Pseudo-achondroplasia masquerading as rickets due to a novel mutation in COMP gene

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Introduction
Pseudo-achondroplasia (PSACH) is a rare variant of skeletal dysplasia with a prevalence ranging from 1/20,000 to 1/30,000 people globally1. It is due to an autosomal dominant mutation in 8-19 exons of the cartilage oligomeric matrix protein (COMP) gene on chromosome 19 p12-13.1 resulting in defective expression of COMP (OMIM: 177170)2,3. The disease presents as rhizomelic dwarfism, characterized by short and broad hands with ulnar deviation, brachydactyly, short forehands, lower limb defects, abnormal gait, arthritic laxity, lumbar lordosis, scoliosis, and degenerative changes of joints4. We present a three and half-year-old child with an early expressed and severe PSACH born to a family with affected three generations, though in a milder form.

Case report
A three and half-year-old boy, born of a non-consanguineous marriage, developed gradual bowing of legs and widening of wrist joints from one year of age. He was treated for rickets by a general physician at a primary health centre for his skeletal deformity and short stature with high doses of vitamin D (20,000IU/day) for the last 6 months without any improvement.

Examination revealed disproportionate short stature with a height of 85cm (<3rd percentile, Indian Academy of Paediatrics (IAP)), mid-parental height of 163.5cm, a ratio of upper segment to lower segment of 1.5:1, a weight of 14.4kg (25th-50th percentile, IAP), and head circumference of 51cm (50th-85th percentile, World Health Organisation).

He had a waddling gait, pectus carinatum, Harrison’s sulcus, short lower limbs with genu varum, short arm and forearm (Figure 1a), short and broad hands with ulnar deviation, widening of bilateral wrist joints, brachydactyly, and joint hyperlaxity. He had a strikingly normal craniofacial appearance with normal intelligence. The other systems were normal. His mother had two first-trimester abortions after the birth of two healthy daughters. His father, grandfather, and grandfather’s brother had minimal bowing of legs which improved gradually with age without any intervention.

At the time of admission, the child’s complete blood count, thyroid profile, liver, and renal function tests were normal. His serum calcium was 2.58mmol/L (normal: 2.2-2.7mmol/L), serum phosphorus 1.29mmol/L (normal: 1.03-1.87mmol/L), serum alkaline phosphatase 158.4 U/L (normal: 100-320 U/L), serum albumin 46g/L (normal: 36-52g/L), 25 hydroxy vitamin D =250 mmol/L (normal: 50-250mmol/L), 1,25-dihydroxy vitamin D 127pmol/L (normal: 42-169pmol/L), serum parathormone 19.4pmol/L (normal: 33-190pmol/L), spot urine calcium to creatinine ratio 0.068 (normal: 0.02-0.41).

X-ray of wrist joints and hands revealed fraying and splaying of the metaphysis of the radius and ulna, hypoplastic epiphysis at the distal end of the radius and ulna with 2 carpal bones, short, irregular metacarpals, and phalanges with cone-shaped epiphysis (Figure 1c). X-ray knee revealed fraying, and splaying of the metaphysis of the femur, tibia and fibula with hypoplastic epiphyses (Figure 1d). X-ray thoracolumbar spine demonstrated platyspondyly, central anterior tonguing of a lumbar vertebra with maintained lordosis and intervertebral disc spaces (Figure 1b). X-ray pelvis showed hypoplastic epiphysis of the femoral head with flat acetabulum. X-ray skull was normal. Father’s X-ray spine and knee were normal.

Based on the clinical and radiological findings, possibilities of spondylo-epi-metaphyseal dysplasia, PSACH, multiple epiphyseal dysplasia (MED) and mucopolysaccharidosis type IV were kept in mind. Ophthalmologic examination was normal and urine glycosaminoglycans were negative.

Whole exome sequencing confirmed heterozygous non-synonymous variation (c.874T>C) in exon 9 of the COMP gene at chromosome 19:18788313 position at depth of 175X which changes amino acid cysteine to arginine at position 292 in the COMP protein. The in-silico predictions of the variant were found to be damaging by SIFT, Mutation Taster2, PROVEAN FATHMM, Polypehn2, MetaSVM, and MetaLR prediction tools. This is confirmed as a novel pathogenic variant in ClinVar and Bione VaringDb database. Sanger sequencing of parents was planned for carrier status detection.

