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Clinical Record

Chondrodysplasia punctata: case report and review of audiological and ENT features

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Abstract
Chondrodysplasia punctata is a term referring to a clinically heterogeneous group of bone and cartilage dysplasias which cause characteristic epiphyseal stippling. The condition can involve the ear, nose and throat in diverse ways at many levels. We present a case of X-linked brachytelephalangic chondrodysplasia punctata, which illustrates the features of this condition particularly relevant to the audiological physician, otolaryngologist and neonatologist.

Key words: Chondrodysplasia Punctata; Hearing Loss; Airway Obstruction; Genetic Diseases

Introduction

Chondrodysplasia punctata (CDP) is a term referring to a not uncommon, clinically heterogeneous group of bone and cartilage dysplasias which cause characteristic epiphyseal stippling seen on X-ray particularly in the neonatal period and early infancy.

There are at least three well defined groups, based on clinical features and mode of inheritance. There are many other subtypes, and there is no standard classification system. Recent work has contributed to understanding of the molecular biology of these groups.

The first group is an X-linked dominant form also known as Conradi–Hunermann disease, first described by Conradi in 1914. Patients suffering this form of CDP have short stature, skin lesions known as follicular atrophoderma, sparse hair with patchy alopecia and cataracts.[1] The condition affects mainly girls and is thought to be lethal in homozygous males. This form of CDP is due to mutations in the emopanil-binding protein (EBP) gene on Xp11, which result in a defect in cholesterol biosynthesis.[2]

The second group is the rhizomelic form, which has autosomal recessive inheritance. This is the most severe form, and cases do not usually survive more than a year. Death usually results from respiratory complications. The molecular basis of this form was elucidated by Braverman *et al*., who demonstrated impairment of peroxisomal function and *PEX7* gene mutations.[3]

The third group, brachytelephalangic chondrodysplasia punctata (BCDP) is characterized by X-linked recessive inheritance and has variable clinical presentation.[4–6] The gene responsible for this group was isolated by Franco *et al*. in 1995 and encodes for arylsulphatase E (ARSE).[7] Features include short stature, deafness, depressed nasal bridge, frontal bossing with hypertelorism (so-called 'koala bear facies'), learning difficulties and cataract.[4–6]

Factors other than genetics have also been reported to produce phenocopies of the disease. These include warfarin and hydantoin drug therapy during gestation, maternal systemic lupus erythematosus, maternal alcohol consumption and maternal malabsorption of vitamin K.[4,8–10]

We present a case of X-linked BCDP along with a discussion of the literature, illustrating the features particularly relevant to the audiological physician, otolaryngologist and neonatologist.

Literature searches were conducted via Ovid Medline, using the terms 'chondrodysplasia punctata', 'chondrodysplasia punctata AND hearing OR hearing loss', and 'chondrodysplasia punctata AND airway obstruction'.

Case report

Our patient was a boy born at term as the result of a normal pregnancy and delivery. His mother took no medication and did not consume alcohol during pregnancy.

The boy was noted at birth to have mid-face hypoplasia, a box-shaped head, a short nose with depressed nasal bridge and anteverted nostrils (Figure 1). He had short terminal phalanges resulting in short digits with small nails. He required treatment in the special care unit as a neonate for jaundice, feeding difficulties and low birth weight. A skeletal survey showed punctate calcification typical of chondrodysplasia punctata.

On the postnatal ward our patient underwent auditory brainstem response testing, which showed no reliable waveform at 90 dBnHL bilaterally. Sound-field distraction

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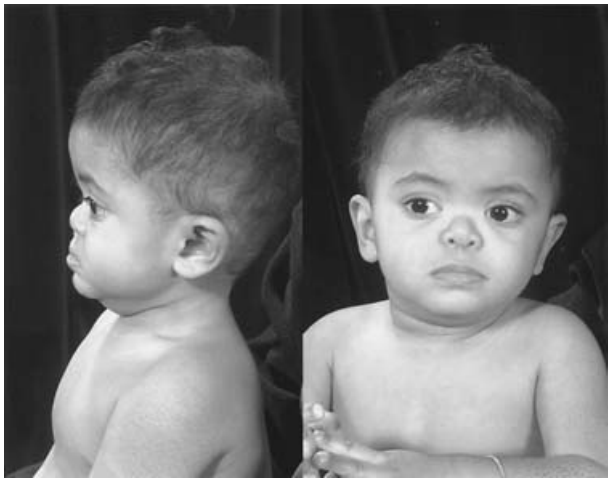

FIG. 1
Mid-face hypoplasia, depressed nasal bridge and ichthyosis.

testing at the age of eight months showed thresholds of 65–70 dBA using a wooden clapper and xylophone tones at 500 Hz and 1 kHz. Visual-response audiometry via sound-field and bone conductor at this time obtained the results shown in Table I.

