

## Case Report

# A case report of acampomelic campomelic dysplasia and operative difficulties in cleft palate reconstruction

M. Pasupathy, Vasant Radhakrishnan, Hirji Sorab Adenwalla<sup>1</sup>, Puthucode V. Narayanan

The Charles Pinto Centre for Cleft Lip, Palate and Craniofacial Anomalies, Jubilee Mission Medical College and Research Institute, <sup>1</sup>Department of Plastic Surgery, Burns and The Charles Pinto Centre for Cleft Lip, Palate and Craniofacial Anomalies, Jubilee Mission Medical College and Research Institute, Trissur, Kerala, India

**Address for correspondence:** Dr. Hirji Sorab Adenwalla, Department of Plastic Surgery, Burns and The Charles Pinto Centre for Cleft Lip, Palate and Craniofacial Anomalies, Jubilee Mission Medical College and Research Institute, Trissur, Kerala, India.  
E-mail: charlespinto102@gmail.com

### ABSTRACT

Acampomelic campomelic dysplasia (CD) is a type of CD (CD; OMIM #114290), a rare form of congenital short-limbed dwarfism and is due to mutations in *SOX9* gene family. Characteristic phenotypes of CD include bowing of the lower limbs, a narrow thoracic cage, 11 pairs of ribs, hypoplastic scapulae, macrocephaly, flattened supraorbital ridges and nasal bridge, cleft palate and micrognathia. The bending of the long bones is not an obligatory feature and is absent in about 10% of cases, referred to as acampomelic CD. A child previously diagnosed with acampomelic CD was brought to our outpatient clinic for cleft palate reconstruction. Our neurosurgeon cautioned us against performing surgery with extension of the neck in view of the possibility of producing quadriplegia, due to narrowing of the spinal canal as part of the osseous anomaly noted in the magnetic resonance imaging study of the spine, thus making the anaesthesia, surgical and post-operative procedures difficult. The cleft palate reconstruction was performed with all precautions and was uneventful.

### KEY WORDS

Acampomelic; campomelic dysplasia; cleft palate; *SOX9* gene

### INTRODUCTION

Campomelic dysplasia (CD; gene OMIM#114290), a rare form of congenital short-limbed dwarfism, is due to mutations in *SOX9*, a member of the *SOX* (*SRY*-related HMG-box) gene family.

The name is derived from *campo* (or *camppto*) meaning bent, and *melia* meaning limb.

It is a sporadic, autosomal dominant disorder that results in skeletal and developmental abnormalities with reported incidence of about 0.05–0.09 per 10,000 live births.

Characteristic features of CD are skeletal hypoplasias and anomalies affecting the face, head, scapulae,

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spine, pelvis and upper and lower limbs. The head is macrocephalic with flattened face, supraorbital ridges and nasal bridge, high forehead, low-set ears often with associated deafness, hypertelorism, long philtrum, small mouth, cleft palate and micrognathia.<sup>[1-5]</sup> The skeletal features are the most prominent characteristics of CD including anterior bowing of the tibia and characteristic pretibial skin dimples. The femurs are also mildly angulated, and talipes equinovarus and dislocation of the hips are usually present. Short fibulae, kyphoscoliosis, brachydactyly and clinodactyly are common. In addition, usually present are flat vertebrae (particularly at the cervical level), hypoplastic scapulae, and a small bell-shaped chest that is often slender with 11 pairs of ribs and a poorly mineralised sternum.<sup>[3-5]</sup> Most cases of CD are caused by heterozygous *de novo* mutations of the *SOX9* gene (a member of the SOX [SRY-related HMG box] gene family) at chromosome 17q 24.3-q25.1.<sup>[6,7]</sup>

Characteristic phenotypes including bowing of the lower limbs, narrow thoracic cage, 11 pairs of ribs, hypoplastic scapulae, macrocephaly, flattened supraorbital ridges and nasal bridge, cleft palate and micrognathia.<sup>[1]</sup>

A secondary feature of CD is male-to-female sex reversal, which occurs in about two-thirds of patients with an XY karyotype. Like the sex reversal and the various skeletal symptoms, the bending of the long bones is not an obligatory feature and is absent in about 10% of cases, referred to as acampomelic CD.<sup>[6]</sup>

## CASE REPORT

An 18-month-old male child was brought by his parents to our outpatient clinic with a request to repair his cleft palate. He was diagnosed to be a case of acampomelic CD by performing a mutation analysis of the *SOX9* gene followed by DNA sequencing, done in Albert-Ludwig's University of Freiburg, Institute for Human Genetic and Anthropology, Germany.

He had delayed milestones corresponding to that of a 7 months child.

Dysmorphic facies included a large dolichocephalic skull (macrocephaly), low-set ears, flattened nasal bridge, elongated philtrum of the lip, micrognathia and a partial cleft of the secondary palate [Figure 1].

Skeletal deformities included a small thoracic cage, short limbs, no femoral bowing. A chest radiograph showed a small bell-shaped thoracic cage with mild T-L scoliosis and hypoplastic scapulae [Figure 2]. The pelvic and lower limbs' radiography demonstrated no bowing of the femur but short fibulae [Figure 3].

