT scanning to better visualize the involvement of bony changes, however. This disease can affect any bone but is more commonly found in long bones, ribs, spine, and the craniofacial complex [6].

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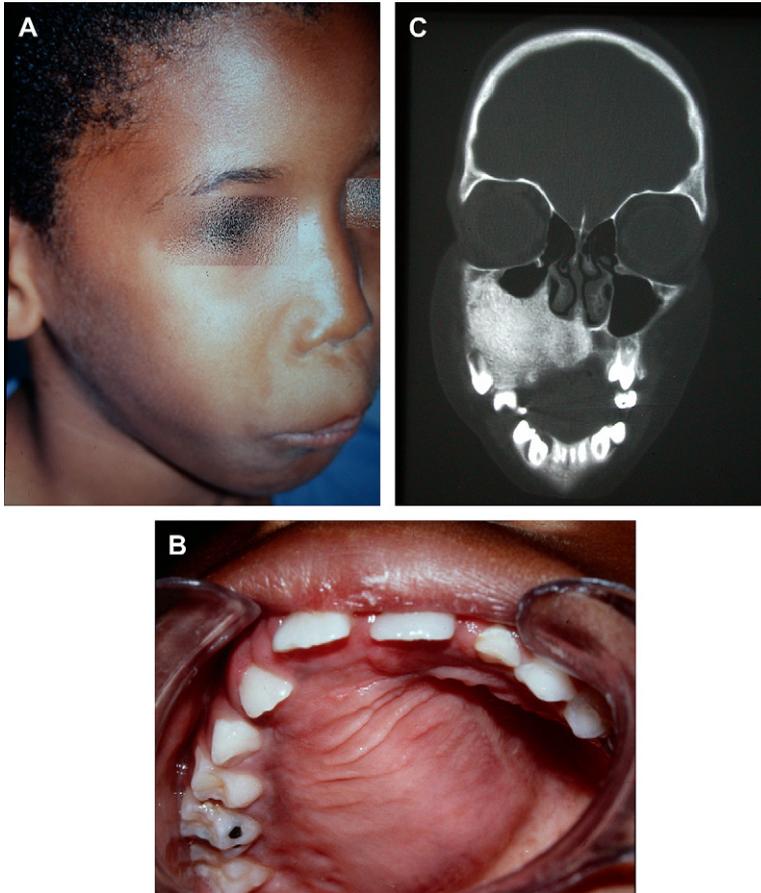*E-mail address:* chacon.4@osu.edu (G.E. Chacon).

Fig. 1. An 11-year-old male patient shows clinical signs of fibrous dysplasia. (*A*) Facial view shows enlargement of the right malar bone. (*B*) Intraoral view shows involvement of the palate on the ipsilateral side. (*C*) Coronal cut of the patient's CT scan shows the classic "ground glass" appearance of the involved osseous structures.

Fibrous dysplasia of the maxillofacial complex most commonly involves the maxilla more than the mandible. Clinical signs include painless expansion of bone and tooth displacement. Radiographic evaluation usually demonstrates mixed radiolucent and radiopaque lesions with a classic presentation of "ground glass" opacity without clearly defined borders. The bony expansion may cause nerve and blood vessel compression with special concern for the optic nerve. These lesions can mimic other diseases, such as osteomyelitis and Paget's disease, and require a biopsy and histopathologic confirmation of fibrous dysplasia. Histologically these lesions demonstrate irregularly shaped trabeculae of woven bone within a fibrous stroma [4,7,8].

The treatment of fibrous dysplasia is only indicated when symptoms persist or cosmetics secondary to psychosocial factors are a major concern. The optimal treatment time is best obtained later in life when an individual has reached young adulthood because this disease seems to decrease in its activity toward the end of the second and beginning of the third decades of life. When expansion has appeared quiescent, the idea of surgical intervention can be introduced. The treatment of choice in these patients is cosmetic recontouring [9]. Patients must be advised that regrowth can occur up to 50% of the time, especially in younger individuals.

In recent years, conservative treatment of fibrous dysplasia with oral and intravenous bisphosphonate therapy has shown some promising results. Zacharin and O'Sullivan [10] ran an open trial of pamidronate treatment in five children and four young adults with polyostotic fibrous

dysplasia associated with McCune-Albright syndrome to assess clinical response, bone turnover, and cardiovascular status over a 2-year period. They found this therapy to be effective in controlling disease progression and it showed improvement in bone pain, mobility, and quality of life. In a similar but longer term study, Chapurlat and colleagues [11] sought predictors of response to treatment with the use of intravenous pamidronate in 58 patients (41 adults and 17 patients younger than 18 years of age). They found that this therapy was associated with substantially decreased pain, diminished levels of biochemical markers of bone turnover, and improved radiologic aspect in approximately half of the patients treated. Although the therapy was considered safe, no clinical or biologic predictors were established. These findings were supported in a similar study by Kos and colleagues [12].

