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Unmasking a rare cause of bone overgrowth: SOST-related craniodiaphyseal dysplasia in an adolescent boy

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Abstract

Background: Craniodiaphyseal Dysplasia (CDD) is an exceptionally rare sclerosing bone dysplasia characterized by progressive hyperostosis of craniofacial and tubular bones, leading to severe deformities and cranial nerve compression. Pathogenic variants in the SOST gene, encoding sclerostin-a negative regulator of osteoblast activity-have been implicated in its pathogenesis.

Case presentation: We describe a 14-year-old Asian-Indian boy who presented with progressive craniofacial enlargement, visual and auditory loss, and delayed puberty. Physical examination revealed macrocephaly, frontal bossing, hypertelorism, broad nasal bridge, and mandibular enlargement. Biochemical evaluation showed markedly elevated serum alkaline phosphatase with secondary hyperparathyroidism, while bone mineral density was profoundly increased (z-score +5.4 at femoral neck). Radiographs demonstrated generalized cranio-tubular hyperostosis sparing metaphyses. Whole-exome sequencing identified a heterozygous missense SOST variant (c.61G>A; p.Val21Met) in the signal peptide region, classified as pathogenic, confirming the diagnosis of SOST-related CDD. He underwent right optic nerve decompression with transient improvement in vision and was initiated on testosterone therapy for hypogonadism.

Conclusion: This report describes one of the few genetically confirmed cases of CDD caused by a SOST signal peptide mutation. The case expands the phenotypic spectrum of SOST-related disorders, highlighting variable expressivity even within identical genotypes. Early molecular diagnosis facilitates timely surgical and endocrine management, guiding prognosis and future exploration of targeted molecular therapies.

Keywords: Craniodiaphyseal dysplasia; SOST gene; Sclerostin, sclerosing bone dysplasia; Hyperostosis; Hypogonadism, Wnt signaling.

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Case presentation

Sclerosing Bone Dysplasia (SBD) are heterogenous group of bone disorders, characterised by significantly increased bone mass, occurring as a result of excess bone formation or impaired bone resorption or disturbed coupling between bone resorption and formation [1]. Hereditary SBD are rare monogenic disorders and each representing a disruption in bone ossification pathway. They vary greatly in their presentation and severity, ranging from mortality at much early age, mild growth retardation, fractures and deformities in childhood to incidental findings on radiographs in adult life. The diagnosis and differentiation of various subgroups are traditionally based on clinical and radiological evaluation, which in many cases, does not lead to a definitive conclusion. Unravelling the molecular-genetic pathophysiological mechanisms over recent decades, helped in better understanding and delineation of these dysplasias.

We are reporting a case of rare SBD presented with craniofacial deformities, progressive deterioration in hearing and vision, and delayed development of secondary sexual characteristics.

A 14-year-old Asian-Indian boy was referred to our Endocrinology unit for the evaluation of facial dysmorphism and increased bone density. His birth history was uneventful and had achieved mile stones appropriate for his age. There was no difficulty in feeding or facial deformities until the age of three years, when his mother noticed persistent mouth breathing and his nose appeared to be smaller and depressed in comparison to his head size. He also developed nasal intonation in his voice which was not there earlier. Gradually, his upper part of face started enlarging more and became prominent over next 2-3 years. With progressive changes in facial features and mouth breathing, family consulted an ENT surgeon. At 6 years of age, he underwent contour correction of upper half of face and reconstruction of nose. During surgery, it was found that bones were thick and hypertrophied but no histopathology reports of resected bones were available. After initial brief improvement for few months, mother noticed further enlargement of face including jaw and progressive decrease in hearing and vision. There were no fractures, bony pain, head ache, vomiting and weakness of limbs. The scholastic performance was good, however, hindered due to progressive compromise of vision and hearing. He was the third child of non-consanguineous parents and there was no history of similar illness in any of the family members.

