

CASE REPORT

Cleidocranial dysplasia—A case report of incidentally found and lately diagnosed disorder

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1 | INTRODUCTION

Cleidocranial dysplasia (CCD) is a rare genetic disorder inherited in an autosomal dominant pattern. *RUNX2* gene (the gene required for osteoblastic differentiation) found on chromosome 6p21 is mutated in this disorder resulting in the impaired differentiation of stem cells into osteoblasts, hence the defective bone formation. About one in a million people is reported to have this disorder. About 20%–30% of reported cases are found to be sporadic, though the majority of cases are inherited.^{1,2}

This disease presents with skeletal disorders of several bones. Based on the degree of skeletal involvement, the term cleidocranial spectrum disorder is used to represent the gamut/clinical continuum ranging from classic CCD (involving delayed closure of the cranial sutures, hypoplastic or aplastic clavicles, and dental abnormalities) to mild CCD to isolated dental anomalies without other skeletal features. Diagnosis is based on clinical grounds and radiological features for classic CCD. Suggestive clinical findings and heterozygous pathogenic variants in *RUNX2* based on molecular genetic testing also establish the diagnosis.³

Herein, we present a case of CCD, along with a review of relevant literature, diagnosed late due to milder symptomatology, scarce health centers in the rural periphery, and financial constraints affecting timely health access.

2 | CASE REPORT

A 73-year-old woman from the rural periphery was admitted to medicine's high dependency unit for acute exacerbation of COPD with type 2 respiratory failure, bilateral lower lobe pneumonia, and acute kidney injury. She presented with complaints of shortness of breath, and cough with sputum production for 5 days. There was no history of fever, chest pain, hemoptysis, jaundice, hematemesis, hematuria, joint pain, and skin rashes. She had a history of smoking (10 pack years) which she left 40 years back. She was a known case of hypertension and COPD under medication for 10 years.

On examination, her general condition was ill-looking, GCS 9/15. She was dyspneic with a respiratory rate of 28 breaths/min. Her blood pressure was 150/90 mm of Hg. Her oxygen saturation was 96% at 6 L per minute. On respiratory examination, there was decreased air entry on the bilateral chest and bilateral diffuse wheeze. Abdominal examination, central nervous system examination, and cardiovascular examinations revealed no gross abnormalities. Blood investigation revealed leukocytosis (WBC-15000/mm³), and deranged renal function tests. Liver function tests, serum glucose, coagulation profile, and urinalysis were within normal limits. She was managed for acute exacerbation of COPD and acute kidney injury with antibiotics, corticosteroids, fluids, and nebulization.

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Of particular attention apart from this morbidity, physical examination revealed a short stature (height of 140 cm), enlarged calvarium with open anterior and posterior fontanelle along with frontal, parietal, occipital bossing, and metopic depression. On facial examination, there was the presence of hypertelorism and a broad flattened nasal bridge along with midface retrusion suggesting underdevelopment of the maxilla and a relative mandibular prognathism. On examining her oral cavity, she had nearly total edentulism with only a few teeth remaining and a high arched palate. (Figures 1 and 2) Pertinent dental abnormalities could not be checked due to edentulism. She had brachydactyly, short and broad fingers, and clinodactyly. In addition, her opposite shoulders could be adducted toward the midline. (Figure 3).

With the suspicion of cleidocranial dysplasia based on physical examination, the radiographic assessment was done to confirm the findings and establish the diagnosis. The routine chest X-ray performed showed no radiologic shadow of the clavicle bone. (Figure 4) Skull radiograph showed enlarged calvarium, osteosclerosis in the occipital bone, open anterior and posterior fontanelles, frontal, parietal and occipital bossing, wormian bones in the



FIGURE 1 Figure of proband showing short stature

parieto-occipital and frontoparietal regions, and hypoplastic maxilla. There was decreased pneumatization of the frontal sinus. Also, there was poor pneumatization of mastoid air cells. (Figure 5) Radiographs of the pelvis showed shortened femoral neck on both sides, chef's hat femoral head, widened sacro-iliac joint, coxa vara in the right hip, and coxa valga in the left hip. Based on clinical findings and radiological features, the final diagnosis of cleidocranial dysplasia was made. (Figure 6).

