CASE REPORT

Cleidocranial dysplasia

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ABSTRACT

We present a 4-year-old girl with persistent anterior fontanelle and narrow sloping shoulders. The X-ray imaging revealed widely open anterior fontanelle, supernumerary teeth, and absence of clavicles. Therefore, the diagnosis was cleidocranial dysplasia, which is a rare autosomal dominant skeletal disease, caused by the mutation in the gene on 6p21 encoding transcription factor *CBFA1* (runt-related transcription factor 2—*RUNX2*). The girl remains under close surveilance, her anterior fontanelle closed spontaneously at the age of 9 years.

KEYWORDS

Clavicle; Skull; Fontanelle; Ossification; Cleidocranial dysplasia.

INTRODUCTION

Cleidocranial dysplasia (CCD) is a rare (prevalence 1:1,000,000) autosomal dominant disorder resulting in skeletal anomalies, such as patent fontanels, late closure of cranial sutures and rudimentary or absent clavicles [1–9]. The diagnosis of CCD remains incidental due to the rare occurrence of this disorder.

CASE REPORT

A 4-year-old girl of healthy parents with an uneventful family and personal history was referred by the general paediatric practitioner and a paediatric neurologist because of 'soft skull', a widely open anterior fontanelle with vertical and horizontal diameters of 4 and 3 cm, respectively, and short stature, to rule out hypothyroidism, rickets or other metabolic bone disorders (hypophosphatasia, osteogenesis imperfecta and pycnodysostosis). Both parents were healthy, both 180 cm tall (mother 97th percentile; father 50th percentile) and of very muscular athletic stature, with fully palpable clavicles. She was the product of first pregnancy, full term (40th gestational week), birth weight 3,670 g, birth length 50 cm, with normal psychomotor development. At the age of 4 years, her height was 98 cm (−1.8 SD; 10th percentile), weight 13 kg (−2 SD), and body mass index 13.5 (−1.2 SD). Upon presentation, she had strikingly narrow, sloping shoulders that could be opposed at the midline, muscular hypotonia, bell-shaped chest, hypoplastic distal phalanges, hypertelorism, mandibular retrognathism, low nasal bridge together with non-palpable clavicles (Figure 1). The serum levels of creatinine, sodium, potassium, calcium, phosphate, magnesium, free thyroxine, thyroid stimulating hormone, parathyroid hormone and the serum activity of

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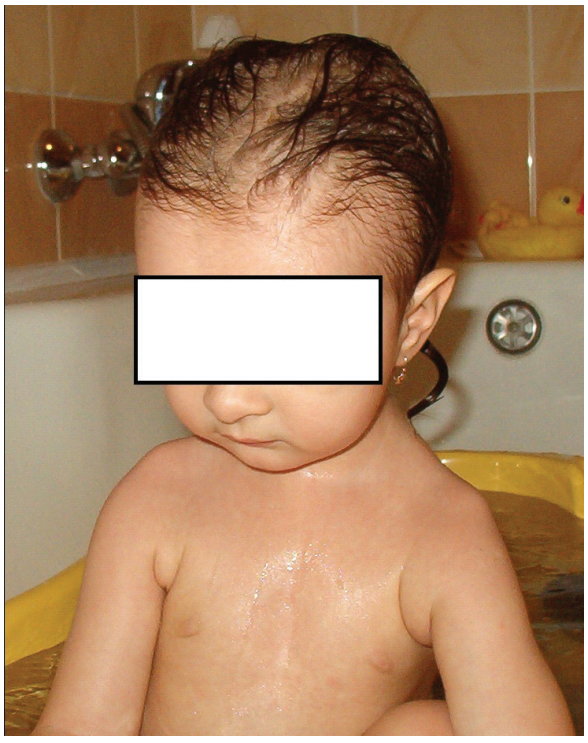

Figure 1. The girl with CCD. Note the narrow, sloping shoulders and pear shaped skull.

alkaline phosphatase, aspartate-aminotransferase and alanin-aminotransferase were within the appropriate reference ranges. Spinal bone mineral density (L1–L4) was within normal reference range, either age- or height-related (−1.8 SD Z-score; within ± 2SD Z-score). Wrist X-ray was normal, without any rachitic changes and with appropriate bone age. The X-ray of the skull revealed widely open large fontanelle, and impacted supernumerary teeth (Figure 2). On chest X-ray, a bell-shaped thorax was apparent and the clavicles were completely absent (Figure 3A and B). Therefore, the diagnosis was CCD (MIM 119600).

