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Short Communication

Cleidocranial Dysostosis in a Family

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Abstract:

Cleidocranial dysostosis is a rare skeletal dysplasia that affects bones, especially the clavicles and the maxillofacial area due to the mutation of the CBFA1/ RUNX2 gene located in the 6p21 site, where genetic information that is responsible of bones and teeth formation may be found; this condition is also related to other mutations in other genes. A clinical, radiographic study is carried out to describe the behavior of cleidocranial dysostosis in a family taking also into account the pedigree of the affected family, four cases of a rare genetic syndromeis described where there is deformity with absence of clavicles and brachycephaly in 100 % of the patients. A lack of both clavicles and brachycephaly were the most common radiographic abnormalities found in four members of a family with a heritage pattern of adominant autonomic scale.

Keywords: Cleidocranial dysostosis, Pierre Marie Sainton disease.

Introduction

Cleidocranial dysostosis (CCD, OMIM # 119600) is an autosomal dominant scale dysplasia of skeletal and dental tissues, characterized by aplasia or hypoplasia of clavicles and multiple Wormian bones, failure of mesenchymal ossification, delayed dental eruption, supernumerary teeth and other skeletal abnormalities. Since it was described, a great deal of information has been published, in particular integral studies to describe skeletal abnormalities. These observations lead researchers to propose the term cleidocranialdysostosis. CCD is a congenital disorder with an incidence of 1 every 1 000 000 newborns, more than 1 000 cases have been reported so far. (1, 2)

This condition was described for the first time in 1766 by Morand, later in 1897 by Pierre Marie and Sainton, in 1898 it received the name of cleidocranial dysostosis (CCD), a rare skeletal alteration that particularly damages the bones of the head and clavicular area. It is also known under the name of Marie Sainton, Scheuthauer, Marie Sainton disease and cleidocranial dysostosis syndrome (3, 4)

Its main clinical characteristic is hypoplasia or definitely aplasia of the clavicle, which generates decreased mobility of the shoulders, imperfection and / or delay of ossification of the fontanelles that generates the voluminous configuration of the head or the depression of the line of the frontal area, these patients are characterized by having a pointed jaw and hypertelorism, we find the presence of hyperdontia that fills the maxillary area and dental misalignment in the oral cavity. (5) The diagnosis is basically clinical and radiological. (6)

This article presents a rare family pathology, little addressed in the literature, its etiology, early diagnosis, and the general characteristics of a family group of patients with this condition. We describe four cases of cleidocranial dysostosis in a family, a rare genetic syndrome, presenting autosomal dominant behavior. The study is based on a family, consisting of great-grandmother, grandmother, mother, and child. Table 1.

In this group, the mother and the child presented a small stature, with a frontal cranial region with the sagittal suture open mainly in the anterior region, brachycephaly, discrete exophthalmia, a wide neck and a reduction in the diameter of the lateral side of the upper portion of the thorax, the most important finding is the absence of clavicular bone.

Table 1. Clinical radiological relationship of the patient.

The clinical examination	Family			
	Great-grandmother	Grandmother	Mother	Child
The absence of the clavicle	X	X	X	X
Hypoplasia Maxillary upper	-	X	X	X
Projecting	X	X	X	X
Dental disorders	X	X	X	X
Hyperdontia	X	X	X	X
Low size	X	-	X	X
Megaloblastic anemia	-	-	-	-

Bone defects in patients with CCD mainly involve the clavicles, head and jaw, although other bone abnormalities can be found, in two generations prior to the two cases seen in consultation there is agenesis of the clavicles. X-rays of the head and chest showed the presence of underdeveloped Wormian bones, supernumerary teeth, with anomalies of dental eruption and absent clavicles, these were the observations made, in the interview people said that two previous generations had similar conditions. According to the findings, a diagnosis of cleidocranial dysostosis was made.

The muscles associated with the clavicles are abnormally underdeveloped, the patient's features have a long neck, absence of the clavicles with unusual mobility of the shoulders, in some cases, the patient may bring the shoulders to the front of the chest, this is an important characteristic of the syndrome, it is considered pathognomonic because of the diagnosis. Although there are defects and variations of the associated muscles, the function is relatively normal, the rib cage is small and bell-shaped, the ribs are short, people are of short stature, with legs abnormally small, plus hand and foot defects, abnormally long second metacarpal.