Otoscopy was normal. Tympanometry showed normal compliance curves. This picture is diagnostic of ossicular fixation. Our patient was fitted with a left-sided, behind-the-ear, air conductor hearing aid, with a view to progressing to bilateral aiding in the future.

Our patient's first year of life was punctuated by admissions to hospital with lower respiratory tract infections, bronchospasm and nasal congestion. At one year of age he was noted to have stridor and weak cry. He had also developed mild ichthyosis over his trunk and limbs (visible in Figure 1). Deoxyribonucleic acid (DNA) testing for ARSE gene mutation confirmed a complete deletion of the gene. Steroid sulphatase (STS) enzyme activity was also absent, suggesting that the patient had X-linked ichthyosis as a result of STS deficiency. This raised the possibility of a contiguous gene deletion syndrome, and review of the patient's chromosome analysis confirmed that he had a cytogenetically visible deletion of chromosome Xp22.3. His mother was subsequently found to be a carrier of this X chromosome deletion.

Microlaryngobronchoscopy was carried out at age 20 months and demonstrated the following features (Figure 2).

There were possible calcific nodules on both vocal folds, with a single calcific nodule in the membranous posterior tracheal wall at about 2–3 cm below the glottis. Both vocal folds were fully mobile. Mild (30–40 per cent) long-segment tracheal stenosis was noted, comprising concentric narrowing of the distal half of the trachea without evidence of complete tracheal rings or extrinsic

TABLE I
AUDIOMETRY RESULTS

Frequency (kHz)	AC threshold (dBA)	BC threshold (dBA)
0.5	45	–
1	55	30
4	75	25

AC = air conduction; BC = bone conduction

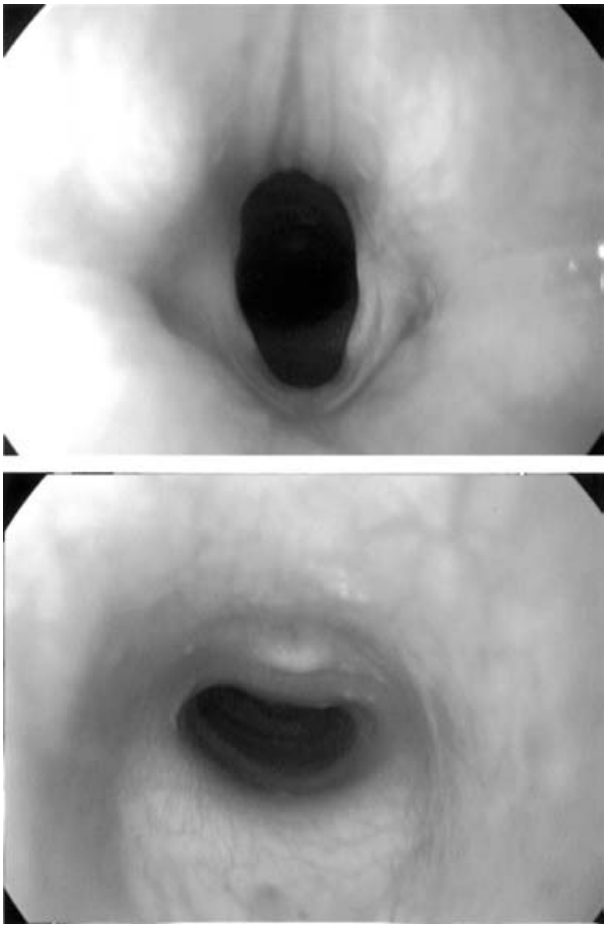

FIG. 2
Microlaryngobronchoscopy findings.

compression or malacia of cartilage. The epiglottis was normal. The patient had active rhinitis but no evidence of nasal airway narrowing or choanal stenosis.

At the time of writing (age 21 months) the patient's stridor was beginning to improve, being restricted to times of exertion and excitement. His motor development was normal and he was able to walk. His speech was delayed; he was babbling but not yet producing any recognizable words.

