CASE REPORT

Management of Severe Obstructive Sleep Apnea in Pediatric Patients with Pycnodysostosis: A Report of Two Cases

Dhruv Jain[1], Sanjeev Datana[2], SS Agarwal[3], Indranil D Roy[4]

Abstract

Pycnodysostosis (PKND) is a rare autosomal recessive disorder caused by molecular mutation in cathepsin K (CTSK) gene, resulting in decreased bone turnover with enfeeblement of bone structure. This report addresses an array of systemic and craniofacial features of two siblings affected with PKND with an association of severe obstructive sleep apnea (OSA), managed conservatively with an oral mandibular advancement appliance.

Keywords: Obstructive sleep apnea, Oral appliance therapy, Pycnodysostosis.

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Introduction

Pycnodysostosis (PKND), also known as Maroteaux–Lamy syndrome and Toulouse Lautrec syndrome, is a rare autosomal recessive disorder that presents with an array of clinical and radiographic manifestations: osteosclerosis with increased susceptibility to fracture, short stature, delayed closure of cranial sutures, craniofacial abnormalities, clavicular dysplasia, spondylolysis, acro-osteolysis of terminal phalanges, and dysplastic nails. Other findings may include ocular abnormalities, platybasia, stridor, and laryngomalacia. Respiratory resistance in the form of snoring and OSA are also common among affected patients. Intelligence is usually normal though psychomotor skills may be mildly deranged.[1–3]

Craniofacial manifestations chiefly include brachydactyly, frontoparietal bossing, open fontanelles, proptosis, bluish sclera, convex nasal bridge, midface retrusion, and mandibular micrognathia with obtuse mandibular angle. Dental findings comprise delayed/abnormal tooth formation and eruption process, short or poorly shaped roots with narrowing of pulp chambers and root canals, hypercementosis, deep and grooved palate, and characteristic malocclusion, such as crossbite, anterior open bite, and crowding. Dental caries and periodontitis are frequently associated with poor oral hygiene.[1–4]

Though this condition gained world academic attention in 1962 when Maroteaux and Lamy[5] described PKND as a distinct entity as "diastrophic dwarfism," it remained an exceedingly rare diagnosis until 1996, when the mutant gene responsible for PKND was mapped to human chromosome 1q21 and was subsequently identified as encoding for CTSK by a positional cloning strategy.[6–8]

Young patients presenting with PKND along with respiratory insufficiency require a multidisciplinary approach and pose a great challenge to an orthodontist with special emphasis on preventive and interceptive management.[9] Currently, there have been no established guidelines pertaining to the orthodontic or orthopedic management of such patients. This paper addresses the systemic and craniofacial features of two siblings affected with PKND along with the conservative management of severe OSA with oral appliance therapy.

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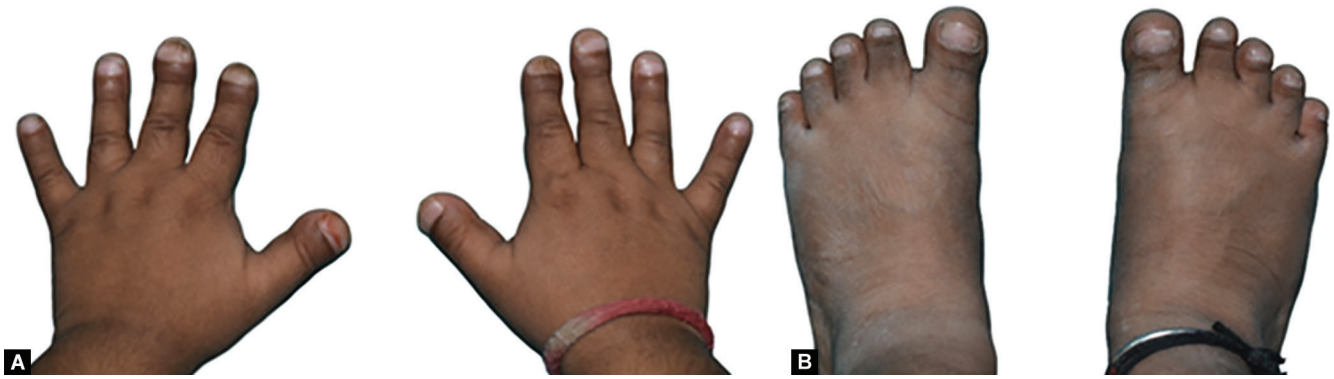
Case 1

Diagnosis and Etiology

A 7-year-old male patient reported with chief complaint of loud snoring and forceful awakening during sleep with no previous intervention. The patient was the eldest among three siblings of consanguineous parents, with normal birth history. He presented with brachycephaly, marked facial convexity, prominent forehead, high nasal bridge with bulbous nose tip, shallow orbits, potentially competent hypotonic lips with increased interlabial gap, shallow mentolabial sulcus, retrusive chin, and short neck. Intraoral examination revealed mixed dentition stage, poor oral hygiene, generalized gingivitis, multiple carious teeth, and anterior open bite with interposed tongue (Fig. 1).

