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Complete absence of rib ossification, micrognathia and ear anomalies: extreme expression of cerebro-costo-mandibular syndrome?

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We describe a newborn with complete absence of ossification of the ribs, extreme micrognathia, absence of external ear canals and the inner ears, and diminished mobility in the upper extremities. It is suggested that this represents an unusually severe expression of the cerebro-costo-mandibular syndrome. Some developmental genes that may have played a role in the pathogenesis are briefly reviewed.

Keywords: Cerebro-costo-mandibular syndrome; ribs, absence of; goosecoid; Myf5

Introduction

The cerebro-costo-mandibular syndrome (CCMS) is an infrequently described condition, consisting of severe micrognathia, posterior rib-gap defects, and developmental delay.[1] The latter is thought to be secondary to perinatal respiratory distress and hypoxia, caused by the glossoptosis and the flail chest, which made Meinecke *et al* suggest that costo-mandibular syndrome might be a better designation.[2] Fifty cases have been described so far worldwide.[3]

Here we report on a newborn with features fitting CCMS, although in an unusually severe expression, and hypothesize on the molecular background of the syndrome.

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Case Report

The proband was the second-born child of a healthy, non-consanguineous parents. Their first child, a boy, was normal. The pregnancy was complicated by polyhydramnios: sonography showed a breech position and retrognathia, but no other abnormalities. The mother denied exposure to any known teratogenic agent. The delivery started spontaneously at 34 weeks, 5 days. The newborn girl weighed 1600g (5th centile), length 43 cm (15th centile), and head circumference 31 cm (25th centile). Multiple dysmorphic features were noted immediately: downward slanting palpebral fissures, high nasal bridge, small mouth, extremely high and narrow palate, micrognathia, and atretic external ear canals (Figure 1). Furthermore, the thorax was very small (chest circumference 19.5 cm – 5 cm below 3rd centile) and there was arthrogryposis in all joints of the upper limbs, with some webbing in the elbows.

She was cyanotic, but intubation was impossible due to the upper airway obstruction caused by extreme

micrognathia and relatively large tongue. Because of other congenital anomalies it was decided to refrain from further intervention. The girl died shortly after.

A post-mortem skeletal survey showed complete absence of ossification of all ribs (Figure 2), and no other abnormalities. The karyotype (650 bands level) was normal female (46,XX); in particular; no changes were visible at chromosome 12 and 14q32 (see Discussion). Autopsy confirmed the absence of any rib ossification; there were no rib gaps or other discontinuities in the ribs; the ribs were present as fibrous tissue. The lungs were hypoplastic (weight 10 g; normal weight at 34 weeks 5 days, 30–35 g). Besides a malrotation of the coecum no other internal anomalies were detected. Brain autopsy gave completely normal results. Careful section of the region where the inner ears were expected failed to show any remnants, indicating complete agenesis. The muscular tissues of the upper extremities appeared normal.

The parents did not show any major dysmorphic symptom, and had normally shaped chests. In both, an X-ray of the thorax was normal.

Discussion

The symptoms in the propositus are unusual. In our opinion they seem best to fit CCMS, although complete absence of ossification of all ribs has not been described before in these circumstances. However, the rib-gap defects in CCMS can vary considerably, from a few affected dorsal rib segments to only four ossified ribs.[3] On the other hand, it is possible that the propositus has a hitherto undescribed condition that only resembles CCMS.

