Condylar Hyperplasia in a Monozygotic Twin Girl: An Argument About Etiology

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Abstract: The diagnosis of unilateral condylar hyperplasia (UCH) requires a combined assessment consisting of clinical, radiological, and histopathological examination. The etiology of this condition is unknown. The purpose of this study is to report a rare case of UCH in a monozygotic twin. A 15-year-old girl was referred to our department complaining of facial asymmetry and malocclusion. Computed tomography and single-photon emission computed tomography imaging reveal enlargement of the left condyle and condylar neck, and an increased uptake that was diagnosed as active UCH. During the investigation of family and co-twin facial profile, no cases of UCH were identified. From the case reported in this study, the authors raise a hypothesis that can exist some environmental factor that is related in the development of condylar hyperplasia given the occurrence of this disease in one of twins.

Key Words: Facial asymmetry, mandibular condyle, twins, unilateral condylar hyperplasia

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Unilateral condylar hyperplasia (UCH) is a disorder characterized by increased or persistent growth of the condyle. Progressive enlargement of head and neck of the condyle results in facial asymmetry, malocclusion, and shifting midpoint of the chin to the unaffected side.[1] The etiology of condylar hyperplasia is controversial and not well understood. Theories include neoplasia, trauma, infection, abnormal loading, hormonal influences, hypervascularity, and heredity.[2]

As the pathogenesis of condylar hyperplasia is unknown, some authors have advocated that insulin-like growth factors using auto- or paracrine influence on the growth process, and that these could play a role since their overexpression has been implicated in the etiology of different overgrowth syndromes; however, no definitive conclusion could be drawn.[3] The disturbance really lies in the condyle; it seems that alterations in condylar cartilage indicate an unusually rapid or a persistent growth.[4]

Female UCH patients outnumber male UCH patients in international study populations; therefore, female sex may be considered a risk factor for UCH, with a 2:1 female–male ratio seem to be a reasonable estimate. Unilateral condylar hyperplasia might have a genetic origin, for example, an X-linked trait. There is, however, not much evidence for this model due to the great variability in sex distribution.[1]

There are 2 reports in the literature that showed a mirror image of UCH in siblings; the parents and children of the affected siblings were unaffected by this disorder and a genetic cause could not be substantiated, and a Y-linked method of inheritance could be ruled out.[5] Mitani[6] reported a case of hemimandibular hyperplasia in a twin girl, with the mandible indicating a generalized increase in size. The right condyle and condylar neck were hyperplasic and the right ramus height was augmented; neither the parents nor the other children were known to have a condition similar to that of the patient. The purpose of this article is to present a rare case of UCH in a monozygotic twin girl.

CLINICAL REPORT

A 15-year-old female was referred to the Oral and Maxillofacial Surgery Department of Universidad de La Frontera for an assessment of facial asymmetry. The patient's mother reported perceiving an asymmetry of face approximately 6 months prior. They consulted a pediatrician who referred them to a maxillofacial surgeon. The patient had a twin sister (monozygotic) who did not have similar condition. No history of trauma or asymmetry cases in the family was reported. The patient's medical history was not significant. Upon her presentation, a physical examination was completed.

In the clinical evaluation, she presented facial asymmetry, skeletal class III relationship, and chin deviation to the right side. Figure 1 showed facial features of the patient (A–C) and her sister (D–F). Both girls showed anterior open bite and dental crowding in the maxilla; however, the patient had a 4-mm mandibular midline deviation to the right side. Cone beam computed tomography showed a three-dimensional increase of the left condyle only for the patient with facial asymmetry (Fig. 2). Single-photon emission computed tomography (SPECT) showed active growth of the left condyle (Fig. 3); it was not present in the twin sister. Through the association of clinical and imaging features, we concluded that this was a case of active condylar hyperplasia. The risks and benefits of surgical treatment with high condylectomy were discussed, and the patient and her sister were referred for orthodontic treatment and systematic follow-up was chosen. The surgical treatment was postponed until age 16; another evaluation using SPECT was planned to be done in 6 months.