Discussion

There are many forms of CDP, with heterogeneous manifestations and aetiologies. All involve the characteristic punctate epiphyseal stippling, which may affect the ankles, feet, patellae, hands and wrists and, less commonly, the pelvis, sternum and mandible.[4]

Radiological findings can be the only manifestation in very mild cases. Cataracts, dermatoses, growth problems and intellectual deficits are variably present.[4,5] Overwhelming infection can occur in infancy, but the prognosis is good once the first year is survived, except in the rhizomelic autosomal recessive form. Epiphyseal calcifications usually resolve in the first few years of life.[5]

Histology of the epiphyseal cartilage shows fibrosis, calcification, new cyst formation, mucodegeneration and neovascularization. Disorganized cellular configurations have been seen in growth plates and in the ocular lens.

X-linked BCDP has been shown to be associated with various missense, nonsense, insertion and deletion

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mutations in the ARSE gene in up to 75 per cent of patients. In nine out of 12 patients in one series the mutations were sporadic, so the typical X-linked pedigree may not be seen.[11] However, mild features can sometimes be identified in first-degree relatives after careful examination.[5,12]

The incidence of the disease is unclear, although one series reported an estimate of greater than one in 30 000 live births for all types, suggesting it is not especially rare.[4]

Brachytelephalangic chondrodysplasia punctata is known to involve the upper airways and can cause significant obstruction. Nasal bridge depression together with shortened columella is almost universally seen. The condition can be associated with bilateral membranous choanal stenosis, reported once only[12] (although need for nasal stenting has also been referred to).[6] In a report of 23 diverse but mild cases of all types of CDP, 29 per cent had neonatal respiratory distress attributable to inadequate nasal airway. This caused feeding difficulties, aspiration pneumonia and head retraction in an unspecified number. Two of these patients were reported to have needed plastic surgery to improve their nasal appearance.[4] In another case series two patients had respiratory insufficiency, one of these requiring assisted ventilation. The authors here attributed this to upper respiratory tract involvement with narrow nasal airway and laryngomalacia.[11]

Stenosis of the trachea and bronchi has been reported in a number of cases.[13–15] In some tracheostomy was required at younger than two years, and there is at least one report of failed extubation after elective surgery necessitating surgical airway control. One case was managed with a Montgomery T-tube.[13] None of these cases report successful decannulation over follow up of up to eight years. Laryngeal and tracheal calcifications have been noted in many cases of all types of CDP.[11,13] The calcification is reported to improve over the years, although there appears to be a relative lack of growth in the diameter of the trachea and main bronchi in one radiological study in which one patient was followed for 18 years.[14]

Hearing loss has been noted in a small number of cases of BCDP. Forms reported have included both conductive and sensorineural losses, ranging, when specified, from mild to moderate and requiring aiding.[6,11–13] In one case the hearing loss was thought to be due to ossicular chain fixation and intermittent serous otitis media.[13]

Diagnosis of permanent conductive, sensorineural or mixed hearing loss of any degree would support the diagnosis of any type of CDP. The precise audiological findings of previous cases have never been published. This report uniquely associates a detailed description of ear, nose and throat manifestations in a genetically proven case of X-linked CDP. Advances in our understanding of the genetic basis of CDP may help clarify further the otorhinolaryngological features of the X-linked form and of other subtypes.

A number of important messages for neonatologists, otolaryngologists and audiological physicians are apparent from our case. Brachytelephalangic chondrodysplasia punctata is not especially rare. A patient diagnosed with BCDP as a neonate or infant is at risk of developing airway problems in the first few months of life. These can be complex and present at multiple levels, and can be severe enough to require tracheostomy. Elective microlaryngobronchoscopy may be considered in the first year of life. As marked tracheal stenosis can be a feature, it must be borne in mind when intubating these children that a small diameter tube may be necessary. Hearing loss is an important feature of this condition. It is recommended that an audiological assessment be carried out at the earliest opportunity to detect any of the variable forms of hearing loss which may be associated with CDP, in order to maximize opportunity for early intervention if required and to optimize speech and language development.

- **Chondrodysplasia punctata is a genetically and clinically heterogeneous group of disorders of bone and cartilage**
- **The condition can cause respiratory distress in infancy**
- **This case report illustrates the ways in which presentation in the ear, nose and throat can occur**
- **Audiological assessment and elective microlaryngobronchoscopy should be considered**

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