In addition, she had a history of recurrent sinus infections and supernumerary teeth. Her elder daughter and younger daughter had similar findings of frontal bossing with midline depression, shoulder approximation, short stature, and hearing loss since birth. Also, her younger daughter's son had similar findings as his mother, which portrayed the complete penetrance of this condition. (Figure 7) We counseled the proposita's younger daughter to monitor her son for various complications that may come along and suggested she seek medical attention for her son regularly. We explained the possible complications including recurrent ear and sinus infections, hearing loss, signs, and symptoms of upper-airway obstruction, dental abnormalities, orthopedic complications, possible developmental effects, and the need to protect the head from blunt trauma.

3 | DISCUSSION

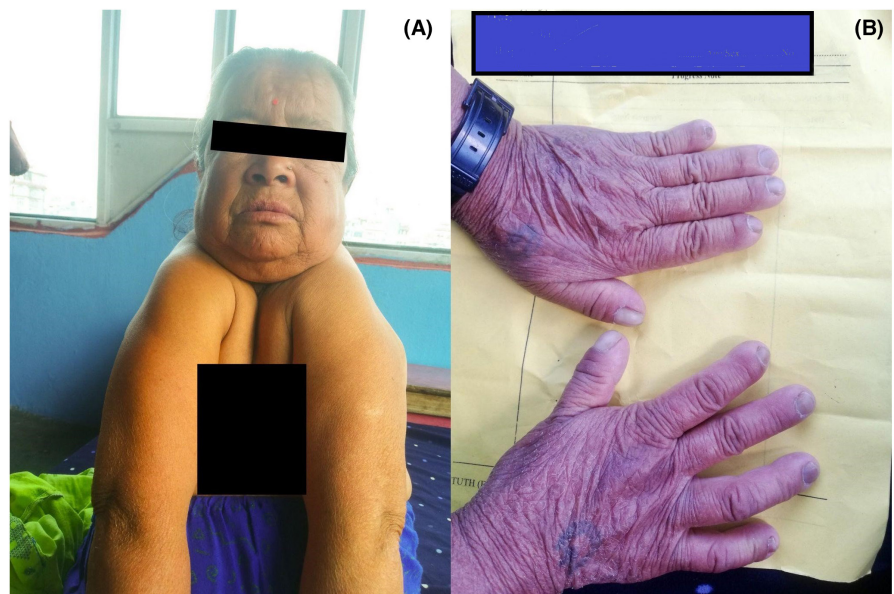
CCD is an autosomal dominant disorder with high penetrance and variable expression and is characterized by dysmorphology of bones located in the skull, face, and thorax. Generally, CCD is diagnosed at birth, childhood, or adolescence.^{1,4} Here, we reported an elderly case with penetrance in three generations, diagnosed late in the first and second generations. The low incidence of CCD, lack of affordable medical access, and residing in a rural periphery of a developing country might have obscured the recognition of this particular case in previous clinical settings.

Mutation of the *RUNX2* gene (OMIM-600211) (loss of function or haploinsufficiency) results in the inability to signal mesenchymal cell-gathering thereby affecting its differentiation towards the intramembranous and endochondral bone formation. The result is the defective bone formation of the craniofacial and axial skeleton and clavicles.^{1,5} The most evident abnormalities include that of the head and clavicles as the name “cleido-cranial” suggests. Hypermobility of the shoulders is one of the most presumptive clinical findings of CCD. The shoulders can be variably approximated in front of the chest due to the partial or total absence of clavicles and associated muscle defects.⁶ The genetic testing was not done in our case due



FIGURE 2 Lateral face image showing midface retrusion and relative mandibular prognathism (A), hypertelorism, broad flattened nasal bridge, frontal bossing and metopic depression (B), and high arched palate (C).