DISCUSSION

Unilateral condylar hyperplasia is a typical growth disorder. The etiology is largely unknown. The value of studying twins and their

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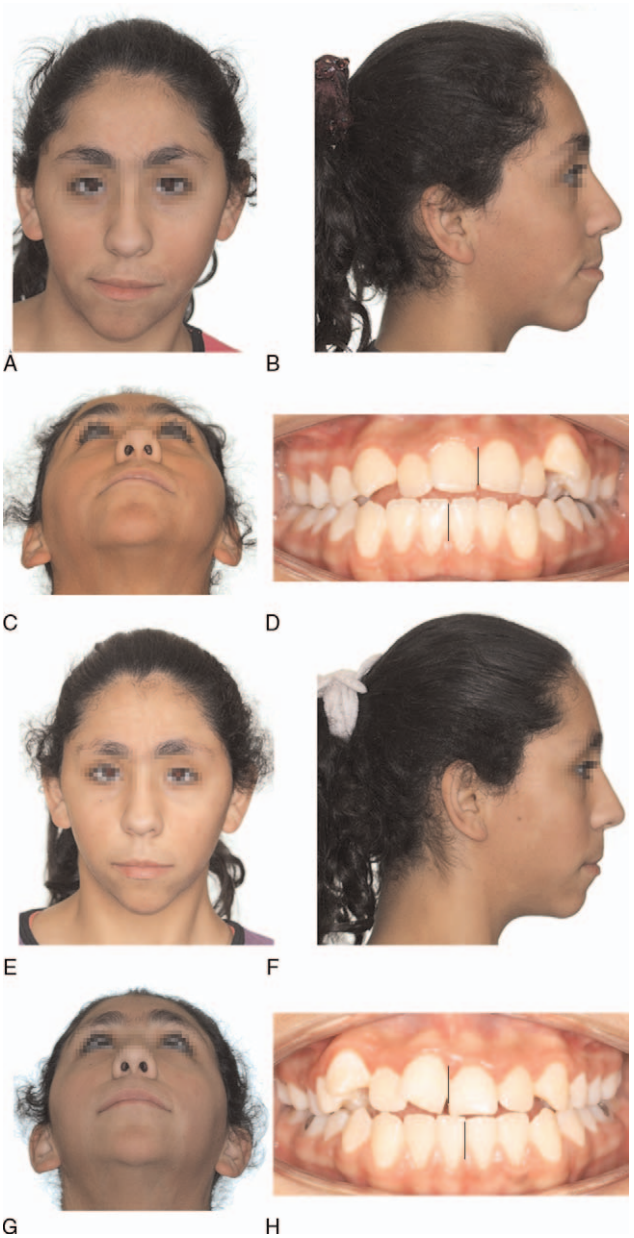

FIGURE 1. 15-year-old female twins. A, Frontal view of face that shows facial asymmetry with chin deviation to the right; B, facial profile; C, inferior view; D, occlusal aspect of the twin with unilateral condylar hyperplasia showing open bite, dental crowding, and mandibular dental midline deviation to the right; E–G, facial aspect of symmetry; H, occlusal aspect of patient without UCH showing open bite, dental crowding, and mandibular dental midline deviation to the left.

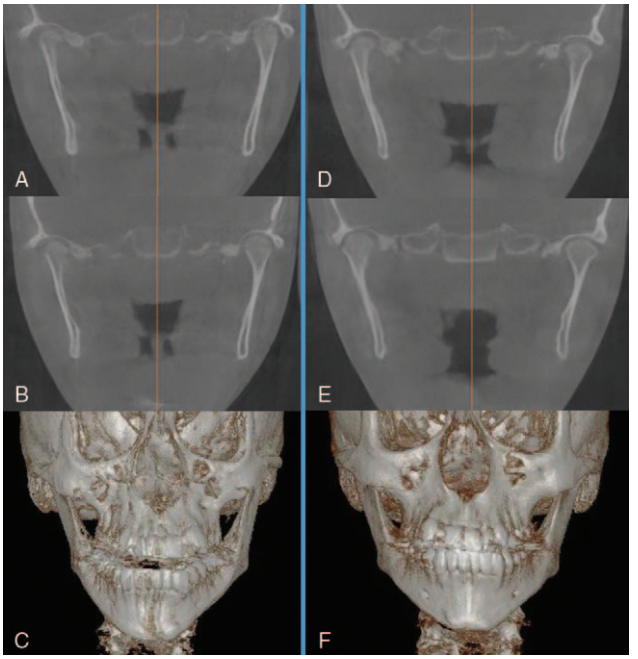

FIGURE 2. CBCT image showing left condylar enlargement in the coronal view. A, Anterior image; B, posterior image; C, three-dimensional craniofacial reconstruction. CBCT image showing symmetry between left and right condyles in the coronal view. A, Anterior image; B, posterior image; C, three-dimensional craniofacial reconstruction.

