Clinical, radiological, and auxological characteristics of patients with cleidocranial dysplasia followed in a pediatric referral hospital in Argentina

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ABSTRACT

Cleidocranial dysplasia is an autosomal dominant skeletal dysplasia caused by mutations in the \textit{RUNX2} gene; its prevalence has been estimated at 1/1 000 000 newborn infants. This study presents 37 patients (22 girls) assessed between 1992 and 2016 at the Skeletal Dysplasias Multidisciplinary Clinics of Hospital Garrahan, Argentina. Findings: 35% of positive family history; median age at the time of diagnosis: 2.61 years old; positive radiological findings in the skull and pubis: 95%; in the clavicles: 100%. Dental and hearing complications were common. Auxology: boys had a median height of -1.81 SD (-3.26 to 0.2) and girls had a median height of -1.36 SD (-4.28 to 1.36). Five out of 13 patients were short for parental height. Adult height (median): 162.8 cm in boys and 149.2 cm in girls. No evident alterations were observed in the sitting height/height ratio. One patient had true macrocephaly; 12 (32%), relative macrocephaly. Intrafamily variability was described in terms of height. Key words: cleidocranial dysplasia, growth, clavicle, cranial fontanelles.

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INTRODUCTION

Cleidocranial dysplasia (CCD) (MIM 119600) is a skeletal dysplasia characterized by persistent fontanelles and aplasia/hypoplasia of the clavicles, with a wide phenotypic variability.\textsuperscript{1,2} The affected population has been described to have moderate short stature,\textsuperscript{1,3-5} but few data have been reported regarding other auxological outcome measures. Its prevalence is 1/1 000 000 births, regardless of sex.\textsuperscript{4}

CCD is caused by autosomal dominant inherited mutations in the \textit{RUNX2} (runt-related transcription factor 2) gene found on the short arm of the chromosome 6.\textsuperscript{1,2,4,6} Insertions, deletions, nonsense mutations, and missense mutations have been identified.\textsuperscript{6-10} In most patients, these are \textit{de novo} mutations.\textsuperscript{4} Germline mosaicism has also been proposed.\textsuperscript{1} Pathogenic variants have been observed in 60-70% of patients with clinical diagnosis.\textsuperscript{4}

The \textit{RUNX2} gene encodes the Cbfal transcription factor, which is essential for osteoblast differentiation and skeletal morphogenesis, and is involved in intramembranous and endochondral ossification. \textit{RUNX2} gene mutations result in a disorder that combines isolated bone defects (dysostosis) with progressive tissue defects (dysplasia).\textsuperscript{2}

Clinical and laboratory characteristics overlapping with hypophosphatasia have been described in a small subgroup of patients, possibly due to an alteration in the expression of the \textit{TNSALP} (tissue-nonspecific alkaline phosphatase) gene.\textsuperscript{2,5,11,12} \textit{RUNX2} knockout mice show a complete lack of bone mineralization and absence of \textit{TNSALP} expression.\textsuperscript{13}
The diagnosis of CCD is based on clinical and radiological findings.1,2,4 The differential diagnoses should include hypothyroidism, congenital pseudarthrosis of the clavicle (MIM 118980), and other skeletal dysplasias.1,4

Follow-up has been recommended to look for orthopedic, dental, and hearing complications, sinus and middle ear infections, upper airway obstruction, and osteoporosis.3,4 Although some authors have reported a delay in motor milestone achievement,3,4 education, life expectancy, and functions are normal.2,3

OBJECTIVES
To provide a clinical and auxological description of patients diagnosed with CCD.

MATERIALS AND METHODS
The medical records of patients with a clinical and radiological diagnosis of CCD were reviewed. This retrospective study was based on data about children, and their parents, assessed between 1992 and 2016 at the Skeletal Dysplasia Multidisciplinary Clinics of Hospital “Prof. Dr. Juan P. Garrahan,” Argentina.

The following outcome measures were considered: age, age at the time of diagnosis, sex, reason for consultation, affected family members, weight, body length, height, sitting height, head circumference, and the presence of associated complications.