FIGURE 3 Proband's image showing an approximation of shoulders in midline facilitated by aplastic clavicles (A) and Hand photograph showing brachydactyly, short and broad fingers, and clinodactyly (B).



to the financial constraints of the patient and the unavailability of the test at our center. However, the diagnosis of CCD can be made based on clinical and radiological features as in our case.

The major characteristics of this disorder include hypoplastic/aplastic clavicles, delayed closure of fontanelles which leads to bosselation, dental abnormalities such as underdeveloped maxilla, prolonged retention of primary teeth, delayed eruption of permanent teeth, supernumerary, impaction, and short stature.^{2,7} The other features include hypertelorism, mandibular prognathism, high arched palate, midface retrusion, narrow thorax, and scoliosis of the spine.² Supernumerary teeth are generally present in the mandibular premolar and

maxillary anterior regions.^{8,9} The paranasal sinuses are underdeveloped and narrow and the mastoid air cells may not pneumatize at all. The abnormalities in hands include brachydactyly, short broad thumbs, and tapering fingers.¹⁰ In our case, permanent non-ossification of cranial sutures and fontanelles was evident on skull radiographs along with other various radiographic features as mentioned.

As with our case, radiographic evaluation forms a reliable means of confirming the diagnosis besides pertinent clinical signs. The radiographic findings pathognomonic of CCD include broad sutures, large fontanelles persisting into adulthood, numerous unerupted supernumerary teeth, and numerous wormian bones. The skull shows

diffuse or generalized areas of rarefaction, with most ossification evident on frontal bones and least on temporoparietal regions. The extent of defect in clavicles may range radiographically from small fragments to the complete absence of clavicles. In radiographs of the hand, brachyphalangy and sharp and tapered form of terminal phalanges is present. Anomalies in carpal, metacarpal, tarsal and metatarsal bones have also been reported.¹⁰ The pelvis also shows characteristic features. Delayed ossification during adulthood leads to widened pubic symphysis (distance between pubic bones). Hypoplasia and anterior rotation

of iliac wings and wide sacroiliac joints are also evident. The femoral neck is broad, femoral epiphyses are large and there is the presence of coxa vara.¹¹ However, in our case, coxa vara on the right hip and coxa valga on the left hip were evident on hip radiographs. Clinical assessment and radiological examination were conclusive in confirming the diagnosis in our case as evidenced by the presence of many pathognomonic clinical features of this disease. Crane–Heise syndrome, mandibuloacral dysplasia, pycnodysostosis, Yunis-Varon syndrome, CDAGS syndrome (Craniosynostosis, anal anomalies, and porokeratosis), and hypophosphatasia are some of the differential diagnoses that share some characteristics with CCD. However, all these are autosomal recessive disorders and have other specific features.³

Facial skeletal abnormalities lead to otologic and audiological manifestations of CCD. Anomalies of speech and language are common in patients with CCD and this may be secondary to malocclusion, anterior open bite, and high arched palate.¹² Recurrent paranasal sinus and middle ear infections may lead to conductive hearing loss.⁷ Pelvic bone deformities may lead to an increased rate of cesarean section delivery in female adult patients.¹¹ Our patient had a high arched palate and her daughter had hearing loss since birth. The aforementioned reasons could be the cause of her hearing loss.