families is likely to be appreciated increasingly in the future, given their specific advantages for elucidating the relative influences of genetic and epigenetic influences, as well as the roles of environmental factors.[7] From the case reported in this study, we raise a hypothesis that can exist some environmental factor that is related in the development of condylar hyperplasia given the occurrence of this disease in one of twins.

The original notion that the roles of genes and the environment could be separated from each other, leading to the commonly used phrases of "nature versus nurture" and "genes versus the environment," is now recognized as being far too simplistic. Much more focus is now being placed on the interactions between genes and the environment, including the role of epigenetic influences.[7]

There are reports of cases of condylar trauma during childhood that later manifested as hyperplastic growth. Other possible causes taken into consideration, but to date not sustained, are inflammation, hypervascularization, and unspecified genetic factors.[4] Meanwhile, a disturbance of the mandibular condyle during the normal growth period may result in condylar hyperplasia, which could be caused by abnormal local growth stimulation.[2]

The overgrowth of mandibular condyle and facial asymmetry has been related to condylar fracture; it seems to be a rare effect and does not have consensus of this possibility. It was described as compensatory growth, periods of accelerated mandibular growth on the side of fracture mainly in adolescent growth. Lineaweaver et al[8] discuss that some cases of UCH could be relate to mandibular injury that not result in condylar fracture or it was missed, and despite the fact that UCH could have multiple causes they believed in the hypothesis that the main cause was related to mandibular trauma. The earlier contralateral condylar trauma has been utilized as hypothesis of increased incidence of right-sided condyle in CH; it can lead to decreased blood flow in the bone, reduced bone growth in the contralateral condyle, and asymmetric mandibular growth. However, no causal relation between the presence of UCH and reduced bone metabolism and blood flow on the contralateral side was established.[9]

Another factor is related to estrogen; this hormone seems to be a regulator of bone growth. Variations in estrogen levels might help to explain the difference in incidence because approximately all UCH patients were in their reproductive years. However, another important factor may be related to a difference in motivation between female and male subjects to seek care for facial asymmetry.[1]

For reasons yet unknown, one condylar growth center becomes more active than the other. The enlargement of the mandibular condyle has been related to abnormally rapid chondrogenesis with subsequent ossification. As the histological picture is relatively normal and the condition is self-limiting, it is not truly neoplastic.[2]