The same observer conducted the anthropometric measurements at the anthropometry laboratory of the Department of Growth and Development using the standardized techniques recommended by the Sociedad Argentina de Pediatría (SAP).14

Harpenden instruments were used to measure body length, vertex - buttocks length, height, and sitting height. A lever scale was used to measure weight. Intraobserver measurement errors were 0.11 cm, 0.10 cm, and 0.10 kg for body length, height, and weight, respectively.

Weight and body length at birth were obtained from the birth records of patients, if available.

Adult family members were considered for the analysis of final height.

Standard deviation scores (SD) were estimated for anthropometric data. Height and body proportions (sitting height/height and head circumference/height) were compared to Argentine standards;15-16 British data from 1990 were used to assess head circumference.17 Body mass index (BMI) values were compared to data from a multicenter study carried out by the World Health Organization (WHO) in children younger than 5 years and data from the Centers for Disease Control and Prevention (CDC) corresponding to children older than 5 years.18,19

The midparental height (MPH) was estimated if both parents were not affected, and described as SD: MPH = (HZsF + HZsM)/2, where HZsF means the height Z-score of the father and HZsM is the height Z-score of the mother, considering MPH ± 1.28 SD as the normal genetic range in prepubertal children.20

Patients were considered to have reached their final height once they had reached their adult pubertal development (Tanner stage V breast development or two years after the menarche in girls; 15-mL testicular volume in boys).

Radiological diagnosis was confirmed by two of the authors (MRC and RRM). The diagnostic criteria for each radiological characteristic were as follows: presence of Wormian bones if the frequency of these bones was 10 or more,21 delayed closure of the anterior fontanelle if it remained open after 2 years old,22 hypoplasia of the clavicles if the lateral half of the clavicle was absent,22 delayed pubic bone ossification if they were not ossified after 6 months old, and lack of ischiopubic branches fusion if there was no fusion in patients aged 12 years and older,22-24 hand anomalies in the presence of delayed carpal bone ossification or if there were cone-shaped epiphyses or pseudoepiphyses.2

Complications were considered if registered in the medical record.

RESULTS
The study included 37 patients with CCD; 59% were girls (n= 22). Patients’ median age was 1.59 years (0 to 16.09) at the first visit and 2.61 years (0 to 16.09) at the time of diagnosis. Patients were followed for a median of 3.67 years (0 to 12.67). In 35% of cases (n= 13), other family members were affected.

The two main reasons for consultation were skull anomalies (skull asymmetry, broad fontanelle, diastasis of the cranial sutures) in 51% of cases (n= 19) and suspected skeletal dysplasia in 19% (n= 7, 2 of them had suspected CCD). Other reasons included coxa vara or valga (n= 6), short stature (n= 4), scoliosis (n= 2), clavicle alterations (n= 2), hypotonia (n= 1), and delayed motor milestone achievement (n= 1). Some patients had more than one reason for referral.
Table 1 shows the clinical findings; data are compared to the bibliography.

AUXOLOGICAL ANALYSIS

Boys (n= 15)

The records of anthropometric measurements at birth were available for four patients. One patient had intrauterine growth restriction (IUGR) in terms of weight, body length, and head circumference for no attributable reason. Figure 1.A shows the height distance curve for boys; it is evident that all, except one, have a normal growth pattern. This patient is being studied for delayed growth; his laboratory parameters are normal. At the last visit, the median height was -1.81 SD (-3.26 to 0.2) and the median age, 6.43 years (0.92 to 16.79). Among the patients for whom parental height was reported (n= 8), the median differences between MPH in SD and boys’ height in SD was -1.12 SD (-2.03 to 1.44); three patients were short and one was tall for their parents’ height.

The median head circumference at the last visit was -0.85 SD (-2.23 to 0.81). No boy had true macrocephaly; however, all but one (n= 14) were above the 50th centile in the head circumference curve. As shown in Figure 2.A, seven patients had relative macrocephaly.

Girls (n= 22)

The records of anthropometric measurements at birth were available for half of the patients (n= 11). Only one girl had IUGR in terms of body length and head circumference for no attributable reason. Figure 1.B shows the height distance curve for girls; at the last visit, the median height was -1.36 SD (-4.28 to 1.36) and the median age, 5.70 years (0.44 to 19.0). One girl had extremely short stature and normal laboratory values. Among patients for whom parental height was reported (n= 5), the median differences between MPH in SD and girls’ height in SD was -0.88 SD (-2.88 to 0.78). Two patients were short for their parents’ height.