Timely diagnosis and early intervention could address a wide spectrum of complications including skeletal/orthopedic problems, dental abnormalities, ENT complications, developmental problems, and endocrine abnormalities.³ Skeletal dysplasia in CCD can result in scoliosis and kyphosis which may require surgical treatment considering the fact that spinal deformities of CCD are progressive in nature.¹² Ultrasound examination can diagnose classic CCD in an offspring of an affected parent as early as 14 weeks gestation. Partially

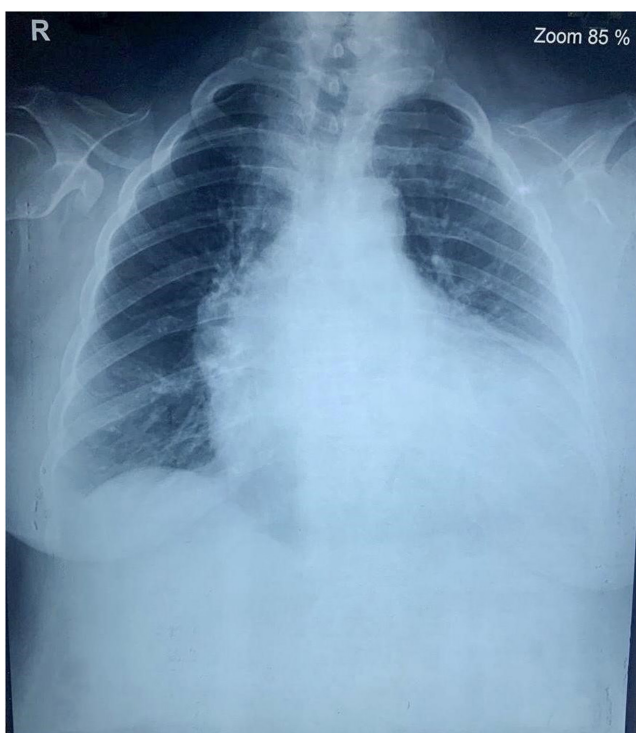


FIGURE 4 Chest radiograph PA view showing absent clavicles

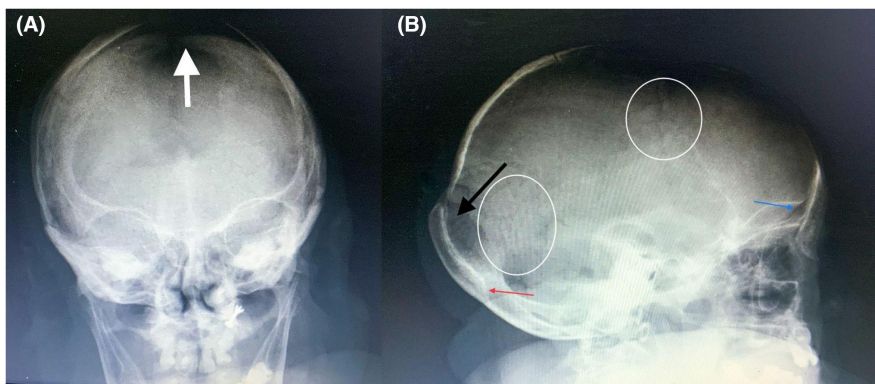


FIGURE 5 Radiograph of skull showing the persistent opening of anterior fontanelle (white arrow) (A) and Lateral skull radiograph showing wormian bones in parieto-occipital and frontoparietal region (white circles), open posterior fontanelle (black arrow), decreased pneumatization of the frontal sinus (blue arrow), osteosclerosis of the occipital bone (red arrow), and decreased pneumatization of mastoid air cells (B).

FIGURE 6 Anteroposterior radiograph of pelvis showing shortened femoral neck on both sides (black arrow), chef's hat femoral head deformity (red arrow), widened sacro-iliac joint (blue arrow) (A), and X-ray of the pelvis showing coxa vara in right hip and coxa valga in the left hip (B).