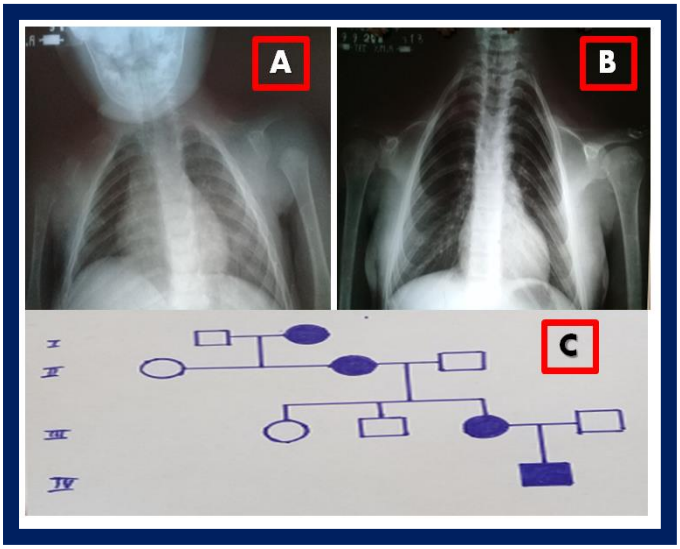

Figure 1. X-ray images of the child and his mother, family phenotype.

Note in figure 1-A as in the image (18-month-old child), there is polydontia, delayed dentition and absence of clavicles, X-ray image 1-B of the mother who has a narrow chest, low implantation shoulders and absence of clavicles, The phenotypic description of the family in four generations can also be seen in image 1- C.

Cleidocranial dysostosis is a genetic defect in the CBFA1 gene, also called RUMX2, once the 6p21 site was located on the chromosome, it acts by mutating chondrocytes and osteoblast non-differentiation. (7, 8)

It was not possible to carried out chromosome studies, but when reviewing the bibliography it was found that most of the conditions of the patients, using markers in the regions of chromosomes 6 and 8, the dominant gene is found once 19CM, in the small arm of the chromosome was located in interval 6, between D65282 and D65291. (9)

It is known that mutations in the fibroblastic receptor apparatus of growth factor 1, 2 and 3 (FGFR1, 2 and 3), and that mutations in the transcription factor RUNX2 (CBFA1) cause cleidocranial dysostosis. It is a disorder that involves a mutation in the transcription factor, which controls the differentiation of osteoblast precursor cells, what is essential for membranous ossification, as well as endochondral ossification. (10)

There are in Cuba several information about families with this disease, Arocha Rodríguez and collaborators present 15 cases in a family in Havana, (11) Márquez Ibáñez N and his team have studied a family for eight generations and show the data of 17 people in Holguín province, (3) also Marchena Idavoy JL, shows a case of absence of clavicle as the fundamental symptom for the diagnosis, in most of these cases. (4)

Its main clinical characteristic is hypoplasia or definitely aplasia of the clavicle, which generates decreased mobility of the shoulders, imperfection and / or delay of ossification of the fontanelles that generates the voluminous configuration of the head or the depression of the line From the front area, these patients are characterized by having a pointed jaw and hypertelorism, we find the presence of hyperdontia that fills the maxillary area and dental malalignment in the oral cavity. (12)

The diagnosis is basically clinical and radiological, which provides proof of the pathognomonic identity of the disease, clavicle agenesis, hyperdontia, and delayed closure of the fontanelles. (13) Due to the bilateral hypoplasia or agenesis of the clavicles, the shoulders fall downwards and forwards until they approach and contact each other, actively or passively, in front of the thorax (Figure 2-a); scapulae appear prominent (winged scapulae); the thorax, in general, is flattened transversely. (14, 15)

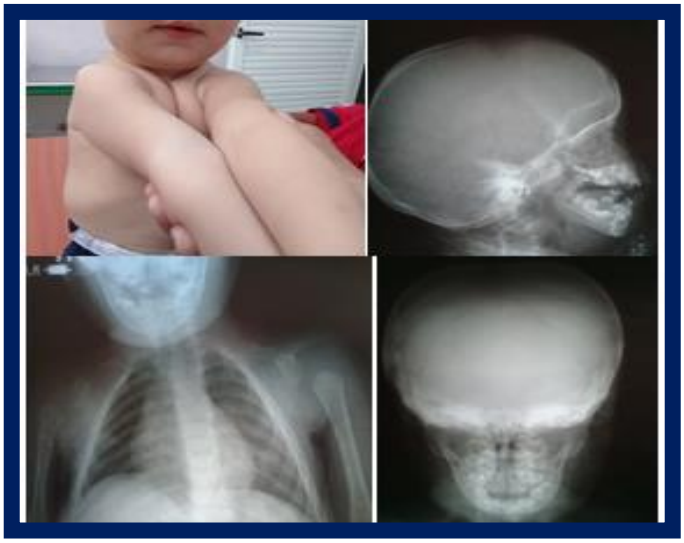

Figure2. Two-year-old male with Cleidocranial Dysostosis. Photograph showing the typical morphology of the condition. (Photos by the author)