A case report from Nippon Medical School in Tokyo found similar clinical and radiographic evidence with the use of oral bisphosphonate alendronate [13]. With recent findings regarding bisphosphonate-induced bone necrosis, the question that immediately arises is what would happen if patients required surgery. With bone healing already compromised by their disease and the added effect of this new treatment modality, are these patients at a higher risk for complications? We believe that currently it may be premature to jump to such conclusions, but we certainly must be cautious when dealing with these individuals.

Malignant transformation of fibrous dysplasia is rare, with a frequency of less than 1%, and has been reported sparingly in the literature. The most common transformation is among the class of sarcomas. Treatment for these malignances remains controversial [14,15].

Osteogenesis imperfecta

Osteogenesis imperfecta is an inherited autosomal dominant genetic disorder that affects up to 50,000 people in the United States and may be found in 1:8000 individuals [5]. This disorder has been termed "brittle bone" disease because of the increased fragility of bone resulting in bony fractures under normal load. It is the most common type of inherited bone disorder. Osteogenesis imperfecta is characterized by injury to formation and maturation of collagen. Three genes are typically associated this disease: COLIA I gene located on chromosome 17, COLIA II gene located on chromosome 7, and the recently

identified CRTAP gene located on chromosome 3 [16,17]. Osteogenesis imperfecta affects multiple aspects of the human body, including the development of bone, cartilage, dentin, skin, and sclera. There are at least four major types of osteogenesis imperfecta: types I, II, III, and IV.

Type I is the most common and is typically categorized by autosomal dominant inheritance. Patients usually develop fractures in the second or third decades of life and develop blue sclera and deafness as they age [5]. Type II is the most severe form of all types of osteogenesis imperfecta and affects 1:20,000 to 60,000 infants [17]. Patients with type II typically fracture bones during delivery, and death occurs before the first year of life [18]. This form is found to be both autosomal dominant and recessive. Type III is the most severe form that is associated with surviving patients who have osteogenesis imperfecta. Patients with type III develop the most severe forms of bone fragility, and most patients die during childhood as a result of cardiopulmonary complications from kyphoscoliosis. Bony deformities of the limbs may lead to altered function and mobility. Type IV is the second most common of the types and displays mild to moderate bone fragility. This type is similar to type I but has a higher incidence of fractures developing in childhood.

Osteogenesis imperfecta has an effect on the formation of dentin in primary and permanent dentitions. The primary dentition is more often affected than the permanent dentition, however. The affected dentin is part of a process known as dentinogenesis imperfecta, which subdivides each type of osteogenesis imperfecta. Some patients have no clinical or radiographic evidence of dentinal involvement, whereas other patients have a varying degree of change in dentin formation. Clinical findings include discoloration of the crowns that varies from opalescent to gray to brown to yellow. Patients with malformed dentin are at higher risk of dental attrition, fractures, and loss of vertical dimension [19]. It is important that these individuals seek dental care at an early age to help maintain appropriate dental and skeletal growth. Radiographically, dentinogenesis imperfecta is suggested by bulbous anatomic crowns, cervical constriction, and pulp chamber and canal obliteration.

There is no specific treatment for osteogenesis imperfecta; however, the importance of seeking dental care at an early age can help prevent skeletal and dental malformations. Prevention and treatment of fractures remain major issues for patients who have osteogenesis imperfecta. For this reason,

implementation of different therapies geared toward preventing fractures has been attempted with a certain degree of success. In 1996, Landsmeer-Beker and colleagues [20] reported on the use of the bisphosphonate olpadronate for the treatment of this condition over a 5- to 7-year period. Their study suggested that long-term continuous administration of the drug to patients with osteogenesis imperfecta and vertebral deformities was effective. This finding was established by looking at radiographs that showed a tendency for restoration of normal vertebral shape and increased calcification of the long bones. Other studies have reported on the use of intravenous pamidronate for this purpose [21–23]. Their combined findings are consistent with the previously referenced study. Probably the most valuable observation was the decrease in the incidence of fractures found in the treatment groups.

It is important to remember that the great variability in disease can result in mild clinical manifestations or death in utero. Treatment is dictated by the severity of each patient's degree of involvement.