The unossified ribs and severe micrognathia in combination with the relatively large tongue and

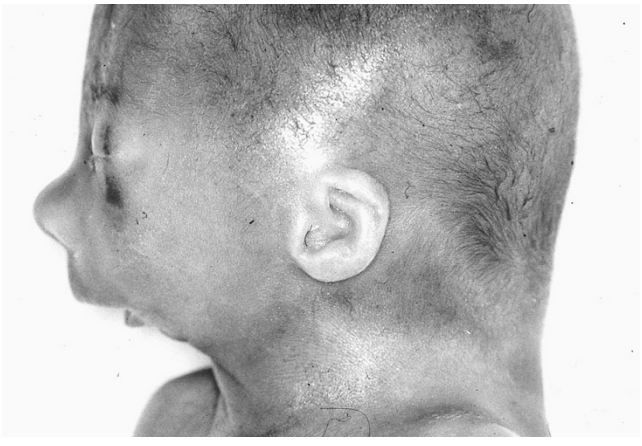

Figure 1 *Lateral view of the proband* post mortem, *showing expressed retrognathia, and absence of the external ear canals*

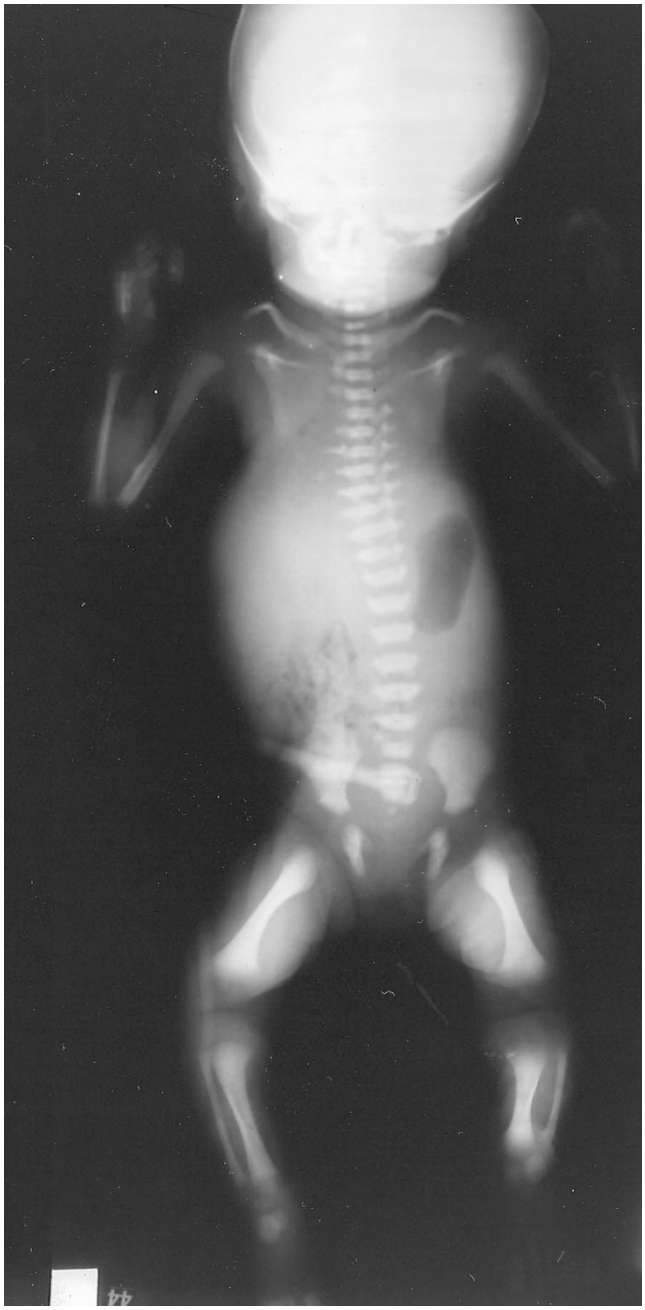

Figure 2 *Babygram of the proband, showing complete absence of ossification of the ribs*

hypoplastic lungs in our opinion are sufficient to account for the respiratory distress in the present case. The pulmonary hypoplasia is probably secondary to the absence of an ossified thoracic cage preventing normal respiratory movements in utero.

There is also some resemblance to the entity described by Seghers[4] and Flannery,[5] with an imperforate oropharynx, and costo-vertebral and ear anomalies. However, the absence of rib gaps, the presence of an imperforate oropharynx, and the more expressed vertebral anomalies allow differentiation. The absence of the external ear canals and inner ears is unusual in CCMS, but has been reported.[6] Normal brain anatomy has been found before in CCMS and is indicative of a secondary cause of the developmental delay in CCMS.

