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Case Report

Craniometaphyseal dysplasia in a 14-month old: a case report and review of imaging differential diagnosis

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ABSTRACT

We report a 14-month-old male with craniometaphyseal dysplasia (CMD). The patient presented with a history of diminishing vision and hearing loss. Cranial computed tomography scan showed diffuse calvarial and skull base hyperostosis with excessive bone narrowing the internal auditory canals and skull base foramina. A subsequent skeletal survey revealed other skeletal abnormalities, which led to the diagnosis of CMD. This was later confirmed by ANKH mutation. CMD is a rare genetic disorder that belongs to the group of craniotubular bone dysplasias. It is important to recognize this condition from other causes of craniotubular bone dysplasias to institute early treatment and explain prognosis.

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Introduction

Craniometaphyseal dysplasia (CMD) is a rare genetic bone disorder characterized by hyperostosis and sclerosis of the craniofacial bones and abnormal metaphyseal widening of the tubular bones. It belongs to a group of diseases called craniotubular bone dysplasias, which share similar pathogenesis of abnormal skeletal modeling [1]. CMD can be classified into more common, relatively mild, autosomal dominant form (OMIM #123000) and rare, severe autosomal

recessive form (OMIM #218400). The autosomal dominant form has AKNH gene mutation linked to chromosome 5p15.2-p14.1 [2]. The transmembrane protein encoded by ANKH helps to transport pyrophosphate ions toward the extracellular environment [2]. Pyrophosphate ion concentration in the bone extracellular matrix plays an important role in bone mineralization.

We describe imaging features of autosomal dominant CMD and discuss other diseases with similar radiologic findings presenting in the pediatric age group.

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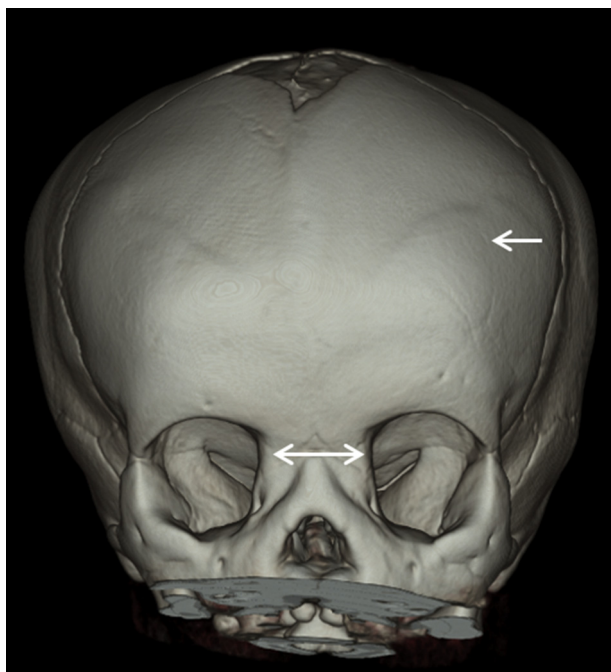


Fig. 1 – Three-dimensional computed tomography reconstruction shows frontal bossing (arrow). Notice depressed nasal bridge and ocular hypertelorism (double arrow).



Fig. 3 – Axial CT scan through the internal auditory canal shows diffuse expansion and sclerosis of the skull base and narrowing of the right canal (arrow). Mastoid process is sclerosed.

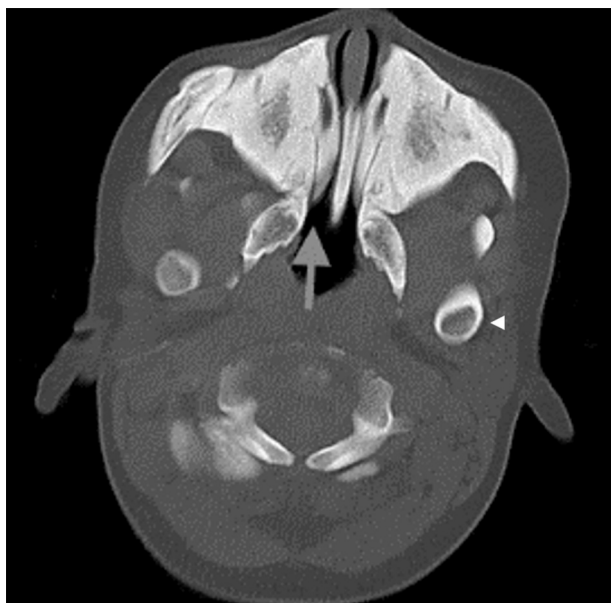


Fig. 2 – Axial computed tomography through the maxillary sinuses shows osseous obliteration of the maxillary sinuses, hyperostosis, and sclerosis of bones around the nasal canal leading to choanal stenosis (arrow). The mandible condyle is thickened (arrowhead)

Case history and imaging findings

A 14-month-old male presented with a history of developmental delay, progressive vision, and hearing loss. On examination, the patient had coarse facial features, large head, deep-set eyes, depressed nasal bridge, and frontal bossing (Fig. 1). He was previously discovered to have bilateral choanal stenosis. There was no history of consanguinity or similar abnormality in the family.