Osteopetrosis (Albers-Schöenberg syndrome)

Osteopetrosis is a hereditary bone disease characterized by abnormal bone remodeling caused by a deficiency of bone resorption that results from failure of production and function of osteoclasts [24]. It was first reported by Albers-Schöenberg in 1904 [25]. The abnormality in bone physiology combined with continuous bone formation leads to thickening of the cortical bone and sclerosis of the cancellous portion. The manifestations associated with this syndrome are pathologic fractures, cranial nerve palsies, anemia, facial deformities, developmental anomalies of teeth, and osteomyelitis. The prevalence of osteopetrosis is low at 1:100,000 to 1:500,000 [5].

Three different types of osteopetrosis have been identified clearly and reported in the literature: infantile malignant autosomal recessive osteopetrosis, intermediate autosomal recessive osteopetrosis, and autosomal dominant osteopetrosis (adult benign osteopetrosis).

Infantile malignant autosomal recessive osteopetrosis

The initial presentation is considered the most severe form of osteopetrosis. Usually diagnosed during the first month of life, this type is associated with pathologic fractures, failure to thrive, frequent respiratory infections, and head and neck or bony infections. Lethargy, small stature, and hepatosplenomegaly are also associated with this form of osteopetrosis. Patients affected by this condition also present with facial deformities, such as macrocephaly, hypertelorism, and frontal bossing. The abnormal resorption process can cause narrowing of the skull foramina, which results in compression of cranial nerves and causes blindness, deafness, and facial paralysis. This form of osteopetrosis can cause death during the first decade of life. Anemia also can be present secondary to the encroachment of the sclerotic bone on the marrow spaces.

Intermediate autosomal recessive osteopetrosis

This unusual presentation of osteopetrosis is similar to the infantile malignant type but appears in a milder expression. Affected patients survive into adulthood with some considerable disabilities.

Autosomal dominant osteopetrosis (adult benign osteopetrosis)

Also considered adult osteopetrosis, this type can present with few or no symptoms. Life expectancy is usually not altered in this presentation. Two types of variations have been described according to the radiologic presentation, both of which have in common a generalized sclerosis. Type I consists of a cranial sclerosis and thickening around the calvarium. In type II, the sclerosis is limited to the cranial base with an almost normal calvarium. Fracture and osteomyelitis secondary to dental extraction are the most common risks associated with this presentation of osteopetrosis. Histologic examination shows different patterns of abnormal endosteal bone formation in cancellous spaces.

Treatment of osteopetrosis consists of stimulating osteoclasts or providing an alternative source of osteoclasts [26]. Bone marrow transplant is the only hope for treating infantile malignant osteopetrosis. Corticosteroids and parathyroid hormone have been used to stimulate bone resorption and treat anemia by an increase in hematopoiesis. Limited intake of calcium and vitamin D can stimulate the production of osteoclasts [27]. Human γ-1b interferon can enhance bone resorption and increase hematopoiesis and leukocyte function in patients who have osteopetrosis [28]. Osteomyelitis of the jaws can happen because of the impaired function of white cells

and poor vascular supply. The most common site is the mandible, but it can affect the maxilla [29,30]. Treatment of the osteomyelitic condition of the jaws includes incision and drainage, saucerization, sequestrectomy, and extraction of teeth in the affected area. Jaw resection and hyperbaric oxygen therapy are the only successful methods of treatment for more involved cases.

Cleidocranial dysplasia

Cleidocranial dysplasia, formerly known as cleidocranial dysostosis, is an autosomal dominant skeletal dysplasia that results from a defect in the CBFA1 gene of chromosome 6p21. This disease is characterized by abnormal clavicles, patent sutures and fontanelles, supernumerary teeth, and other skeletal changes [31]. Early diagnosis of cleidocranial dysplasia is difficult because craniofacial abnormalities become evident during adolescence. Most cases present with hypoplastic clavicles and, in some instances, with unilateral or bilateral absence of the clavicles. In some cases, patients can approximate their shoulders in front of the chest. Short stature, hypertelorism, broad nose, and frontal bossing are clinical features found in these patients. Narrow, high, arched palate, cleft palate, prolonged exfoliation of the primary dentition, and unerupted supernumerary teeth are common intraoral findings. Young individuals have normal jaw proportions and morphology but because of delayed or lack of eruption of permanent teeth may experience short lower face height and mandibular prognathism as they grow [32].

There is no specific treatment for cleidocranial dysplasia. Early diagnosis and interdisciplinary management are important in the management of this disease. Serial extractions and orthodontic extrusion of permanent teeth can prevent abnormal jaw relationships. Full-mouth extractions with denture fabrication are other modalities of treatment.

Cherubism

Cherubism is a rare genetic disease of the maxilla and mandible that results in a painless swelling of one or both of these entities. Its clinical characteristic is reminiscent of cherubs displayed in Renaissance paintings. This disease is described as an autosomal dominant nonneoplastic disease mapped to the 4p16 chromosome [33]. This condition is generally inherited, but cases of nonfamilial origination have been documented [34,35].