Physical examination revealed disproportionate short stature with a height of 85 cm (<third percentile), weight of 15 kg (<third percentile), BMI of 20.8 kg/m^2, head circumference of 42 cm (<third percentile), short stubby digits with dysmorphic nails, and sandal foot deformity (Fig. 2). Liver function test and thyroid function test were within normal limits. Visual and neurological assessments were normal. However, 2D echocardiogram revealed tiny atrial septal defect, and chest examination revealed pectus excavatum.

Fig. 1: Pretreatment facial and intraoral photographs



Figs 2A and B: Physical examination. (A) Short stubby digits with dysmorphic nails; (B) Sandal foot deformity

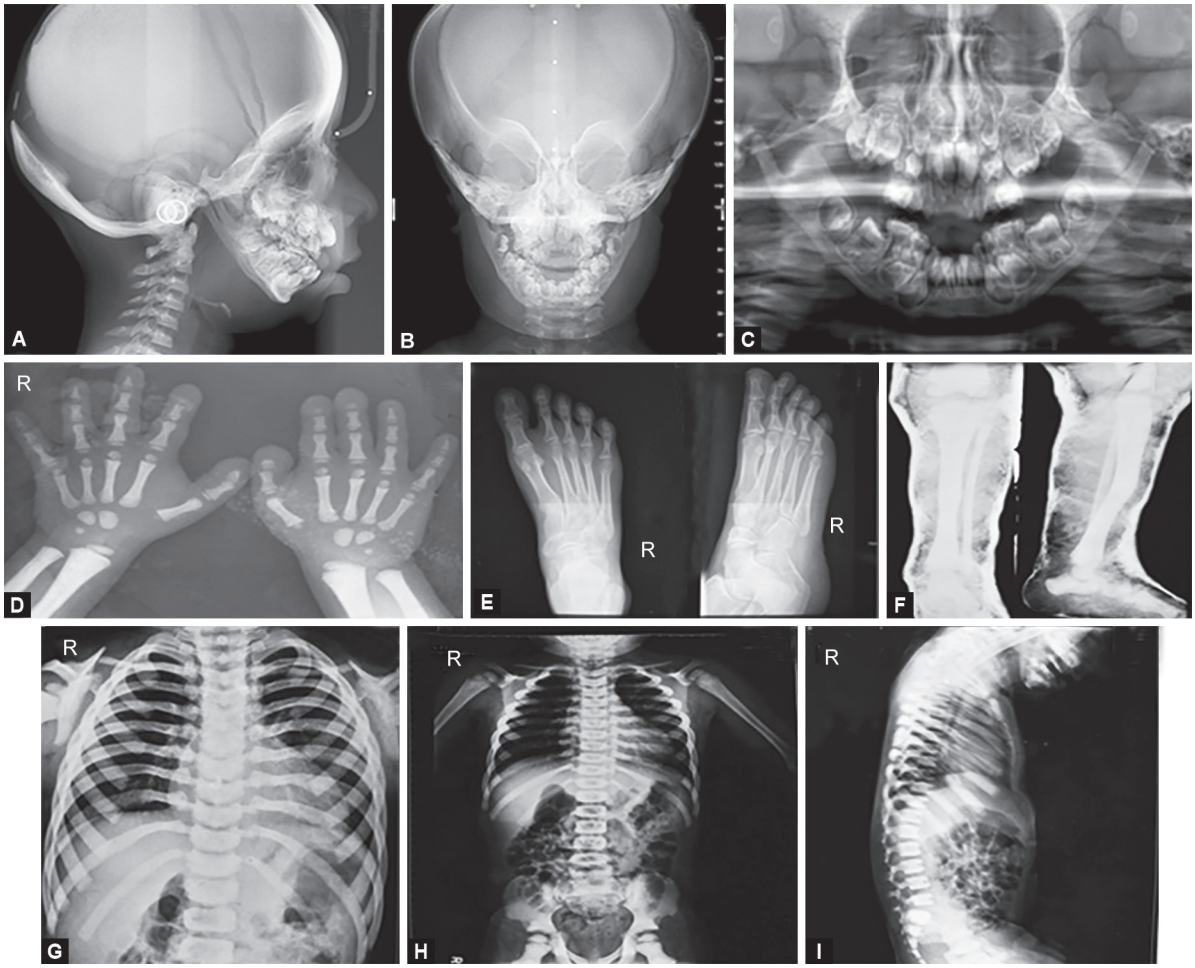
Skeletal survey revealed a generalized increase in bone density, persistent open fontanelles, wormian bones, hypoplastic paranasal sinuses, spur-shaped vertebrae, distal erosion of both clavicles, acro-osteolysis of distal phalanx, and radiolucent horizontal fracture line with cortical breach in mid-tibia (Fig. 3).