The head circumference at the last visit was -0.04 SD (-3.47 to 2.4). Most girls (n= 19) were above the 50th centile in the head circumference curve; one had true macrocephaly. The head circumference/height chart (Figure 2.B) shows that five girls had relative macrocephaly.

No alterations were observed in the sitting height/height ratio.

Table 1. Clinical characteristics of the sample (37 patients). Findings reported in the bibliography3,25

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>Cases (n= 37)</th>
<th>Cooper3 (n= 283), Golan25 (n= 90)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dento-maxillary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delayed primary and secondary eruption, hypoplastic teeth, enamel defects</td>
<td>73</td>
<td>98</td>
</tr>
<tr>
<td>Archea palate</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Cleft of the soft palate</td>
<td>3</td>
<td>4,4</td>
</tr>
<tr>
<td>Hearing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pathological audiometry</td>
<td>30</td>
<td>38</td>
</tr>
<tr>
<td>or otoacoustic emissions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Language delay</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Upper airways</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic otitis media</td>
<td>14</td>
<td>62</td>
</tr>
<tr>
<td>Chronic sinusitis34,4</td>
<td>11</td>
<td>34.4</td>
</tr>
<tr>
<td>Rhonchopathy / adenotonsillectomy</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td>Respiratory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent bronchospasm</td>
<td>19</td>
<td>11</td>
</tr>
<tr>
<td>Orthopedics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hip anomaly (8 coxa vara, 1 coxa valga)</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Scoliosis</td>
<td>16</td>
<td>17</td>
</tr>
<tr>
<td>Pectus deformity (6 pectus excavatum, 1 pectus carinatum)</td>
<td>19</td>
<td>19</td>
</tr>
<tr>
<td>Education</td>
<td>normal</td>
<td></td>
</tr>
</tbody>
</table>
The BMI at the last visit was 0.23 SD (-1.46 to 1.6). One girl was overweight.

Final height

The data about adult height were available for four boys (two patients who reached maturity and two affected fathers); their median height was 162.8 cm, which corresponded to -1.47 SD (-2.41 to -0.67) (Figure 1.A).

The data about adult height were available for seven girls (four patients who reached maturity and three affected mothers). The median height was 149.2 cm, corresponding to -1.89 SD (-3.45 to 0.62) (Figure 1.B).

Although data were scarce, the comparison of height between affected parents and their children indicated that there could be intrafamily variability. In 5/10 cases, differences were observed between the father/mother’s height and that of his/her child of more than 1 SD (Table 2). In a family with six affected members, the variability in height ranged between -0.74 and -2.05 SD (Figure 3).

Radiological findings

The radiological characteristics of CCD were positive in a high number of studied X-rays: skull anomalies were observed in 95%; clavicle alterations, in 100% (both clavicles in 75%); delayed pubic bone ossification, in 96%; and hand alterations, in 100% of patients (Figure 4, Images 1, 2, 3, and 4).

DISCUSSION

Our study provides a longitudinal description of the auxological characteristics of a series of patients with CCD. Out of a total of 1409 patients assessed between 1992 and 2016 at the Skeletal Dysplasias Multidisciplinary Clinics of Hospital Garrahan, 37 (2.7%) were diagnosed with CCD. Their median age at the time of diagnosis was 2.61 years. No patient had had an antenatal diagnosis of CCD, although some had a family history. This is consistent with the bibliography, where the early diagnosis of CCD has been described to be difficult because of the often mild manifestations due to its wide phenotypic variability.  

\[\text{Figure 1 (A and B). Height curves for boys and girls, respectively}\]

\[\text{Figure 2 (A and B). Head circumference/height curves for boys and girls, respectively}\]
Similar to what has been mentioned in the bibliography, dental anomalies, upper airway and hearing disorders were frequent.\textsuperscript{1,3,4,25} Other described skeletal anomalies, such as pubic bone ossification delay, coxa vara or valga, scoliosis, and pectus deformity, were also found in this group of patients.\textsuperscript{3,4}