Our patient was checked annually and we observed a slow spontaneous closure of the fontanelle, completed at the age of nine years and confirmed by the X-ray. Nowadays, the anterior fontanelle is not palpable and the skull X-ray revealed the fontanelle closure with a thin layer of bone tissue. Currently, the girl is 13-year-old, doing well, under close stomatologic surveillance, her hearing is not impaired, and ear infections never occurred. Her growth curve is stable, body height remained all the time between −1.4 SD and −1.7 SD; 10th

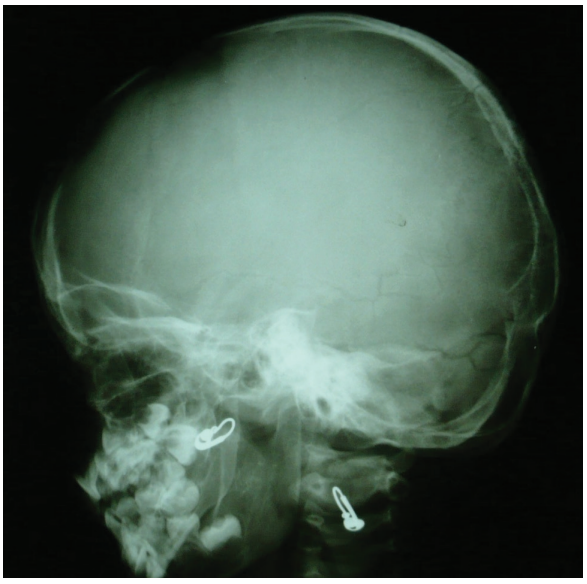

Figure 2. Skull X-ray revealing widely open anterior fontanelle.

percentile, respectively. Final height prediction based on calculated mid-parental height was 174 ± 5cm (75th–97th percentile). Therefore, in spite of her growth being stable without any changes exceeding two growth chart lines, her body height remains below expected age-related values. At the time, this article is being written genetic assessment is underway.

DISCUSSION

CCD (synonyms cleidocranial dysostosis, osteodental dysplasia and Marie–Sainton Disease) was first described in 1898 by Pierre and Sainton [10,11]. In 1951, Jackson reported 70 CCD individuals in a large family of 356 relatives [12]. The relevant gene, Core Binding Factor Alpha-1 (*CBFA1*) or Runt Related Transcription Factor 2 (*RUNX2*; MIM 600211), has been mapped to the short arm of chromosome 6p21 in 1993 [13]. *RUNX2* is a member of the runt family of transcription factors and its expression is restricted to developing osteoblasts and a subset of chondrocytes [1–3]. In CCD patients, chromosomal translocations, deletions, insertions, nonsense and splice-site mutations, as well as missense mutations of the *RUNX2* gene have all been described [2]. Approximately 70% of patients have point mutations in *RUNX2* gene and <20% are due to copy number variations [6]. *RUNX2*