Physiotherapy and limb-strengthening exercises were advised. On serial follow-ups at 3, 6 & 12 months, the child was found to have a minimal increment in height (gain of 2 cm in 1 year) without any further worsening of the existing deformities.

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Discussion

PSACH is a type of osteochondrodysplasia due to an autosomal dominant mutation in the COMP gene on chromosome 19p12-13. In response to the mutation, the COMP protein folds abnormally and accumulates in the endoplasmic reticulum of metaphyseal chondrocytes, causing oxidative stress and cell death as well as chondrocyte loss in the growth plate. The development of the osteogenic disease, or the transformation of cartilage into bone tissue, is the result of this deficiency, which is characterized by penetrance and is followed by recognizable epiphyseal, metaphyseal, and vertebral abnormalities.

These children are normal at birth and start manifesting around 2 to 3 years of age with lower limb deformities and walking difficulties. Their facial appearance and intelligence are normal. Gradually, rhizomelic dwarfism becomes apparent as the child grows with progressive degeneration of joints. Limb deformities resemble rickets, which can be excluded by complete metabolic evaluation.

Radiologically, rhizomelic dwarfism is more apparent in the proximal part of the limbs than the distal part, with metaphysis showing flaring with small and poorly formed epiphyses. The femur and humerus are the most commonly affected long bones. Metacarpals and metatarsals are short and stubby with small and immature epiphyses. A roentgenogram of the pelvis shows an irregular, small, and flattened femoral head, short neck of the femur, and wide pubic symphysis. The acetabulum is poorly formed and flattened. The skull is normal. The pathognomonic feature is the persistence of the oval shape of vertebrae along with tongue-like protrusion of the anterior aspect of lower thoracic and upper lumbar vertebrae, giving a central anterior tongue appearance.

This feature disappears gradually as the child grows older which then culminates in platyspondyly, eventually leading to short trunk and short limb dwarfism. PSACH closely mimics achondroplasia as well as MED. Achondroplasia patients have disproportionately big heads with a pronounced frontal area and depressed nasal bridge. The interpedicular distance is decreased in the lumbar spine with the absence of platyspondyly. It has also the classical trident hand with champagne glass pelvis. Epiphyses are largely normal in achondroplasia.

MED shares the same COMP gene mutation with significant overlap in the age of presentation as well as radiographic abnormalities. It is distinguished by a mostly normal pelvis with slight acetabular edge scalloping and the classical double-layered patella. The joints have restricted, and painful movements as compared to PSACH which is associated with joint and ligamentous laxity. Since it is believed that PSACH is a more severe form of the same gene mutation, dwarfism and limb shortening are more dramatic in PSACH compared to MED.
Diagnosis of all skeletal dysplasias requires a combination of family history, physical examination, biochemical and radiological investigation. Decreased levels of serum COMP may aid as a diagnostic marker of PSACH\(^6\); genetic verification of this disorder is advised whenever feasible. Considering the family history in our case, with multiple affected family members in 3 generations, the expression of the disease has been variable. Penetrance in this disease is thought to be complete, despite a previous report of a case with possible incomplete penetrance\(^9\). Therefore, it is more plausible that phenotypic expression is varied, with the potential for mild phenotypes or somatic mosaicism, both of which cannot be completely ruled out\(^10\).

The most significant complication is joint pain that starts in childhood as a result of precocious osteoarthritis predominantly affecting the knee, hip, and spine. Treatment involves the management of spinal deformities, physiotherapy, and corrective orthopaedic surgery, which should be planned after the completion of the growth period\(^8\). Novel therapeutic modalities like antioxidants (aspirin and resveratrol), anti-inflammatory drugs, and antisense oligonucleotide therapy have shown promising results in murine models but human trials are still ongoing\(^11\). Treatment with mega doses of vitamin D for a prolonged time is probably the reason for high serum Vitamin D markers in our patient.

**Conclusion**

PSACH is an achondroplasia like rhizomelic dwarfism which mimics rickets as well as various other skeletal dysplasias. It results from a genetic mutation with a variable phenotypic expression that continues to evolve throughout life. A high index of clinical suspicion, thorough evaluation, and genetic workup can differentiate it from others, which will guide further management and genetic counselling of parents.

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**References**


