Cleidocranial Dysplasia: Management of the Multiple Craniofacial and Skeletal Anomalies

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Abstract: Cleidocranial dysplasia (CCD) is a rare autosomal dominant disorder caused by mutations in the Runx2 gene. The CCD is characterized by frontal bossing, a patent anterior fontanelle, presence of Wormian bones, midface hypoplasia, multiple dental abnormalities, clavicular hypoplasia or aplasia, skeletal abnormalities, and short stature. The aims of this study are to report the phenotypic manifestations of all patients who presented with CCD and to review the multidisciplinary management of these patients. The longitudinal data of patients with a diagnosis of CCD treated at The Australian Craniofacial Unit from 1980 to 2019 were reviewed. Fourteen patients were identified for inclusion in this study. The age at referral to the unit ranged from 1 week old to 49 years old (mean 11.2 years old). All patients had clinical features of frontal bossing, a patent anterior fontanelle, multiple Wormian bones, midface hypoplasia, abnormal dentition, clavicular hypoplasia/aplasia, and normal intellect. Eleven patients had obstructive sleep apnea. Eight patients had positive family history. Speech issues were found in 6 patients and abnormal hearing was found in 4 patients. Seven patients who underwent skeletal survey were found to have skeletal abnormalities. All patients were evaluated and managed by the multidisciplinary team, which consisted of craniofacial surgeons, pediatric dentists, orthodontists, ENT surgeons, pediatricians, clinical geneticists, radiologists, orthopedic surgeons, and social workers. All patients were treated by dentists/orthodontists requiring multiple surgical interventions and orthodontic treatment. Seven patients who had recurrent ear infection underwent ventilation tube insertion. Seven of 11 patients who had obstructive sleep apnea underwent adenotonsillectomy. Four patients underwent orthognathic surgery to correct midface hypoplasia and malocclusion. Two patients had cranioplasty for correction of metopic depressions. The characteristic findings of patients with CCD involving multiple regions of the body should draw clinicians’ attention to the need for multidisciplinary management of these patients.

Key Words: Cleidocranial dysplasia, craniofacial anomalies, multidisciplinary management, skeletal anomalies

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Cleidocranial dysplasia (CCD) is a rare autosomal dominant disorder, affecting 1 in 1,000,000 individuals worldwide and is caused by mutations in the transcription factor, RUNX2. RUNX2 plays important roles in osteoblast differentiation, skeletal morphogenesis, chondrocyte proliferation and differentiation, and tooth formation. The CCD is characterized by frontal bossing, a patent anterior fontanelle, presence of Wormian bones, midface hypoplasia, delayed exfoliation of primary teeth, delayed or failing eruption of the permanent dentition, multiple supernumerary teeth, clavicular hypoplasia or aplasia, skeletal abnormalities (such as a narrow and cone-shaped thorax with short ribs, pes planus, genu valgus, and scoliosis), and short stature† (Supplementary Digital Content, Table 1, http://links.lww.com/SCS/B227, Figs. 1–3). Clinical manifestations in patients with CCD include recurrent upper respiratory tract and ear infections, hearing loss, and speech problems. About two-thirds of patients with CCD are associated with mutations of RUNX2.² Multiple mutations have been identified in the Runx2 gene, primarily clustered in the Runt domain. Recent studies have shown that microdeletions (allelic heterogeneity) lead to abnormalities in the craniofacial complex emphasizing the need for more studies evaluating the genotype-phenotype correlations of patients with CCD.³–⁶ Because of multiple effects of CCD on the craniofacial region and other skeletal abnormalities, successful treatment requires a thoroughly planned, multidisciplinary approach. Notwithstanding advances in surgical and clinical techniques, clinicians treating patients with CCD still face numerous challenges due to the complexity of this condition. The aims of this study are to report the phenotypic manifestations of all patients who presented with CCD and to review the multidisciplinary management of these patients.

METHODS

After approval from WCHN Human Research Ethics Committee, information was collected using standardized Pro forma. The data of patients with a diagnosis of CCD treated at Australian Craniofacial Unit from 1980 to 2019 were reviewed. The data included age, gender, clinical reports, laboratory reports, radiographic findings and treatment.

RESULTS

Fourteen patients were included in this study. Eight patients were male and 6 patients were female. The age at referral to the unit ranged from 1 week old to 49 years old (mean 11.2 years old). All
patients had patent anterior fontanelle, frontal bossing, midface hypoplasia, abnormal dentition, clavicular hypoplasia/aplasia, and normal intellect. Eleven patients had obstructive sleep apnea. Seven patients who underwent skeletal survey were found to have positive radiologic findings, including spina bifida, wide pubic symphysis, hallux valgus, pes planus, genu valgus, scoliosis, pectus carinatum, and pectus excavatum. Speech and language anomalies were found in 6 patients and abnormal hearing was found in 4 patients. Eight patients had positive family history. RUNX2 mutation was found in all the 3 patients who had genetic analysis.

In terms of management, all patients were evaluated by a multidisciplinary team, which consists of craniofacial surgeons, pediatric dentists, orthodontists, ENT surgeons, pediatricians, clinical geneticists, radiologists, orthopedic surgeons, and social workers. All patients were treated by dentists/orthodontists requiring multiple surgical interventions (surgical removal or exposure of impacted teeth, extraction of primary, and supernumerary teeth) and orthodontic treatment. Seven patients who had recurrent ear infection underwent ventilation tube insertion. Seven of 11 patients who had obstructive sleep apnea underwent adenotonsillectomy. Four patients underwent orthognathic surgery to correct midface hypoplasia (2 had bimaxillary osteotomy and the other 2 had Le Fort I osteotomy). Two patients had cranioplasty for correction of metopic depressions (Supplementary Digital Content, Table 2, http://links.lww.com/SCS/B227).