Computed tomography of head demonstrated diffuse hyperostosis and sclerosis of the craniofacial bones causing osseous obliteration of the maxillary sinuses and mastoid air cells (Fig. 2), choanal stenosis (Fig. 2), and narrowing of the internal auditory canals and all skull base foramina (Fig. 3).

A skeletal survey showed metaphyseal widening and cortical thinning in long bones, with distal femur being most affected resembling an Erlenmeyer flask (Fig. 4). The frontal skull view again showed skull base and cranial vault sclerosis and prominent mandible (Fig. 5). Other osseous abnormalities were widening of the metacarpal and phalangeal shafts (Fig. 6) and diffuse broadening of the ribs and clavicles (Fig. 7). The spine and pelvis were normal (Figs. 7 and 8).

Magnetic resonance imaging (MRI) was done to evaluate the optic and vestibulocochlear nerves and the foramen magnum. Magnetic resonance imaging of the brain demonstrated stenosis of the internal auditory canals with resultant effacement of cerebrospinal fluid around bilateral 7 and 8th

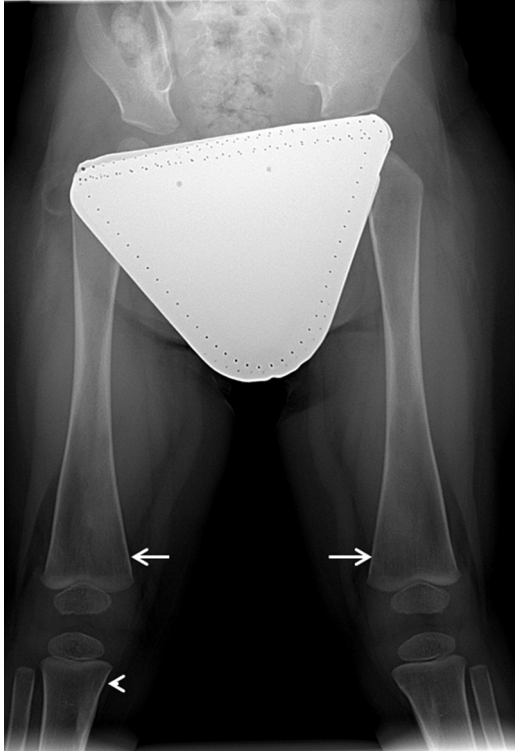


Fig. 4 – Anteroposterior plain radiograph of bilateral femurs shows metaphyseal widening most prominent in distal femur leading to Erlenmeyer flask deformity (arrow). Notice decreased bone density and pencil thin cortex. Similar changes are also seen in proximal tibia (arrowhead) and fibula.

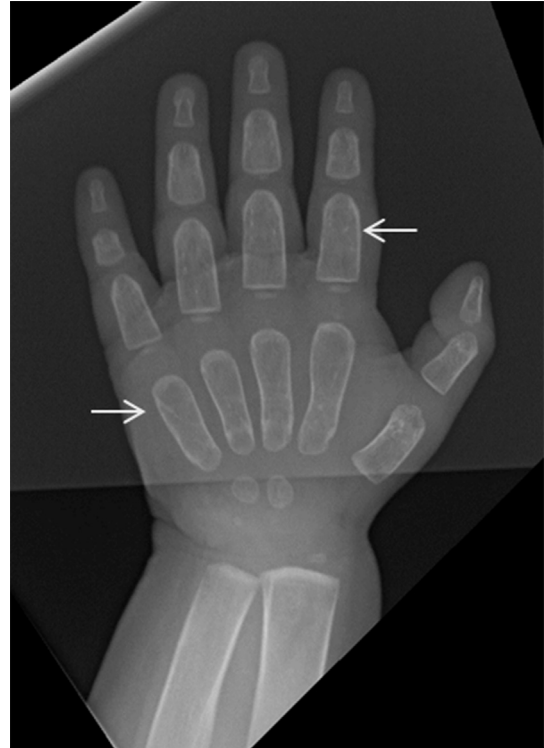


Fig. 6 – Plain radiograph of the hand shows broad phalanges and metacarpals without diaphyseal constriction (arrows).