On examination, he was 162 cm tall (50th centile of 2017 IAP Growth charts) with a mid-parental height of 163 cm. His weight was 61 kg and BMI was 23.82 kg/m^2. He had macrocephaly with head circumference of 67 cm, frontal bossing, hypertelorism and protruded eyes. The nasal bridge was broad and depressed with small upturned nose, prominent zygomatic, maxillary bones and facial veins. He had broad enlarged mandible with malocclusion teeth and loss of upper incisors (Figure 1). On neurological examination, bilateral lower seventh cranial nerve palsy and markedly reduced vision (finger counting in right eye; 6/60 in left eye by Snellen's chart) with changes of optic atrophy in both eyes were present. Audiometry revealed bilateral severe mixed hearing loss. No signs of myelopathy were elicited. He was prepubertal (Tanner stage 1, testicular volume bilateral <2 ml). There was no pallor, hepatosplenomegaly, digital malformations, nail hypoplasia, bony deformities or scoliosis.

His biochemical studies showed normal renal, liver function tests, hemogram, serum calcium and phosphorous. The serum alkaline phosphatase was markedly increased to 1078 U/l (RR, 80-240), 25 hydroxy vitamin D was low (14 nmol/l (5.6 ng/ml) and intact parathyroid hormone level elevated to 98.9 pg/ml (RR,15-65)). Basal hormonal evaluation showed decreased serum testosterone (<0.025 ng/ml) and supressed LH (<0.1 IU/L) and FSH levels (<0.0025 IU/L), normal thyroid function tests ((T4:8.01 ug/dl RR:5.1-14.1, T3: 1.64 ng/ml (RR:0.8-2), TSH: 2.7 ulU/ml (RR:0.27-4.2)). Bone mineral density measured by DEXA was grossly elevated at lumbar spine, femoral neck and whole body (z-score +4.9, +5.4, +4.2 respectively). In skeletal survey, there was bilateral symmetrical hyperostosis of tubular bones like clavicles, ribs, metacarpals, metatarsals and diaphysis of long bones sparing epi-metaphyses and marked sclerosis of skull, facial bones and mandible (Figure 2). CT scan showed diffuse sclerosis with hyperostosis of cranio-tubular bones and narrowing of the bilateral skull base foramina, internal auditory meatus, obliteration of sinuses, bilateral nasal-orbital cavities and optic canal. In MRI Sella, the pituitary gland appeared to be normal with no stalk deviation.

Considering the clinical, biochemical findings and radiological involvement of sclerosis affecting cranio-tubular bones sparing metaphysis, a possibility of Hyperostosis corticalis generalisata was suspected. On whole exome sequencing, a heterozygous missense variation in exon 1 of the SOST gene (chr17: g.43758681C>T), resulting in the amino acid substitution of Methionine for Valine at codon 21 (p. Val21Met), was detected. The observed variation was classified as pathogenic in the ClinVar database and confirmed diagnosis of Craniodiaphyseal dysplasia in this patient.

In view of his debilitating visual symptoms, bilateral optic nerve decompression was planned and navigation guided right optic nerve decompression was initially performed along with reconstruction of right nasopharynx. His vision in right eye improved to 1/60 over a period of four weeks but over a follow up of 6 months visual acuity deteriorated to absent perception of light. Bone anchored hearing aids were offered and due to his psychological concerns regarding hypogonadism, testosterone injections was initiated at 100 mg im once a month.

Discussion

Increased skeletal mass is often a diagnostic challenge due to the significant variability in severity. Hereditary SBD was classified earlier, according to the site of abnormal bone formation, as proposed in Greenspan [2]. Disorders of intramembranous bone formation involves cortex of tubular and flat bones, calvaria and facial bones as seen in progressive diaphyseal dysplasia, hereditary multiple diaphyseal sclerosis and hyperostosis corticalis generalisata. While disorders of endochondral bone formation cause changes in axial skeleton, skull base and tubular bones. It is grouped into a) failure of resorption of primary spongiosa as seen in osteopetrosis and pyknodysostosis and b) disorder in remodelling of secondary spongiosa to form trabeculae and medullary cavity as seen in osteopoikilosis and osteopathia striata. CDD is considered due to a defect in both types of ossification and is grouped under mixed sclerosing type with predominant involvement of intramembranous bone formation.