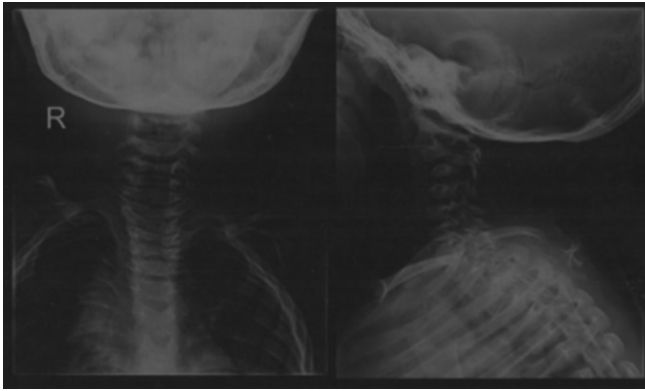
The cervical spine lateral and anterior-posterior radiography showed an atlas that was not well developed; this was normal for that age, but no apparent movement was noted between atlas and axis during flexion and extension of the neck. However, a magnetic resonance imaging of the cervical spine showed an arrow spinal canal with no obvious atlas-axis abnormalities but mild invagination [Figures 4-6]. The brainstem auditory evoked potentials were normal. The patient's karyotype was 46 XY with male external genitalia.

The neurosurgeon provided clearance with a caution to proceed with anaesthesia and palate reconstruction with limited extension or flexion of the neck for fear of quadriplegia developing on the extension.

This led to careful planning of the positioning of the child in view of intubation and operation. The child was successfully intubated by a senior anaesthetist with very little extension of the neck. We proceeded with the operation on this child in a supine position with adequate stabilisation of the neck by gauze roll wrapped head ring, with no extension or flexion of the neck. The Surgeon's usual seated posture while performing surgery needed a change while operating from the head end. During the procedure, the surgeon had to stand and flex his head for a prolonged



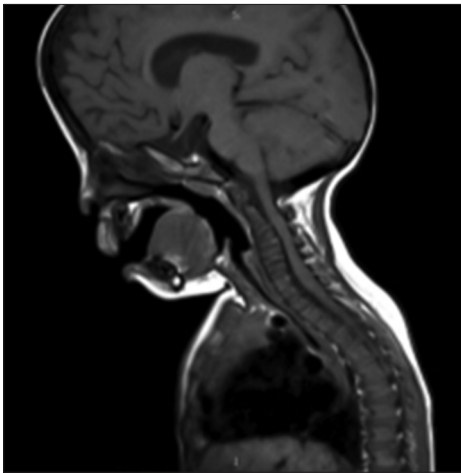
**Figure 1:** Dysmorphic facies with dolichocephalic skull (macrocephaly), low-set ears, flat nasal bridge, elongated philtrum of the lip, micrognathia



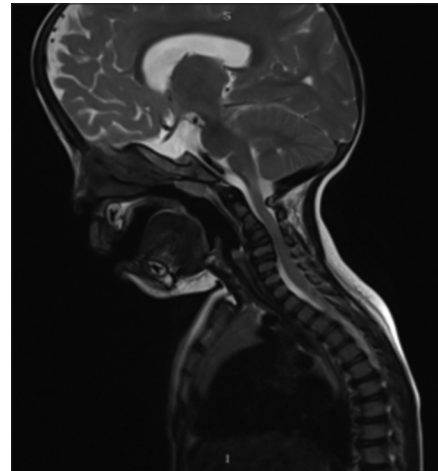
**Figure 2:** Small bell-shaped thoracic cage with mild thoracic-lumbar scoliosis and hypoplastic scapulae



**Figure 3:** The pelvic and lower limbs' radiography demonstrated no bowing of the femur but short fibulae



**Figure 4:** Spinal canal narrowing at C2, C3, C4



**Figure 5:** T2-weighted image showing Cerebrospinal fluid space narrowing, posterior longitudinal ligament is fused or calcified at C1, C2, C3, C4, C5

duration. The partial cleft palate was reconstructed by Veau-Wardill-Kilner's V-Y procedure and repositioning of the levator veli palatini muscle. The extubation and recovery of the child from anaesthesia were uneventful.

The post-operative staffs in the recovery unit, intensive care unit and the ward were given special instructions to avoid any extension or flexion of the child's neck during routine nursing care.

The child was discharged from the hospital on the 7<sup>th</sup> post-operative day uneventfully.

We have been following this child for 3 years with good speech results and a satisfied family.