Lateral cephalogram revealed abnormal morphology of sella turcica, maxillomandibular hypoplasia, short mandibular ramus with long body, elongated condylar and coronoid process, obtuse mandibular angle, interdental alveolar crest resorption, and short dental roots. There was no evident facial asymmetry as evaluated by posteroanterior cephalogram. However, generalized sclerosis of facial skeleton, more pronounced in circumorbital region ("harlequin appearance"), was evident (Fig. 3). Cephalometric findings are presented in Table 1.

Since excessive day sleepiness, loud snoring, and forceful awakening during sleep were the chief concerns of the patient, a thorough airway analysis was carried out along with a real-time recording of sleep (Video 1). Lateral cephalogram suggested severe compromise in airway dimension (Table 1). Otolaryngological evaluation revealed adenoid hypertrophy may be a contributing factor for snoring. Furthermore, polysomnography (PSG) was carried out to assess the severity as well as the underlying cause of airway disorder, which confirmed the diagnosis of severe OSA with apnea-hypopnea index (AHI) of 25.3 per hour, the lowest oxyhemoglobin saturation of 37% and 155 out of 190 total events of obstructive apnea (Fig. 4). Central cause of sleep apnea was ruled out.

Video 1: Real-time sleep of case 1 (Above-mentioned video is available online on the website of www.ijsm.in.)

On consultation with pediatrician, the provisional diagnosis of PKND was formulated, which was confirmed through genetic testing revealing CTSK exon 6 homozygous mutation (c.749A > G p.Asp250Gly). Further, the youngest sibling and both the parents



Figs 3A to I: (A) Craniofacial radiographic manifestations as depicted by lateral cephalogram; (B) Posteroanterior cephalogram showing pronounced sclerosis in periorbital region ("harlequin appearance"); (C) Orthopantomogram; (D and E) Radiograph showing acro-osteolysis of terminal phalanges; (F) Radiograph of tibia and fibula demonstrating diffused sclerosis; (G) Chest radiograph revealing pectus excavatum; (H) Coxa valga deformity; (I) Lateral spine radiograph depicting vertebral deformity

Table 1: Cephalometric evaluation for case 1 and case 2

Cephalometric parameter	*Normal value*	*Case 1*	*Case 2*
Sagittal measurements			
SNA	82°	74°	76°
SNB	80°	59°	63°
ANB	2°	15°	13°
Effective length of maxilla (Co-A)	81.7 ± 3.4 mm (M) 79.8 ± 2.2 mm (F)	67 mm	63 mm
Effective length of mandible (Co-Gn)	99.3 ± 3.6 mm (M) 97.7 ± 3.4 mm (F)	70 mm	68 mm
Maxillomandibular differential	17.5 ± 2.2 mm (F) 17.9 ± 8.1 mm (F)	3 mm	5 mm
Anterior cranial base length (S-N)	—	55 mm	57 mm
Vertical measurements			
Anterior facial height (N–Me)	—	81 mm	74 mm
Posterior facial height (S-G0)	—	20 mm	21 mm
Jarabak ratio (%)	62–65%	25%	28.3%
Lower anterior facial height (LAFH)/anterior facial height	65–70%	62%	55%
Go-Gn to SN	32°	66°	56°

were heterozygous for the CTSK gene variant, while the second sibling was homozygous for the same (Fig. 5).

Treatment Objectives

The primary treatment objective was to increase the upper airway volume through maxillomandibular advancement, thereby reducing the severity of OSA and improving the stomatognathic function along with the quality of life.