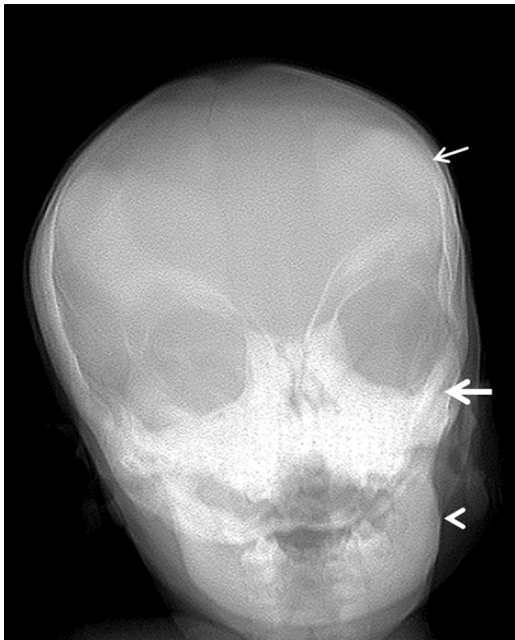


Fig. 5 – Anteroposterior view of the skull has calvarial and skull base sclerosis (arrows). Mandible is enlarged and sclerosed (arrowhead).



Fig. 7 – Anteroposterior plain radiograph of the chest and abdomen shows diffuse widening of the ribs. There is widening of the medial aspect of the clavicles with osteopenia (arrow). The thoracic and lumbar vertebrae appear normal. Metaphyseal widening in bilateral proximal humeral metaphysis seen (arrowheads).

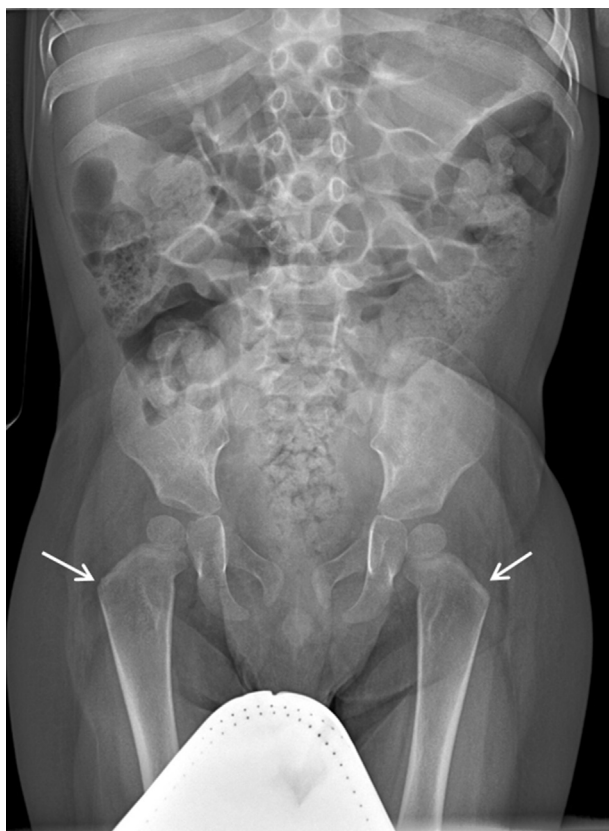


Fig. 8 – Anteroposterior plain radiograph of the lower abdomen and pelvis. Pelvis and lower lumbar and sacral vertebrae are normal. There is proximal femoral metaphyseal widening and cortical thinning (arrows).

nerve complexes. There was a mild diffuse narrowing of the optic canal causing cerebrospinal fluid distention around the intraorbital optic nerves (Fig. 9).

The imaging features were suggestive of CMD. The diagnosis was confirmed by genetic testing for ANKH gene mutations.

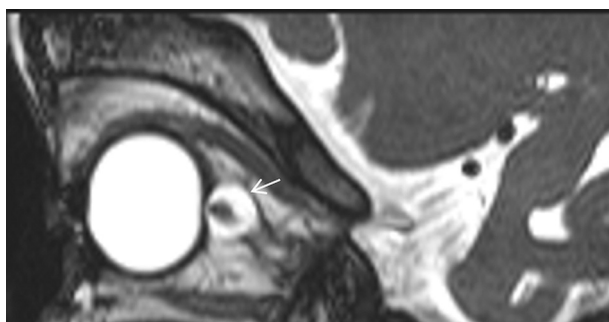


Fig. 9 – Sagittal Fiesta image through the right orbit shows distension of cerebrospinal fluid around the distal optic nerve and mild flattening of the posterior globe (arrow) due to optic canal stenosis.