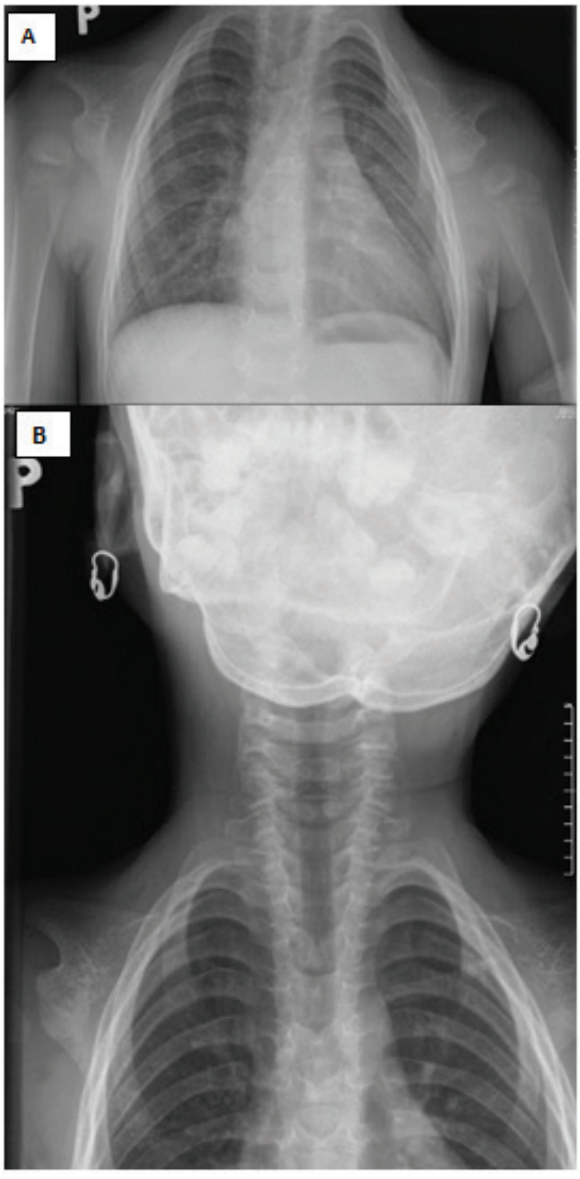

Figure 3. (A and B) Chest X-ray: bell-shaped thorax and bilateral absence of clavicles.

mutations result in defective intramembranous and endochondral ossification [4]. Besides patent anterior fontanelle, late closure of cranial sutures and absent or rudimentary clavicles, patients with CCD frequently present with late erupting secondary dentition, impacted and supernumerary teeth, an inverted pear-shaped calvaria, hypertelorism, general midface retrusion, high palate, mandible prognathism, brachydactyly, pubic bone abnormalities, such as wide pubic symphysis and short stature [1,3,5,7–9]. There is no clear phenotype-genotype correlation and a wide spectrum of clinical features ranging from dental abnormalities to all CCD manifestations exists in the affected children [2,3,5,6,9].

Individuals with CCD spectrum disorder are at increased risk of developing recurrent sinus and ear infections leading to conductive hearing loss [1,3,7]. There is no causal therapy in CCD; management of CCD patients consists predominantly of preventive measures, such as trauma prevention, skull protection and efficient treatment of otitis and sinusitis. Dental care is represented by orthodontic treatment, removal of the supernumerary teeth and, eventually, orthognathic preprosthetic surgery [1,3,5–7]. In case of stunted growth, growth hormone treatment was reported as beneficial [8]. Regarding our patient, both parents were tall, with palpable clavicles and without history of late closure of anterior fontanelle; therefore, CCD in their daughter was most probably the result of *de novo* mutation. The course and outcome in our CCD patient was quite favourable, as the anterior fontanelle has closed spontaneously at the age of nine years. Also her growth chart was stable, compared to other children with CCD where body height might drop below −2 SD at the age of 4–8 years, respectively [14].

CONCLUSION

Paediatricians should be aware of CCD as a cause of late closure or persistence of anterior fontanelle and distinguish such finding from rickets. The absence of clavicles may go unrecognised; therefore, the CCD diagnosis is often delayed.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

FUNDING

None.

ETHICAL APPROVAL

All procedures performed were fully in accordance with the current EU legislative. The authors declare that ethics approval was not required for this case report. Signed informed consent

for participation and publication of medical details was also obtained from the parents of the presented child. Confidentiality was ensured at all the stages.

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