Cherubism usually manifests before the age of 6, and patients typically present with painless bilateral mandibular and maxillary mandibular expansion. This clinical feature produces the cherub-like appearance. Some cases involve the inferior orbital rim and orbital floor, which results in scleral show and an upward gaze of the eyes. An intraoral examination may reveal clinically missing teeth, widened alveolar ridges, and tooth displacement. Radiographically, patients typically have multilocular radiolucent lesions of the posterior mandible consistent with the bilateral mandibular expansion clinically (Fig. 2) [36,37]. Histologically these lesions are similar to giant cell granulomas, with a large volume of vascular fibrous connective tissue containing a variable number of focal giant cells [33,38]. Perivascular eosinophilic cuffing is commonly present.

Early treatment of cherubism is limited to assisting dental development and addressing specific concerns with family regarding physical appearance. These lesions are typically self-limiting, and regression is seen after puberty. If physical appearance remains an issue, treatment can be more aggressive in the third and fourth decades of life, when cosmetic recontouring is the treatment of choice.

Familial gigantiform cementoma

Gigantiform cementoblastoma is an uncommon autosomal true dental tumor. This term has been used in the past to describe florid-osseous dysplasia; currently the term should be reserved to describe this rare hereditary disorder. This disorder consists of a slow-growing, multifocal/multiquadrant, expansile lesion that involves the jaws. Radiographic examination resembles cemento-osseous dysplasia. The initial phase of the disease is characterized by radiolucencies in the periapical regions. As the lesion matures it acquires a mixed radiolucent/radiopaque appearance as it replaces normal bone. A mature familial gigantiform cementoma presents as a multiple, circumscribed, lobular, and expansile lesion with a mixed radiographic appearance that crosses the midline. The lesion continues to mature until it becomes predominately sclerotic with a thin radiolucency around its circumference. Elevated alkaline phosphatase levels with subsequent improvement after

Fig. 2. A 31-year-old female patient diagnosed with cherubism. (*A*) Notice the enlarged mandible, bilateral malar prominences, and increased scleral show. (*B*) Classic ocular findings associated with cherubism. Notice the relative upward rotation of the globes as a result of abnormal tissue invading the orbits. (*C*) Panoramic radiograph shows large bony and dental involvement. (*D*) Coronal cut of the patient's CT scan shows the severity of her condition.

surgical removal of the lesion have been reported [39].

Histologically, familial gigantiform cementoma is indistinguishable from cemento-osseous dysplasia. The lesion consists of fibroblastic tissue proliferations with variable degrees of cellularity intermixed with cemental deposits and limited bone formation [40]. Treatments performed before the sclerotic phase consist of shave-down surgical procedures but are not usually successful because of the rapid growth of the disease. Attempts to perform partial resection during the sclerotic phase can lead to sequestration of the affected bone [5]. Extensive resection of the tumor with reconstruction is recommended and has been reported with good aesthetic and functional results [40].

Gardner syndrome

Gardner syndrome is a rare autosomal dominant disease in which chromosome 5 (5q21) has been mapped as the responsible gene. This gene is

also known as the adenomatous polyposis locus [41]. The disease is characterized by gastrointestinal tumors, multiple osteomas, dental abnormalities, and skin and other soft tissue tumors. The prevalence of Gardner syndrome varies from 1:8300 to 1:16,000 live births [5].

Gastrointestinal polyps have been reported to undergo malignant transformation, and their early identification is vital. Osteomas consist of single or multifocal proliferations of compact or cancellous bone in a periosteal or endosteal location that can vary greatly in size [42]. The osteomas can occur in the mandible, maxilla, sinuses, and long bones. In some instances, large osteomas of the mandible, particularly in the condylar region, can cause limited mouth opening [43]. Dental abnormalities include odontomas, supernumerary teeth, and dental impactions. Epidermoid cysts and desmoid tumors can be found in the face, scalp, and extremities.

Treatment of the cutaneous manifestations depends on the symptoms, cosmetic nature, and location of the lesions found. The major concerns regarding Gardner syndrome are the high rate of transformation of gastrointestinal polyps into invasive adenocarcinomas in 100% of the cases [44]. Prophylactic colectomy is recommended once the diagnosis has been confirmed [45].

Summary

Genetic disorders of bone constitute a large number of alterations approaching almost 300 types. Because of the limitations of this article we focused our discussion on the most common diseases in this group, which at the same time are the most clinically significant because of their incidence and degree of involvement of the craniofacial skeleton.

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