The cause of CCMS is unknown. Both an autosomal recessive[7–10] and autosomal dominant[6, 11, 12] pattern of inheritance has been described. No case has been described with a chromosome anomaly.

A literature search for developmental genes that, mutated, may fit CCMS, showed several candidates, of which two deserve more extensive attention: myogenic factor 5 (*Myf5*) and the *goosecoid* gene.

Myf5 is one of the basic helix–loop–helix (bHLH) transcription factors, which play an important regulatory role in the development of skeletal muscles.[13] The group includes *MyoD*, myogenin, *Myf5* and *Myf6*. *MyoD* and *Myf5* are structurally and functionally strongly related. It has been speculated that both might have duplicated from a common ancestor, with later diversification of their activity in different parts of the embryo.[14] The human *Myf5* has been mapped on chromosome12.[15]

The various bHLH proteins have each a distinct spatio-temporal expression in myogenesis.[13,16] *Myf5* has a major early role in the determination of the muscle precursor cells. In a series of excellent experiments, Braun *et al*[17] have shown that mice lacking *Myf5* died because of absence of the major distal part of the ribs, and furthermore, in these mice the appearance of muscle precursor cells was delayed by several days. The mice formed essentially normal muscles thereafter, indicating that *Myf5* is dispensable. The same group of authors has suggested that the most likely explanation for the defective rib formation is that the early muscle precursor cells may provide a permissive environment for sustaining continued proliferation of rib anlage.[18]

The *goosecoid* gene is a homeobox containing gene that has been isolated in amphibia, zebra fish, chicken, mouse, and man.[19] The human gene has been mapped to chromosome 14q32.1.[19] In mice, *goosecoid* is biphasic in development: in the early phase it is involved in the process of gastrulation in the developing primitive streak;[20] in the later phase it is involved in the spatial programming in discrete embryonic fields, especially the head mesenchyme and the limb buds.[21] In knockout mice it was found that the mice had multiple congenital anomalies involving predominantly the mandible, the nasal cavity and nasal pits, the inner ear, the external meatus, and the sternum and ribs.[22, 23] Some mice had rib fusions, especially between the first and second ribs; other mice had a reduced number of ribs and an abnormal attachment of the ribs to the sternum.[23] Although *goosecoid* is abundantly expressed in the developing limbs, the knockout mice did not show limb abnormalities.

The anomalies found in mice with a defective function of either *Myf5* or *goosecoid* are not completely identical to those found in CCMS, but the overlap is of sufficient importance to urge further molecular analysis of these genes. The nature of the rib defects in *goosecoid*, and the combination of rib and ear anomalies in the knockout mice make *goosecoid* the better candidate. As the number and the size of families with CCMS is limited, direct mutation analysis seems more appropriate than linkage studies. Such studies are presently in hand.

Recently, another interesting gene, the core-binding factor *Cbfa1* was the subject of several studies and was found to be causative of cleidocranial dysostosis.[24, 25] *Cfba1* is a transcription factor of the runt family and essential for the activation of osteoblast differentiation.[26, 27] Knockout mice for *Cbfa1* showed a complete lack of both intramembraneous and endochondral ossification. However, the clinical features in the human homologue of heterozygous loss of *Cbfa1*, cleidocranial dysostosis, differ widely from the features in the present case,[28] making it a less likely candidate gene.

In conclusion, the present case showed complete absence of ossification of ribs, micrognathia, and ear anomalies, which in our opinion are most compatible with an unusually severe expression of CCMS. The formation of the rib cage is highly dependent on *Myf5*. Parts of the first branchial arch and, to a lesser extent, the ribs are dependent on *goosecoid*. We hypothesize that mutations in *goosecoid* or (less likely) *Myf5* may have a causal role in CCMS. Further molecular studies are needed to evaluate this hypothesis.

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