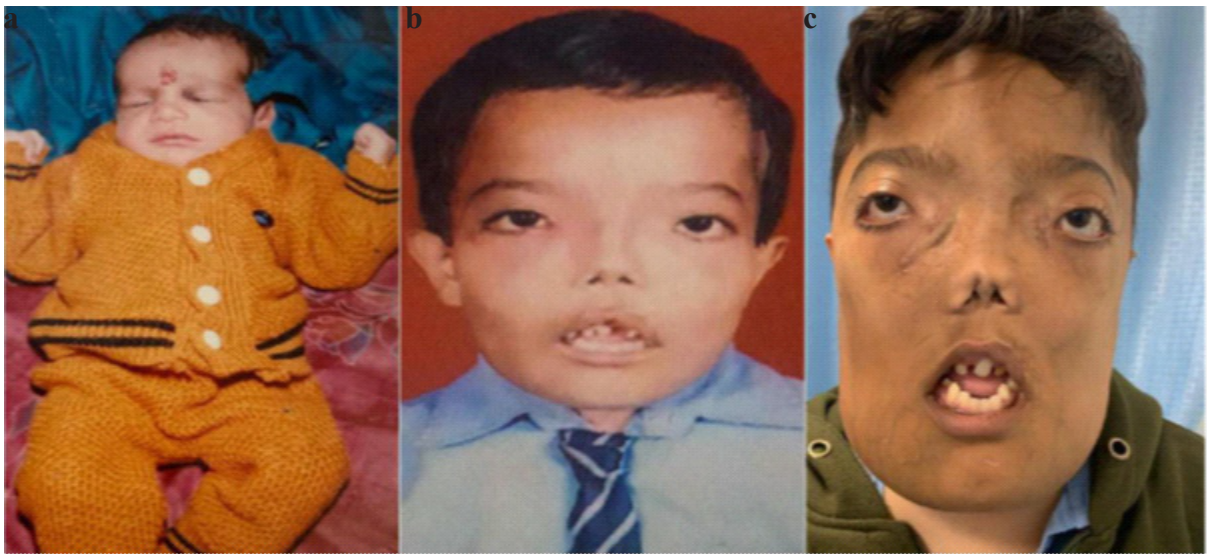

Figure 1: Clinical appearance of the patient with cranio diaphyseal dysplasia at age of **(a)** 16 days after birth **(b)** at 6 years and **(c)** at 14 years showing progressive facial features like macrocephaly, paranasal bossing, hypertelorism, broad flat nasal bridge with saddle deformity and enlarged mandible.