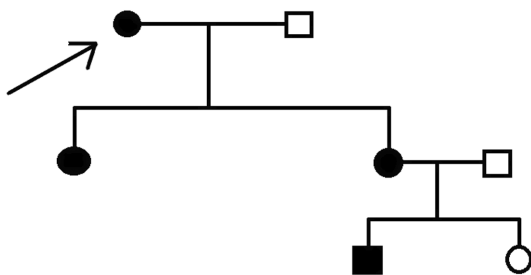
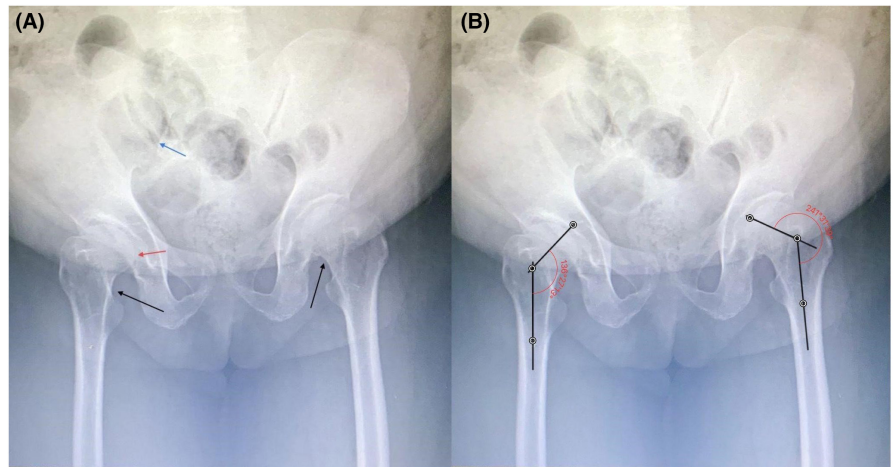


FIGURE 7 Pedigree chart showing hereditary characteristics in probanda's family (arrow)

or totally absent clavicles is the most consistent feature. Skull findings include brachycephaly, frontal bossing, and generalized defective ossification.^{3,13,14} Particularly in our case, being unknown of the condition, the patient may not have understood many aspects of the disease which might have led to the little elaboration of complications. Given the early diagnosis, the patient would have been aware of seeking further medical advice and would have bought time for early interventions. This puts further emphasis on the need for timely diagnosis and appropriate intervention. Moreover, early recognition and timely genetic counseling would have made prognostic implications on the decision of probanda's and her daughter's pregnancy. Stressing on this, we explained to them the hereditary characteristics of the disease and advised her daughter to take genetic counseling if further pregnancy is planned.

Management of this disorder consists of multidisciplinary teams involving craniofacial surgeons, dentists, orthodontists, ENT surgeons, radiologists, and orthopedic surgeons.^{2,3} Significant cranial vault defect needs caution and surgical cosmesis can be considered for the depressed forehead. Protection of the head from blunt trauma and avoidance of high-risk activities is crucial.

Dental procedures including prosthesis replacement, removal of supernumerary teeth, and surgical repositioning of permanent teeth are required to address dental abnormalities. As a part of surveillance, children should be monitored for orthopedic complications, dental abnormalities, ear and sinus infections, hearing loss, and upper airway obstruction.³ Corrective femoral osteotomy for coxa vara, timely treatment of recurrent middle ear infections with consideration of tympanostomy tubes, removal of clavicular fragments in cases of symptomatic brachial plexus compression, monitoring pregnancies for cephalopelvic disproportion are other important measures to consider in patients with CCD.⁷

4 | CONCLUSION

CCD presents with typical clinical and radiological findings with facial, dental, and skeletal impairments. Timely diagnosis of CCD and early intervention can help address various functional and aesthetic issues the patient goes through. Hence, clinicians should be aware of characteristic clinical features and work up for well-planned, multidisciplinary management.

AUTHOR CONTRIBUTIONS

Aayush Adhikari (AA), Suraj Shrestha (SS), Prabin Bhattarai (PB), and Surendra Khanal (SK) were involved in medical treatment, data collection, and drafting of the manuscript. Rajan Lamichhane, Ramesh Balayar, and Sobin Panta were involved in editing and revising the manuscript. Kundan Marasini interpreted the radiological findings. All the authors read and approved the final version of the manuscript.

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DATA AVAILABILITY STATEMENT

All the necessary data and information are within the article.

CONSENT

Written informed consent was obtained from the patient for publication of this case report and images of her. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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