In terms of cognitive development, in our group, like what has been described by Cooper, no significant differences were observed in relation to the level of education achieved by affected individuals and their healthy counterparts.\textsuperscript{3}

This pathology is not known as an extremely short stature condition.\textsuperscript{3} In relation to growth, only two patients had IUGR, without other known cause. In spite of the small size of our sample (11 adults), the final height was close to the values reported in the bibliography; for boys, the median height was 162.8 cm and for girls, 149.2 cm, whereas the bibliography describes 165.0 cm and 156.0 cm for boys and girls, respectively.\textsuperscript{3}

Some of the patients were short for their genetic height range when their parents were not affected. In addition, one boy had delayed growth and one girl, extremely short stature (\textminus 4.28 SD), which has not been reported in the bibliography. In the case of the girl, no other reason for short stature was found; her father was affected but he did not have extremely short stature (162.0 cm, \textminus 1.64 SD), which demonstrates intrafamily variability.

In relation to head circumference, only one patient had true macrocephaly, whereas 32.4\% of patients had relative macrocephaly.

No alteration was observed in the body proportions assessed, as sitting height/height ratio, when compared to the Argentine standard.\textsuperscript{16}

Our interpretations are limited due to the absence of a molecular analysis, which, in this group, may show molecular variations.

**Table 2. Comparative data about the height of affected parents and their children, and among affected siblings**

<table>
<thead>
<tr>
<th>Case</th>
<th>Affected parent’s height (SD)</th>
<th>Patient’s age (years old)</th>
<th>Patient’s height (cm)</th>
<th>Patient’s height (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-1.64</td>
<td>7.04</td>
<td>95.80</td>
<td>-4.28*</td>
</tr>
<tr>
<td>2</td>
<td>-0.74</td>
<td>19.00</td>
<td>152.90</td>
<td>-1.28</td>
</tr>
<tr>
<td>3</td>
<td>-0.74</td>
<td>19.00</td>
<td>148.20</td>
<td>-2.05*</td>
</tr>
<tr>
<td>4</td>
<td>-2.05</td>
<td>3.51</td>
<td>94.00</td>
<td>-2.05</td>
</tr>
<tr>
<td>5</td>
<td>-2.05</td>
<td>0.44</td>
<td>61.00</td>
<td>-1.57</td>
</tr>
<tr>
<td>6</td>
<td>-1.28</td>
<td>1.58</td>
<td>78.40</td>
<td>-1.11</td>
</tr>
<tr>
<td>7</td>
<td>-2.76</td>
<td>14.36</td>
<td>107.80</td>
<td>-1.85</td>
</tr>
<tr>
<td>8</td>
<td>-1.40</td>
<td>6.43</td>
<td>67.00</td>
<td>-3.26</td>
</tr>
<tr>
<td>9</td>
<td>-2.94</td>
<td>0.92</td>
<td>99.40</td>
<td>0.20*</td>
</tr>
<tr>
<td>10</td>
<td>-1.98</td>
<td>3.45</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SD: standard deviation score.
Cases 2, 3, 4, 5, and 6 correspond to members of the same family. Cases 2 and 3 are siblings. Cases 4 and 5 are siblings, and the children of case 3. Case 6 is the child of case 2.
In 5/10 cases, marked with an asterisk (*), differences were observed between the father/mother’s height and that of his/her child of more than 1 SD. It is worth noting the differences among the affected siblings.
CONCLUSION

The median height of patients with CCD was within the normal limits; however, both boys and girls were below the 10th height centile and some patients even had mild short stature. In relation to body proportions, no alterations were observed in most patients, although one third had relative macrocephaly. Although few data were available about affected family members, intrafamily variability was observed in terms of height.

REFERENCES


Figure 4. Radiological findings among affected patients

Image 1: skull, front and lateral views. Girl, 5.9 years old. Permeable anterior fontanelle, Wormian bones (thin white arrow), midfacial hypoplasia.
Image 3: pelvis, front view. Adult male. Lack of ischiopubic branches fusion (thin arrow).
Image 4: left hand, front view. Girl, 6.0 years old. Delayed carpal bone ossification. Pseudoepiphyses of the metacarpal bones (thin arrow). Cone-shaped epiphyses (thin white arrow).