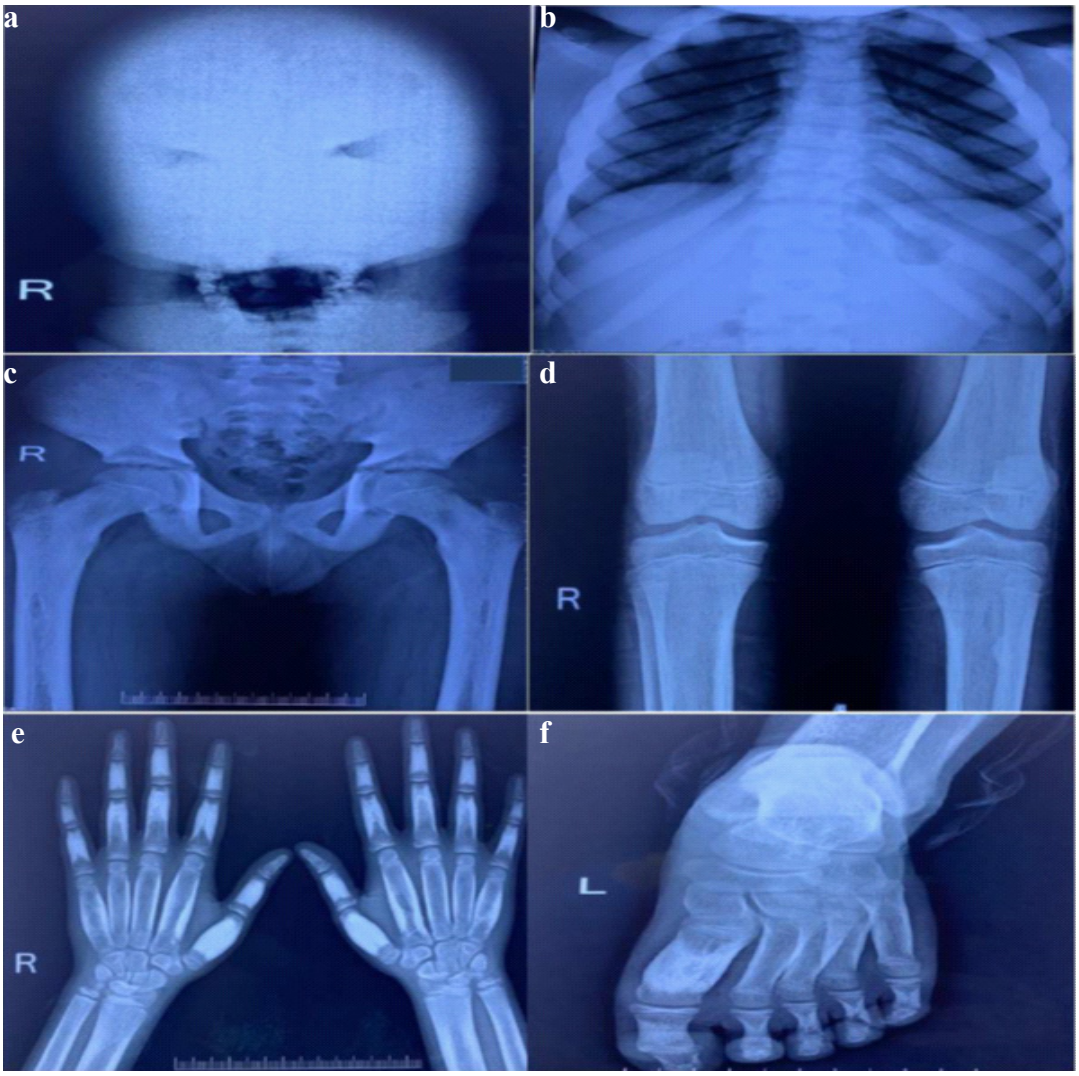

Figure 2: Radiograph showing generalised osteosclerosis and hyperostosis **a)** AP radiograph of skull showing diffuse sclerosis and hyperostosis of facial bones and skull **b)** AP radiograph of chest showing sclerosed ribs and vertebrae **c)** AP radiograph of pelvis showing bone in bone appearance of iliac wings and cortical thickening of femur at it diaphysis portion with focal obliteration of the medullary cavity **d)** AP radiograph of knee showing epi metaphyseal sparing of tubular bones **e)** and **f)** hand and foot radiograph showing diaphyseal sclerosis of all the tubular bones.

Table 1: Clinical features of various sclerosing bone dysplasia caused by SOST gene mutations.

Features	Craniodiaphyseal dysplasia	Sclerosteosis (Truswell-Hansen disease)	Van Buchem disease
Mutation in SOST gene	Signal peptide	Inactivating	Deletion of 52 kb downstream of the SOST gene that affect its transcription
Mode of inheritance	Autosomal dominant and recessive	Autosomal recessive	Autosomal recessive
Onset	Early; noticeable at birth to around 3 months of age	Apparent by 5 years of age	Manifests in second decade
Craniofacial deformity	Forehead and paranasal bossing, hypertelorism with increased head circumference	Mandibular enlargement and bossing of forehead with increased head circumference	Mandibular enlargement is the predominant manifestation, head circumference is increased in few of the patients
Unique clinical feature	Craniofacial deformity pattern	Syndactyly of second and third digits (66% of cases), nail dysplasia and radial deviation	Enlargement of jaw with no syndactyly and nail hypoplasia
Stature	Normal or short stature	Tall stature	Normal stature
Progression of disease	Progressive	Clinical course usually does not progress after third decade of life	Clinical course stabilises in adulthood with no progression of symptoms or development of complications
Life expectancy	Severely affected children die before first decade	Larger proportion of patient die in third decade due to increase in intracranial pressure or following craniotomy	Appears to be normal

The advent of identification of underlying molecular defect not only helped in distinguishing subtypes among those with similar phenotypic characteristics but also to recognise the phenotypic heterogeneity arising from a single gene. Hence, incorporating the molecular definition also, the latest Nosology of genetic skeletal disorders (2023) have simplified the classification of the inherited SBD into "Osteopetrosis and related osteoclast disorders" and (non-osteopetrotic) "Osteosclerotic disorders" where CDD is grouped under Osteosclerotic disorders [3].