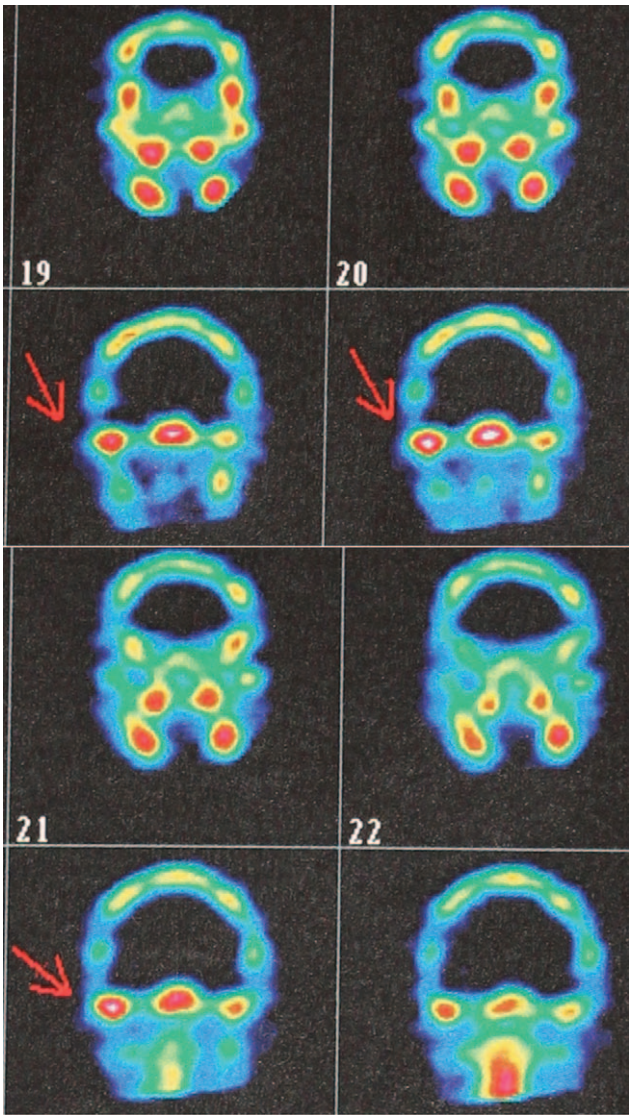

FIGURE 3. Single-photon emission computed tomography shows active growth of the left condyle in 15-year-old female with unilateral condylar hyperplasia.

The condylar cartilage seems to mimic the epiphyseal cartilage of the mandible and function as a growth center; however, from another point of view condyles are just like other parts of the mandible in terms of growth capability, with the only difference being that chondrogenesis occurs.[5] The presence of cartilage islands in trabecular bone indicates proliferative activity of the condyles in normal growth and in hyperplasia; in UCH the hyperplastic cartilage layer undergoes a significant increase in thickness.[10] Some authors tried to establish the relationship between the histological features and activity or aggressiveness of disease. Histological preparation using staining of the agyrophilic nucleolar organizer region (AgNOR) could show nucleolar protein activity that relates to cell duplication. This seems to be related to activity of the disease; however, more studies are required to reach definitive conclusions.[11]

Some authors have been studied the role of growth factors in the etiology of condylar hyperplasia. It is possible that growth factors like the insulin-like growth factors (IGFs) could be involved in its pathogenesis because overexpression of IGF-II is implicated in the etiology of different overgrowth syndromes that showed same features of CH (local postnatal overgrowth syndrome). Götz et al[3] evaluated specimens of hyperplastic condyles from 12 patients. They investigated histologically and immunohistochemically to obtain the distribution of the IGF-I and IGF-II and the IGF-1 receptor. The results revealed juvenile and adult subtypes. In the juvenile cases, strong immunostaining for IGF-I in cartilage and bone supposes an influence on pathological growth processes.

The different expression of the molecules in condylar hyperplasia could be the cause of the persistence activity of chondrocytes. Meng et al[12] performed a study to identify the expression of molecules in condylar hyperplasia according to age and histological type. They used the expression of IGF-1, bone morphogenetic protein-2 (BMP-2), and transforming growth factor-b1 (TGF-b1). Unilateral condylar hyperplasia was divided into 4 histological types according to Slootweg and Miiller.[13] The presence of IGF-1 and BMP-2 was mainly found in the proliferative chondrocyte layer and the hypertrophic chondrocyte layer. Age in type I is younger than that of type II, and the expression of IGF-1, BMP-2, and TGF-b1 in type I is stronger than that in type II. They suggest that the proliferative activity of cartilage in condylar hyperplasia is strongly associated with age and cartilaginous thickness.

Chen et al showed that chondrocytes of patients with condylar hyperplasia seem to enhanced cellular proliferation capacity and expressed significantly higher levels of messenger RNA and protein expressions of IGF-1 and IGF-1R, as compared with chondrocytes of normal condyles. The IGF-1 overexpression for autocrine-driven proliferation is the cause of abnormal cartilage and condylar growth; the secretion IGF-1 from CH chondrocytes is utilized by themselves to enhanced chondrocytes proliferation. This process has a positive feedback loop.[14]

Puberty is a critical period in the development of such a deformity: remarkable growth generally occurs in the jaws during this period and such growth activity might accelerate the growth of the affected condyle, condylar neck, body, and ramus of the mandible.[6] The question as to whether condylar growth is active or has ceased is critical for selecting the appropriate treatment procedure. SPECT is superior to bone scintigraphy because it can isolate the 2 condyles fairly accurately. A single measurement of mandibular MDP–SPECT using the percentage difference in the isotope uptake of the 2 condyles was accurate enough to separate ''active growth'' from ''growth cessation'' of the condyle. Isotope count seems to be the most logical parameter because paired anatomical structures were compared.[15]

