Rare disease

A rare presentation of cleidocranial dysplasia

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Summary

Cleidocranial dysplasia (CCD) is a rare skeletal dysplasia characterised by a defect in ossification. Frequently reported clinical findings are delayed closure of the fontanelles and cranial sutures, hypoplastic clavicles, dental abnormalities and short stature. Our patient suffered from complete absence of ossification of both parietal bones. This is a rare and severe defect that has been reported in only a few patients with CCD.

BACKGROUND

Cleidocranial dysplasia (CCD) is an autosomal-dominant skeletal dysplasia affecting intramembranous ossification. The diagnosis of CCD is based on clinical and radiographic findings. In 60–70% of patients, mutations in the RUNX2 gene are responsible for the clinical picture.^{1–3} Manifestations range from isolated dental anomalies to full-blown disease presenting with poorly ossified cranium and absent clavicles (table 1).⁴

A thorough diagnostic work-up is essential to confirm diagnosis, determine the severity of disease and enable proper counselling by the paediatrician and clinical geneticist. Long-term follow-up is needed by a multidisciplinary team including the paediatrician, dentist and orthopaedic surgeon as more symptoms can become apparent during growth and different stages of childhood.

Based on the experience with this patient and review of the literature, a flowchart is proposed.

CASE PRESENTATION

We present a firstborn female infant of a non-consanguineous couple. During routine ultrasound examination in the second trimester, incomplete mineralisation of the skull was found. This finding could not be confirmed during subsequent ultrasonographic examinations. She was born by vaginal delivery at 39+6 weeks of gestation. Upon examination during labour, a soft presenting body was palpated and a breech presentation was suspected. Her Apgar scores at 1, 5 and 10 min were 9, 10 and 10, respectively. Birth weight was 3240 g. After birth, the skull had a normal outer appearance with an intact skin but felt soft when palpated. A skull ultrasound revealed no definite abnormalities. Subsequently, a low-dose three-dimensional CT scan of the skull was performed and complete absence of ossification of both parietal bones was found (figure 1). This finding prompted the fitting of a protective helmet. CCD was suspected by the clinical geneticist. The family history identified no other members with bone abnormalities, delayed ossification or short stature.

Table 1 Clinical and radiological findings in CCD^{1 3}

Clinical	Radiological
Skeletal	Skeletal
Skull	Skull
Abnormally large, wide-open fontanelles at birth	Wide open sutures and patent fontanelles
Delayed closure of the cranial sutures	Wormian bones
Soft skull: calvaria dysplasia, brachycephalic skull	Delayed ossification
Midface hypoplasia	Hypoplasia of maxilla
Frontal bossing	Segmental calvarial thickening
Hypertelorism	Hypoplastic sinuses
Thorax and shoulders	Thorax and shoulders
Clavicular hypoplasia: shoulders brought to midline	Complete absence, hypoplastic clavicle
Respiratory distress on early age	Cone-shaped thorax with narrow upper diameter
Increased mobility	Hypoplastic scapulae
Hands	Hands
Brachydactyly	Deformed and short middle phalanges
Tapering fingers	Hypoplastic distal phalanges
Short, broad thumbs	Long second metacarpal
Spine	Spine
Kyphosis	Hemivertebrae, posterior wedging
Scoliosis	Spondylolysis, spondylolisthesis
Pelvis and hips	Pelvis and hips
Pelvic dysplasia	Hypoplasia of iliac wings
Other orthopaedic	Widening of sacroiliac joints
Pes planus, genu valgum	Delayed ossification of pubic bone
	Wide pubic symphysis
Dentition	
Supernumerary teeth	
Eruption failure of permanent teeth	
Normal deciduous dentition	
Auditory	
Recurrent ear infections	
Partial hearing loss	
Other	
Submucous cleft palate	
Osteopaenia	
Short stature	
Normal intelligence

Figure 1 CT scan of the skull: Complete absence of ossification of both parietal bones in case 2 with CCD.

INVESTIGATIONS

Additional radiographic investigations showed complete aplasia of the right clavicle, a hypoplastic left clavicle, decreased/delayed ossification of the pubic bones and wide sacroiliac joints. DNA investigation of the RUNX2 gene identified a heterozygous nonsense mutation at nucleotide 1113 in exon 7.

DIFFERENTIAL DIAGNOSIS

The combination of hypoplastic clavicles and delayed closure of fontanelles were suggestive of CCD. Solitaire clavicular dysplasia or delayed closure of sutures is a rather non-specific sign. The combination of normal deciduous teeth, delayed eruption of permanent teeth and multiple impacted supernumerary teeth is practically diagnostic of CCD. However, a small number of other diagnosis can be considered. Delayed closure of fontanelles, Wormian bones, and hypoplastic clavicles are also features of pyknodysostosis, mandibuloacral dysplasia and Yunis-Varon syndrome.³ The finding of increased bone density (osteosclerosis, with risk of fractures) and dwarfism distinguishes pyknodysostosis from CCD.

Mandibuloacral dysplasia is characterised by progressive loss of bone from the distal phalanges. Yunis-Varon syndrome also features prenatal growth retardation, failure to thrive and limb malformations. Furthermore, this syndrome is usually lethal.

OUTCOME AND FOLLOW-UP

The child is currently 12 months of age and is doing well. Audiological evaluation was unremarkable. Orthopaedic and dental follow-up has been initiated. Radiographic evaluation of parietal bone formation will be performed in due time.