CDD is a severe sclerosing bony dysplasia, characterised by generalised progressive hyperostosis and osteosclerosis predominantly involving the craniofacial and tubular bones. It is one of the rarest skeletal dysplasia and fewer than 30 cases have been reported. The first report dates back to 1949 but as a distinct disorder, CDD was first described by Gorlin and associates in 1969 [4].

They have a distinctive facial dysmorphism referred to as "leontiasis ossea", due to its typical pattern of bony involvement, leading to a prominent zygomatic bone, broadening of the centre of face, hypertelorism, small upturned tip of the nose and a prominent jaw. Besides the deformities, the overgrowth of facial bones causes choanal and lacrimal duct obstruction, dental malocclusion and strabismus. Progressive bony encroachment upon the cranial foramina results in severe neurological impairment in childhood leading to hearing loss, visual impairment, facial palsy and in increased intracranial pressure which causes severe head ache, seizures, quadriparesis or even sudden death. Mental retardation as well as delayed sexual maturation have also been described [5].

CDD exhibits autosomal dominant inheritance, caused by heterozygous mutation in the SOST gene on chromosome 17q21, encoding for sclerostin. Recessive form of inheritance has also been reported [6]. Sclerostin, an osteocyte specific secreted protein, suppress bone formation by inhibiting canonical Wnt/β-catenin signaling in osteoblasts. Hence the consistent biochemical abnormality reported is markedly raised alkaline phosphatase suggesting that the disorder is associated with excess osteoblastic activity. Kim et al. [7] observed the signal peptide mutations ((c.61G[A(Val21Met), c.61G[T(Val21Leu)) of SOST gene in two children with CDD and demonstrated that it was associated with the reduced secretion of sclerostin in transfected 293E cells. Hence CDD may represent the severe end of spectrum of the disease, caused by mutations in SOST gene, which includes sclereostosis and Van Buchem's disease (Table 1).

Diagnostic radiographic features include severe sclerosis and hyperostosis involving the whole skull including the facial bones and mandible with obliteration of sinuses. The distribution and severity of involvement of tubular bones varies from patient to patient and are marked by diaphyseal expansion and endosteal cortical thickening. The characteristic description is "policeman truncheon" appearance in long bones having diaphyseal endostosis without metaphyseal flare. There is moderate sclerosis and thickening of ribs and pelvis. Sclerosis of the spine is less found, if involved changes are more marked in the vertebral arches than in the bodies [8].

Currently no medical treatment has been available to halt the continuous bony growth and management is aimed at the amelioration of complications. Surgical decompression of cranial foramina provides temporary relief of compression of cranial nerves. The low calcium diet and calcitriol therapy, dexamethasone, heparin and somatostatin have shown failed to arrest the progression of disease. The use of synthetic calcitonin, however resulted in delayed progression of increase in head circumference and a change in alkaline phosphatase in a patient [9]. With the molecular studies elucidating the underlying pathophysiology of CDD, the administration of recombinant sclerostin is a potential therapeutic strategy that deserves further investigations. Recently, Chan et al. [10] demonstrated in vitro in mouse MC3T3-E1 cells, that the signal peptide mutations in SOST gene could lead to activation of endoplasmic reticulum stress and a phenotypic cure of hyperostosis is possible by treatment with sodium 4 phenobutyrate, a chemical chaperone that assists in protein folding. In future, targeted therapy would evolve, to arrest the relentless bone growth thereby improving the prognosis and outcome of these set of diseases.

Although a couple of cases of CDD have been reported in literature, all are diagnosed based on clinical and radiological features. The genetic basis of CDD as SOST gene mutation was shown previously, only in two patients and our paper is the second case demonstrating a similar signal peptide mutation variant (p. Val21Met), reinforcing the finding of SOST gene as the molecular target. However, in comparison with the child previously reported with similar mutation, our patient has a different phenotype with the less aggressive disease, longer survival and normal stature. Early diagnosis of this inevitably progressive disease is crucial for planning a proper follow up thereby enabling timely surgical intervention and helps to establish prognosis.

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