Case discussion

In CMD, a defect in plasma membrane pyrophosphate transporter encoded by ANKH gene leads to low levels of pyrophosphate ion in the bone extracellular matrix. Low extracellular concentration of pyrophosphate causes increased hydroxyapatite formation and mineralization [2]. Cranial sclerosis may be related to abnormally increased bone deposition overwhelming the normal rate remodeling by osteoclasts. The osteopenic, widened metaphysis of the long bones could be due to remodeling defect and decreased osteoid deposition caused by abnormal calcification of hypertrophic cartilage in epiphyseal plates [2].

The disease usually presents in early childhood with progressive facial weakness, vision, and/or hearing loss secondary to stenosis of skull base foramina caused by calvarial hyperostosis. Hyperostosis of the facial bones results in distinctive facial features such as a wide nasal bridge, ocular hypertelorism, prominent forehead, and large jaw. Development of dentition may be delayed and teeth may fail to erupt if alveolar bone is involved. Severe cranial hyperostosis, like in autosomal recessive form, can lead to a lethal rise in intracranial pressure due to foramen magnum narrowing [3,4].

The skeletal survey shows abnormal metaphyseal widening of the tubular bones with relative sparing of the diaphysis. The appendicular bones have decreased density and thin cortex, unlike the skull base. The medial portions of the clavicles and costochondral junctions of the ribs may be involved. The spine and pelvis are spared [3,5]. The diffuse widening of the ribs and small tubular bones of hand in the presented case is more associated with craniometadiaphyseal dysplasia (CMDD) than with CMD [6,7].

Craniofacial hyperostosis with or without appendicular skeletal involvement in children is not unique to CMD and has a wide differential diagnosis (Table 1) [8–10]. These include other members of craniotubular dysplasia group such as the frontometadiaphyseal dysplasia, craniodiaphyseal dysplasia and CMDD [11].

In contrast to progressive diffuse craniofacial involvement in CMD, frontometadiaphyseal dysplasia has localized frontal bone ridging, skull base sclerosis, and characteristic mandibular spur [9].

CMDD shows poor ossification of the skull with wormian bones in infancy, with delayed closure of the anterior fontanelle. The skull base sclerosis in adults with CMDD does not manifest in children. Other distinguishing imaging features of CMDD are diaphyseal undertubulation, metaphyseal sclerosis, and lack of metaphyseal flaring [6,12].

Craniodiaphyseal dysplasia shows much more severe sclerosis and hyperostosis of the craniofacial bones along with more significant flaring and sclerosis of the diaphysis without much metaphyseal involvement. Most patients with craniodiaphyseal dysplasia have mental retardation and die in their second decade of life as compared to normal intelligence in CMD and CMDD [6]. The lifespan of people with uncomplicated autosomal dominant CMD is normal, except in the rare severe cases of foramen magnum narrowing, which can lead to brainstem compression.

Table 1 – Differential diagnosis for cranial sclerosis with appendicular involvement in children.