a.- Clinical characteristic in the position of his shoulders.
b.- X-rays showing the bilateral absence of the clavicle.
c.- Alterations of the dentition (Hyperdontia).
d.- Typical characteristics of the bones of the head.

Palpation makes it possible to verify the absence of the clavicles, which inspection already makes us suspect due to

the lack of their corresponding relief. When the clavicular aplasia is partial and a medial or lateral end of it persists or there are both, but joined by a fibrous tract, the depression on these causes a "piano key" ridge. The clavicular insertion muscles: trapezius, deltoid, pectoralis major, etc., appear atrophic and, particularly, the subclavian, reduced to a small muscular band.

The typical anesic or hypoplastic alterations of the clavicles can range, from a complete absence of them, the rarest eventuality (Figure 2-b), to the most frequent form, represented by the presence of two clavicular fragments with an intermediate hiatus, which can lead to confusion with a post fracture pseudoarthrosis; In 40% of the cases, what is found is the persistence of a medial or lateral end of the clavicle as the only representation of it; fragmentation into three clavicular portions has been reported twice in the literature. (12)

Alterations in the dentition are frequent (Figure 2-c): delay in the appearance of the primary dentition and its replacement by the secondary one, both of which coincide in an irregular double row; the teeth, on the other hand, without hyperplasia, but deformed, with alterations in the enamel and frequent cavities.

Palpation of the skull shows that the fontanelles are open and the sutures are not welded, although the consistency of the bones of the vault is normal. In the skull, the alterations correspond to the bones of the vault (desmocranium) and not to those of the base (condocranium). The anterior fontanelles appears open, the fronto-parietal and occipito-parietal sutures are normally fused, while the interparietal, parieto-temporal and metopic remain unfused, thus allowing the transverse or brachycephalic growth of the skull (Figure 2-d) to the adulthood. The base of the skull is relatively narrow; the frontal sinuses, hypoplastic, and the fusion, at the level of the mental symphysis, does not get to be carried out normally. The lack of normal fusion of the frontal bones with the nasal bones leads to sinking and elongation of the base of the nose ("saddle" nose). The zygomatic arches may be aplastic, or fail to fuse with the malar bone. (16)

In the pelvis, at the level of the pubis, the hypoplastic pubic branches appear, tapered and leaving a wide space between them, instead of the linear narrowness typical of the pubic symphysis. The sacroiliac joints may appear widened; on the spine, a spine bifida or spine bifida, sitting on the back of the lumbar region, in the corresponding neural arches.

The stature is reduced in a moderate dwarfism, around one and a half meters in males, when they reach adulthood, and a few centimeters less in females; it is the presence of kyphoscoliosis that mainly determines this reduced size due to the shortness of the trunk.

The long bones are of normal development and appearance, and only one coxa vara or coxa valga can be highlighted in the infantile forms; the metacarpals are shortened, highlighting, due to their greater length, the second; terminal phalanges are sharp; those of the thumb and big toe develop from two nuclei of ossification; frequently, the flat bones, scapula, iliacs, ribs, are never affected.

Although it has been included as a diaphyseal dysostosis, the alterations of the diaphysis are actually reduced to a decrease in the process of growth in diaphyseal thickness in the elongated, metacarpal and metatarsal bones.

Genetic counseling for the family about the disease is essential and therapeutic management is based on it, it causes a 50% risk of affecting a child of each patient, we clarify that this disease varies in its clinical presentation and that its main complications are development of the young child and should be assessed early.

Conclusions

CCD is a familial disorder of clinical variability, several bones are affected in these patients, absence of the clavicle bone, upper jaw and teething disorders are the most common condition. It must be managed by a multidisciplinary team of specialists made up of orthopedic, radiologist, geneticist and pediatricians who should evaluate patients to provide the best medical care.

The contribution of the authors: The authors carried out assistance of the cases, writing of the work and documents analysis.

Conflicts of interest: There are no conflicts of interest.

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