**DISCUSSION**

Clavicular abnormality in patients with CCD was first described by Meckle in 1760; however, the clavicular abnormality in combination with calvarial defects was recognized by Scheuthauer in 1871.7 The term CCD was first introduced in 1898 by Marie and Sainton.8 The CCD is an autosomal disorder with a generalized involvement of bone. This is a trait with high penetrance and marked variability of expression. As the name “cleido-cranial” suggests, the most apparent characteristics are abnormalities of the head area and clavicles, producing a characteristic and distinctive appearance of the face and shoulders.

The CCD can be diagnosed prenatally. The first reports on the prenatal diagnosis of CCD based on ultrasound were published in the mid-1990s.9,10 Both reports focused on hypoplasia and hypocalcification of the clavicles in the fetus. Using ultrasonography, Hassan et al observed abnormal skull ossification combined with short clavicles in a fetus with CCD.11 Stewart et al observed that the cranium appeared less well ossified than expected for gestational age in a fetus with CCD; this fetus also had hypoplasia of the clavicles.12

The dental lamina for the primary and permanent dentition is structurally normal in CCD. However, the subsequent dental lamina and the lamina for the permanent molars do not undergo apoptosis at the expected time. Consequently, the dental lamina extends distally to form supernumerary molars. Markedly delayed or arrested eruption of the first formed permanent teeth even in regions without supernumerary teeth is probably caused primarily by reduced bone resorption and decreased resorption of the roots of the primary teeth, and secondarily by the presence of multiple supernumerary teeth in the eruption pathway.13

Otologic and audiologic manifestations of CCD are mainly due to facial skeletal abnormalities. Membranous and endochondral ossifications centers are found in the outer ear, middle ear, and skull base. As a result, they are vulnerable to malformations in patients with CCD.14 Visosky et al reported nine patients with CCD in which all 9 patients showed highly variable expression of hearing abnormalities and hearing loss was present in 3 patients.15 In our study, 7 from 14 patients required ventilating tube insertion due to recurrent middle ear infections and hearing loss was found in 4 patients. Because of high rates of otologic issues, patients with CCD should be routinely evaluated by an otolaryngologist.

Kulczyk et al reported that children with CCD had underdeveloped maxillary sinuses with significantly diminished volume as...
well as smaller vertical and horizontal dimensions of midface compared with control group.18 In our series, all 14 patients have maxillary hypoplasia, which is comparable to the previous study by Kulczyk et al.

Patients with CCD normally do not commonly have central nervous system abnormalities. However, Myers et al found a report of male neonate diagnosed with CCD who also had asymptomatic tonsillar herniation revealed on computed tomography and magnetic resonance image studies.17 In our study, there was 1 patient with asymptomatic middle cranial fossa meningocele, which was managed conservatively.

Takenouchi et al reported a middle-aged patient with CCD with progressive cognitive decline due to repetitive cerebral trauma with neuroimaging studies revealed extensive cystic encephalomalacia beneath the defective skull.19 The authors suggested that protective helmets might be necessary for some patients with CCD to prevent repeated brain injury through the defective skull.

Speech and language anomalies are common in patients with CCD. Difficulties with articulatory placement are sometimes secondary to malocclusion, anterior open bite, and high arched palate. Problem with hypernasality is denasal vocal quality secondary to malocclusion, anterior open bite, and high arched palate. Also, because of the long period of dental treatment, speech therapy is often requisite for the patients. In this study, 6 patients had speech and language problems, which included hypernasality, disarticulation, and delayed speech development.

Most patients with CCD have maxillary deficiency, class III malocclusion, short lower 3rd of the face, and anterior open bite. Combined orthodontic treatment and orthognathic surgery should be used for the correction of the dentofacial discrepancy.17,18 From our report, 4 patients underwent orthognathic surgery to correct midface hypoplasia and malocclusion (2 had bimaxillary osteotomy and the other 2 had Le Fort I osteotomy).

McGuire et al reported a series of 7 adults with CCD who expressed concerns about the appearance of their forehead and were treated using a cranioplasty technique to correct visible metopic suture defects in the forehead region.20 Cranioplasty procedures can be used to address aesthetic concerns or to correct skull defects. The procedures can be offered to CCD patients as part of their overall comprehensive craniomaxillofacial management. Hwang et al demonstrated successful clinical outcome after surgical interventions for correction of frontal bossing using forehead plasty with bone cement.21 Two of our patients with metopic depressions who had aesthetic concerns underwent cranioplasty using hydroxyapatite bone substitute with satisfactory outcome (Fig. 4).

Orthopedic problems in patients with CCD have been well described in the literature.22 The problems involve clavicle, scapula, thorax, sternum, hands, feet, pelvis, hips, and spine. The CCD may lead to complications such as scoliosis and kyphosis concurrent with various orthopedic involvements due to skeletal dysplasia. BAlioglu et al reported a successful treatment of progressive scoliosis in 2 adolescent patients with CCD.23 The authors also suggested that surgical treatment might be necessary because spinal deformities in CCD are of progressive nature. Positive radiologic findings from skeletal survey in our patients included spina bifida, wide pubic symphysis, hallux valgus, pes planus, genu valgus, scoliosis, pectus carinatum, and pectus excavatum. All patients were under the care of orthopedic surgeons as part of the multidisciplinary team.

CONCLUSION

The CCD is a congenital skeletal disorder which has multiple effects on the craniofacial region and clavicles along with other skeletal abnormalities. Patients with CCD endure both functional and aesthetic issues. While dental abnormalities are one of the most reported features that cause significant trouble to the patients, other characteristic findings involving multiple parts of the body should draw clinicians’ attention to the well-planned, multidisciplinary management of these patients.

REFERENCES

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