DISCUSSION

CCD is a rare autosomal-dominant skeletal dysplasia most prominently affecting bones derived from intramembranous ossification, such as the cranium and the clavicles. However, it is a generalised skeletal dysplasia, and can therefore affect the entire skeleton.^{1 3} Common clinical and radiological findings are presented in table 1.² However, the clinical presentation is heterogeneous even

within families. Severe parietal bone dysplasia is very rare and only a few case reports have been described.^{4 5}

In 1997, mutations in the RUNX2 gene were identified as the molecular aetiology. CCD is inherited in an autosomal-dominant manner or may result from new mutations in the gene.^{1 3} There is variable expression, clinical manifestations vary greatly between individuals with the same causative mutation.^{3 4} RUNX2 is a transcription factor which controls the differentiation of bone.⁵ Sequence analysis of genomic DNA of the RUNX2 gene detects mutations in 60–70% of individuals with a clinical diagnosis of CCD.¹ Many RUNX2 mutations are known, but no clear phenotype–genotype correlation has been established.⁵

In this case, DNA investigation of the RUNX2 gene identified a heterozygous nonsense mutation at nucleotide 1113 in exon 7. This mutation leads to premature termination of protein synthesis, affecting the C-terminal region of the resultant protein distal to the runt domain.

The common clinical and radiological findings of CCD are presented in table 1. If a diagnosis of CCD is suspected, a complete diagnostic work-up (table 2) is recommended to confirm the diagnosis, tailor treatment and enable proper counselling.^{1 2}

We will briefly discuss the potential symptoms and clinical course of CCD. Because the various aspects of the disease may become apparent at different stages during childhood and adolescence, long-term follow-up by different specialists is needed (table 3).

Skeletal

The suspicion of defects in skull mineralisation will need prompt identification and in the case of large defects protection with a helmet. With increasing age the un-ossified areas become smaller and true wormian bones develop, particularly around the lambdoid suture.³ Cardoso *et al*⁴ described a patient with severe parietal bone dysplasia at birth and spontaneous partial regrowth. Thoracic anomalies have been reported to cause respiratory distress in early infancy.³ Hypoplastic clavicles do not necessarily imply disability. The pelvis is invariably involved and results from a delay in ossification during adulthood. A dysplastic pelvis in pregnant women with CCD may explain the increased prevalence of caesarean section delivery.²

Auditory/ear–nose–throat disorders

Recurrent ear infections and hearing loss is prevalent in CCD due to maxilla-facial hypoplasia and underdeveloped ossicles.^{2 3} The incidence of submucous cleft palate is increased in CCD and individuals with CCD should thus be evaluated for this condition.^{2 3}

Table 2 Diagnostic work up in CCD

Radiographic investigation: Anteroposterior (AP) and lateral projections of the skull* and thorax, AP of the pelvis, lateral of the lumbar spine and AP of the long bones, hands and feet.

Referral to cleft team if submucous cleft is present or suspected

Audiological screening

Molecular genetic testing

*If the cranial vault defect is significant, low-dose three-dimensional CT scan is recommended and the head needs protection with a helmet.¹

Table 3 Recommendations for long-term follow-up by different specialists

Monitoring growth	General paediatrician
Monitoring for osteoporosis in early adolescence (DEXA scan)—general paediatrician	General paediatrician
Dental evaluation	Dentist
Orthopaedic complications	Orthopaedic surgeon
Sinus and ear infections, audiometry, respiratory obstruction	ENT department*
Skull mineralisation	Craniofacial surgeon Rehabilitation services
Genetic counselling	Clinical geneticist

*Ear Nose and Throat.

Dentition

Dental anomalies are common. Follow-up by a dentist should start at a young age.^{1 3}

Osteopaenia

If there are clinical signs of osteopaenia (increased number of fractures), evaluation and treatment of osteoporosis should be started early. Otherwise, bone mineral density should be measured by dual photon x-ray absorption scan early in adolescence, and every 5–10 years thereafter.¹

Stature

Final height is reduced in patients with CCD.^{1–3} Length is usually normal at birth but height drops below or around the second centile between the ages of 4 and 8.³ Males achieve an average final height of 165 cm (± 8 cm), females 156 cm (± 10 cm).^{1 2}

Development

Motor development may be slightly delayed (age of walking). In most cases, intellectual development is normal.^{1 2}

If CCD is suspected prenatally by ultrasonographic findings of hypomineralisation or absence of skull bones, an elective caesarean section can be performed to prevent intracranial haemorrhage.⁴

Upon examination during labour, the skull is palpated as a soft presenting body and can be mistaken for a breech presentation.

Postnatal in individual patients with severe defects, the diagnosis of CCD will likely be made soon after birth. However, diagnosis may be delayed in mildly affected patients until, for example, dental anomalies become apparent. If CCD is suspected prenatally by ultrasonographic findings of hypomineralisation of skull bones, an elective caesarean section is recommended to prevent brain injury.^{2 4}

Learning points

- Cleidocranial dysplasia is an autosomal-dominant skeletal dysplasia affecting intramembranous ossification.
- Clinical characteristics are heterogeneous, ranging from mild dental abnormalities to more severe defects, such as complete absence of ossification of parietal bones.
- Long-term follow-up is needed by a multidisciplinary team as more symptoms can become apparent during growth and different stages of childhood.

Competing interests None.

Patient consent Obtained.

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