Disease entity	Gene defect	Inheritance	Pathogenesis	Key imaging features
Frontometaphyseal dysplasia	FNL1 gene Xq28	X-linked dominant	Unknown; FNL1 encodes filamin A	Localized frontal bone and skull base sclerosis; anterior mandibular spur; widening of long bone metaphysis; curved long bones; scoliosis; arachnodactyly; twisted dysplastic ribs.
Cranio-metadiaphyseal dysplasia	Gene locus not identified	Autosomal recessive	Abnormal bony remodeling	Cranial sclerosis with wormian bones; long bone diaphyseal undertubulation without normal metaphyseal flaring; metaphyseal sclerosis; wide short tubular bones; broad ribs and clavicles
Cranio-diaphyseal dysplasia	Gene locus not identified	Autosomal recessive	Abnormal bony remodeling	Severe sclerosis and hyperostosis of the craniofacial bones; early craniosynostosis; sclerosis and flaring of the diaphysis without much of metaphyseal involvement; mental retardation.
Van Buchem disease	SOST gene on chromosome 17q12-q21	Autosomal recessive	Active overgrowth of the bony tissue due to osteoblast hyperactivity	Bilateral, symmetrical diaphyseal cortical thickening; milder sclerosis and thickening of the calvaria, mandible, shoulder and pelvic girdles, and thoracic cage; mandibular protrusion
Sclerosteosis	SOST gene on chromosome 17q12-q21	Autosomal recessive	Osteoblast hyperactivity	More severe bilateral, symmetric diaphyseal cortical thickening of the long and short tubular bones; severe cranial sclerosis and thickening of the mandible; second and third finger syndactyly with hyperphalangy; tall stature
Infantile osteopetrosis	ATP6I homozygous mutations in the chloride 7 channel	Autosomal recessive infancy	Defect leads to impaired acidification of bone –osteoclast interface in the resorption lacunae leading to impaired dissolution of osteoid matrix	Diffuse cranial sclerosis starting at skull base leading to progressive neural foramina narrowing; diffuse skeletal involvement including spine; bones are dense and sclerotic with narrow medullary cavity; increased fragility with multiple fractures
Craniofacial fibrous dysplasia	GNAS on chromosome 20q13	Somatic mutation	Localized defect in osteoblastic differentiation and maturation, with replacement of normal bone with large fibrous stroma and islands of immature woven bone.	Mono-ostotic or polyostotic; characterized by diffuse bone expansion with appearance ranging from homogenous ground glass opacity to varying degree of sclerosis and mixed lucencies; usually focal, asymmetric involvement of the long bones with ground glass, sclerotic, lytic, or mixed densities.
Pyknodysostosis (Maroteaux-Lamy disease)	Cathepsin K	Autosomal recessive	Abnormal function of lysosomal cysteine proteinase in osteoclasts required for collagen degradation	Diffuse cranial sclerosis and thickening; wide lambdoid sutures and fontanelles; wormian bones; mandibular hypoplasia; pectus excavatum; dense vertebral bodies with spared transverse processes; short stature; diffuse long tubular bone hyperostosis with preserved medullary cavities; acro-osteolysis.
Camurati-Engelmann disease (progressive diaphyseal dysplasia)	Transforming growth factor B1 on chromosome 19q13.1	Autosomal dominant	Causes premature activation of TGF1, which leads to proliferation of the bone matrix along the periosteal and endosteal surfaces of long bones	Symmetric periosteal and endosteal diaphyseal thickening of long bones; skull base may be involved but the mandible and rest of the calvarium is spared.
Osteosclerosis	LRP5 on chromosome 11q13.4	Autosomal dominant	Osteoblast differentiation abnormality	Diffuse symmetric sclerosis of the calvarial bones, tubular bones, and pelvic girdle; torus platinus may be seen

Craniotubular hyperostosis group of disorders have similar cranial sclerosis, but in addition, have diffusely thickened, sclerotic cortex of long bones. The skeletal abnormality is due to active bony overgrowth caused by increased osteoblastic activity rather than a defect in bone remodeling. Sclerosteosis type I and Van Buchem disease belong to craniotubular hyperostosis group [10]. Sclerosteosis type I in addition has characteristic syndactyly of 2nd and 3rd digits, hyperphalangy, increased height, and prominent mandible enlargement [13].

Osteoscleroses include osteopetrosis and pyknodysostosis. They are caused by abnormal osteoclastic activity leading to generalized increased skeletal density, including the spine, pelvis, and skull [8–10]. The severe infantile recessive form of osteopetrosis presents early in infancy with hematologic derangements caused by shrinking medullary cavity can result in early death.

Progressive diaphyseal dysplasia (Camurati-Engelmann disease) is an autosomal dominant disorder characterized by proliferation of the bone matrix that may involve all bones. It primarily affects the diaphyses of long bones. The skull base may be involved, but the mandible and rest of the calvarium are spared [14].

Erlenmeyer flask deformity of long bones is classically described in metaphyseal dysplasia (Pyle disease). This disorder can be differentiated from CMD, by their involvement of pelvic bones and little or no involvement of the cranial bones [1].

Patients with CMD require regular neurologic, ophthalmologic, and hearing assessment as the bone thickening is progressive. Craniofacial surgery in these patients has a high failure rate, although surgical decompression may become necessary to manage the life-threatening rise in intracranial pressure [4,5]. The medical management is based on modulating osteoclast and osteoblast activity by calcitonin therapy or by a low calcium diet supplemented by calcitriol [4].

Conclusion

An understating of subtle differences in imaging features of craniotubular disorders is required to diagnose CMD. The diagnosis is confirmed by genetic testing.

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