In the case reported, the patient and family realized worsening of facial asymmetry at the age of 14, which could coincide with the onset of puberty. The patient presented an active growth of the left condyle as evaluated by SPECT. When growth is still ongoing, nonsurgical treatments are not useful because it is a condition where there has been no information to date regarding the point at which the pathology ends.[16] In this situation, a high condylectomy is considered the best option to avoid secondary adaptive deformation of soft tissue and the maxilla. Corrective surgery for a facial deformity should be envisaged when growth has ceased.[4] In the case reported, the treatment was postponed until age 16, and another evaluation using SPECT was planned to be done in 6 months. In case the condylar hyperplasia remains active, the patient will receive treatment with condylectomy and orthognathic surgery.

The increasing availability of high-precision imaging equipment, coupled with the ability to construct accurate 3D models of the face, will enable practitioners to gather detailed records of interesting patient cases and compare them, including twin pairs who may show similar or different orofacial phenotypes.[7] This development could be applied in the treatment field; using virtual

planning in orthognathic surgery and UCH allows the removal of proportional enlargement of a hyperplastic condyle and the repositioning of the jaw with accuracy.

In the case presented by Mitani, hemimandibular hyperplasia occurred in a patient at the age of 5, which showed a slight enlargement of the right hemimandible that seemed to be accentuated after the age of 12. The patient presented a large open bite at the right buccal segment. The authors state that it was not possible to determine whether the case was monozygotic or dizygotic twins. Monozygotic twins are of the same genotype, whereas dizygotic twins are no more alike than any other siblings.[6] In the case reported in this study, photos of the patient in childhood were reviewed and no sign of asymmetry was found.

Twin studies are particularly useful in assessing facial asymmetry, as they provide the opportunity to assess the phenomenon of mirror imaging, where facial features of one twin are essentially the mirror images of those in the cotwin.[7] Two brothers (siblings) from a Hispanic family presented an unusual case of a mirror image of condylar hyperplasia, and the father had a similar abnormality of his left mandibular condyle.[5] Other authors presented a case of a mirror image of UCH in a brother and sister. The authors performed a bibliographic search and there was no direct confirmation of this in any of the 37 papers on the subject consulted by the present author. The occurrence of a brother and sister exhibiting a ''mirror image'' condylar hyperplasia would seem to be unique.[17] In the case presented, only one twin was affected by condylar hyperplasia and facial asymmetry. About one-fourth of all monozygotic pairs are believed to demonstrate some aspect of a phenomenon known as mirror imaging. Mirror imaging is typically limited to bodily tissues that derive from the ectodermal layer during development; it rarely extends to internal organs such as the heart and stomach. The biological basis of this fascinating phenomenon is still unclear.[7]

Unilateral and bilateral overgrowth of the mandible without condylar hyperplasia have been associated with familial evidence of a protruding chin (hereditary origin).[18] In some individuals the condylar head on the prognathic side was larger than the one on the other side. However, the authors did not consider these cases related to condylar hyperplasia.[18] In an investigation about facial deformity in the family of twins, mandibular prognathism was not found in parents or the other 2 siblings. There is no consensus about this subject, thus more research was required.

The presence of dentofacial deformity with class III skeletal relationship in one of the twins without asymmetry could represent an overgrowth of both condyles that was not possible to identify using SPECT.[19] However, the diagnosis of this condition is complex and involves facial and occlusal analyses over time. Thus, this patient will be monitored regarding mandibular growth and the worsening of the class III relationship.

The discussion about etiology involves genetic or environmental factors; when monozygotic twins are studied, it supposed that genetic factors are equal and they shared most of environmental factors; this results in a common environmental effect. Although an environmental modification may alter the development of the phenotype at a particular moment, gross structural morphology already present may not change readily unless the environmental modification is sufficient to alter preexisting structure.[20] What effects of the environment could have affected one of the twins and not the other? How have these effects contributed to the pathogenesis of condylar hyperplasia? Although the trauma hypothesis has been raised, it is unlikely that this is true for most cases. The result is more questions than definitive answers.

This article presented a rare case of UCH in a monozygotic twin. The genetic investigation and the follow-up of the case may clarify in part the questions raised in this study.

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