## DISCUSSION

Characteristic features of CD are skeletal hypoplasias and anomalies affecting the face, head, scapulae,

spine, pelvis and upper and lower limbs. The head is macrocephalic with flattened face and nasal bridge, high forehead, low-set ears often with associated deafness, hypertelorism, long philtrum, small mouth and micrognathia.<sup>[3-6]</sup> The skeletal features are the most prominent characteristics of CD including anterior bowing of the tibia and characteristic pretibial skin dimples. The femurs are also mildly angulated, and talipes equinovarus and dislocation of the hips are usually present. Short fibulae, kyphoscoliosis, brachydactyly and clinodactyly are common. In addition, usually present are flat vertebrae (particularly at the cervical level), hypoplastic scapulae, and a small bell-shaped chest that is often slender with 11 pairs of ribs and a poorly mineralised sternum.<sup>[4-6]</sup> Most cases of CD are caused by heterozygous *de novo* mutations of the *SOX9* gene at chromosome 17q 24.3-q25.1.<sup>[2,7]</sup>

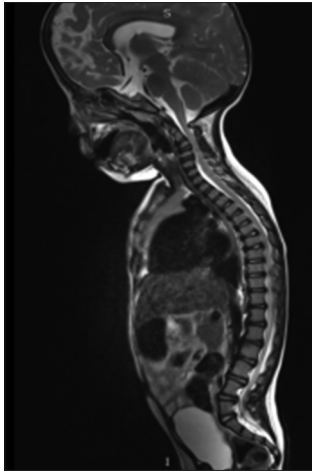


Figure 6: No other spinal abnormalities

Clinical, radiological and pathological data on known or suspected cases of Campomelic dysplasia in the United Kingdom were collected and analysed. Forty cases were initially ascertained by contact with clinical geneticists, radiologists and paediatric pathologists. Five radiological features were chosen as diagnostic criteria. These were hypoplastic scapulae, bowed femora (marked or mild), bowed tibiae (marked or mild), vertically narrow iliac wings and non-mineralised thoracic pedicles. Clinically, seven or more of the following: macrocephaly, micrognathia, cleft palate, flat nasal bridge, low-set ears, talipes equinovarus, congenital dislocation of hips, bowed femora, bowed tibiae, pretibial skin dimples, respiratory distress or sex reversal and bowed lower limbs. Any patient scoring three or more features was included in this study.<sup>[6]</sup>

The bending of the long bones is not an obligatory feature and is absent in about 10% of cases, referred to as acampomelic CD.<sup>[2]</sup>

There is a striking change in the disproportion of the short stature with age. At birth, there are short limbs with normal length of the trunk, but with the progression of the kyphoscoliosis, the trunk becomes relatively shorter than the limbs.

Mutations in the human SRY-related gene, *SOX9*, located on chromosome 17, have been associated with the sex reversal and skeletal dysmorphology syndrome, CD. To clarify the role of the gene in skeletal development, Wright *et al.*<sup>[8]</sup> studied the expression of mouse *SOX9* during embryogenesis in a potential animal model for CD and stated that *SOX9* is expressed predominantly

in mesenchymal condensations throughout the embryo before and during the deposition of cartilage, consistent with a primary role in skeletal formation. Interspecific backcross mapping has localised mouse *SOX9* to distal chromosome 11. The expression pattern and chromosomal location of *SOX9* suggest that it may be the gene defective in the mouse skeletal mutant tail-short.

Lee *et al.*<sup>[9]</sup> reviewed and described *SOX9* expression during embryonic development and loss of function experiments in frog, fish and mouse embryos highlighting the role of *SOX9* in regulating morphogenesis of the face. They also discussed the mutations in and around *SOX9* responsible for craniofacial defects in CD patients since most endochondral bones of the face fail to develop resulting in multiple defects such as micrognathia, cleft palate and facial dysmorphism. Loss of function experiments in frog, fish and mouse embryos highlighting the role of *SOX9* in regulating morphogenesis of the face.

During embryonic development in all species examined *SOX9* is expressed in a broad array of tissues including the gonad, otic vesicle, lung, notochord, neural tube, pancreas and cardiac cushions.<sup>[8,10-13]</sup> The multilineage expression of *SOX9* suggests the existence of complex regulatory mechanisms to control its tissue-specific expression during embryogenesis.<sup>[14]</sup>

In our patient, the cervical spine was stiff in the occipitus-atlas-axis region though no obvious abnormality detected by magnetic resonance imaging, except a narrow spinal canal. This raised perioperative concerns regarding positioning the child for anaesthesia and surgery avoiding extension and flexion of the child's neck. This required expertise in intubation technique with minimal extension of the cervical spine and additional neck supports during the cleft palate surgery. The palate reconstruction can be performed with the child in supine position with no extension or flexion of the neck, supporting the head within custom fit gauze rolled head ring. However, the surgeon has to stand while performing some maneuvers, especially in the anterior region of the hard palate while elevating and suturing the palatal flaps.

The nursing team and the parents involving in the post-operative care of the child need to be given careful instructions of avoiding extension or flexion of the child's neck.

## CONCLUSION

Acampomelic CD, a rare variant of the CD with no bending of the long bones presenting with a cleft palate can be challenge to the nurse, anaesthetist and operating surgeon in rendering care and corrective surgery for the cleft palate. The emphasis on avoiding any extension or flexion should be made to all those handling the child both during the course in the hospital and at home after discharge. The neck should be well supported in the supine position all through the perioperative phase.

### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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