Treatment Plan

As an interdisciplinary approach, the case was thoroughly discussed conjointly with a team of pediatricians, otolaryngologist, oral and maxillofacial surgeons, and orthodontists regarding the comprehensive management of severely compromised airway of the patient. Distraction osteogenesis (DO) was given a serious thought to address the chief complaint; however, because of the associated potential risk factors, such as pathologic fracture and maxillary osteomyelitis, there was no general consensus on DO. Alternatively, conservative measurement with oral appliance therapy was adopted as a treatment mode.

Appliance and Treatment Progress

As an immediate therapy for airway improvement, oral appliance was fabricated comprising of maxillary and mandibular acrylic

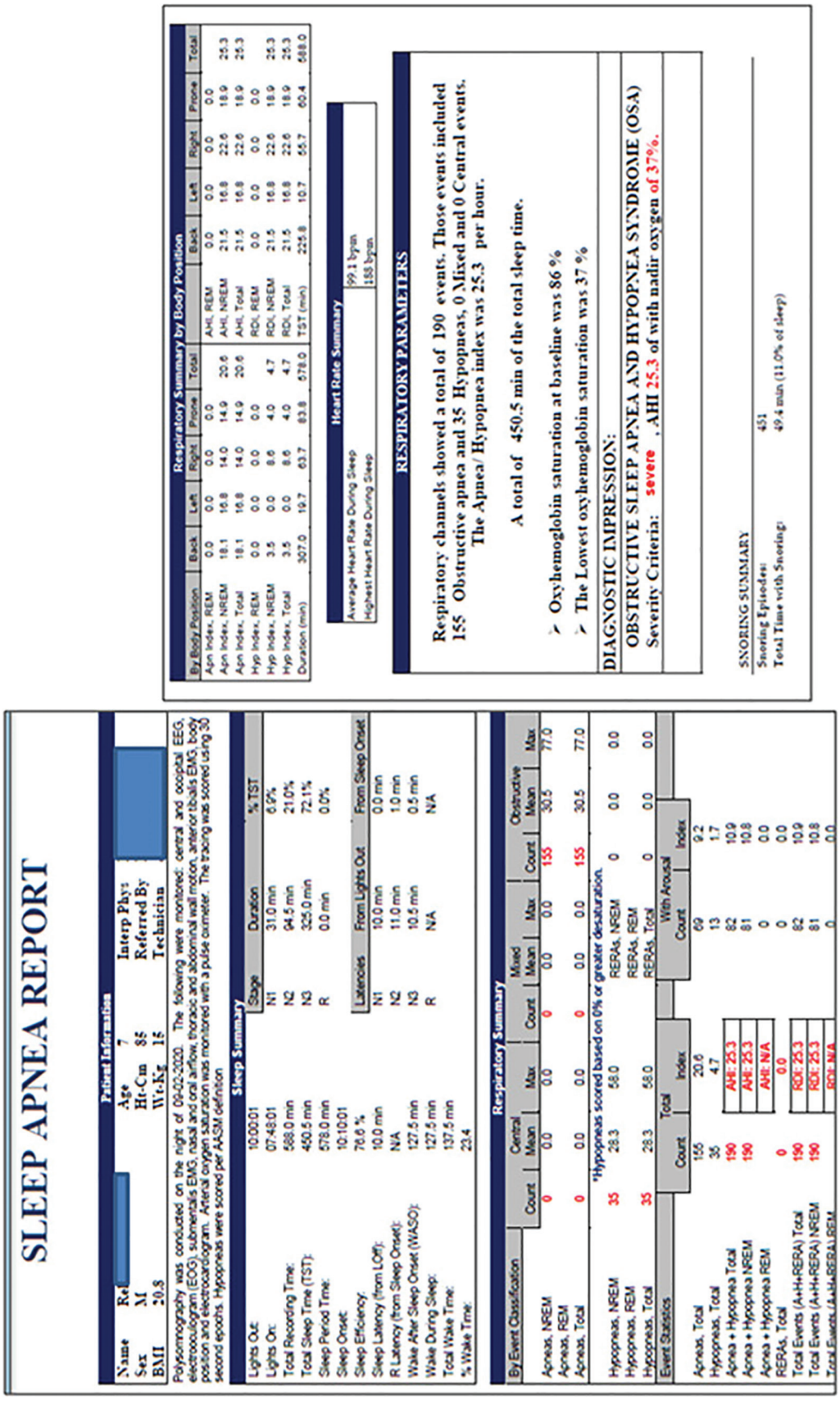
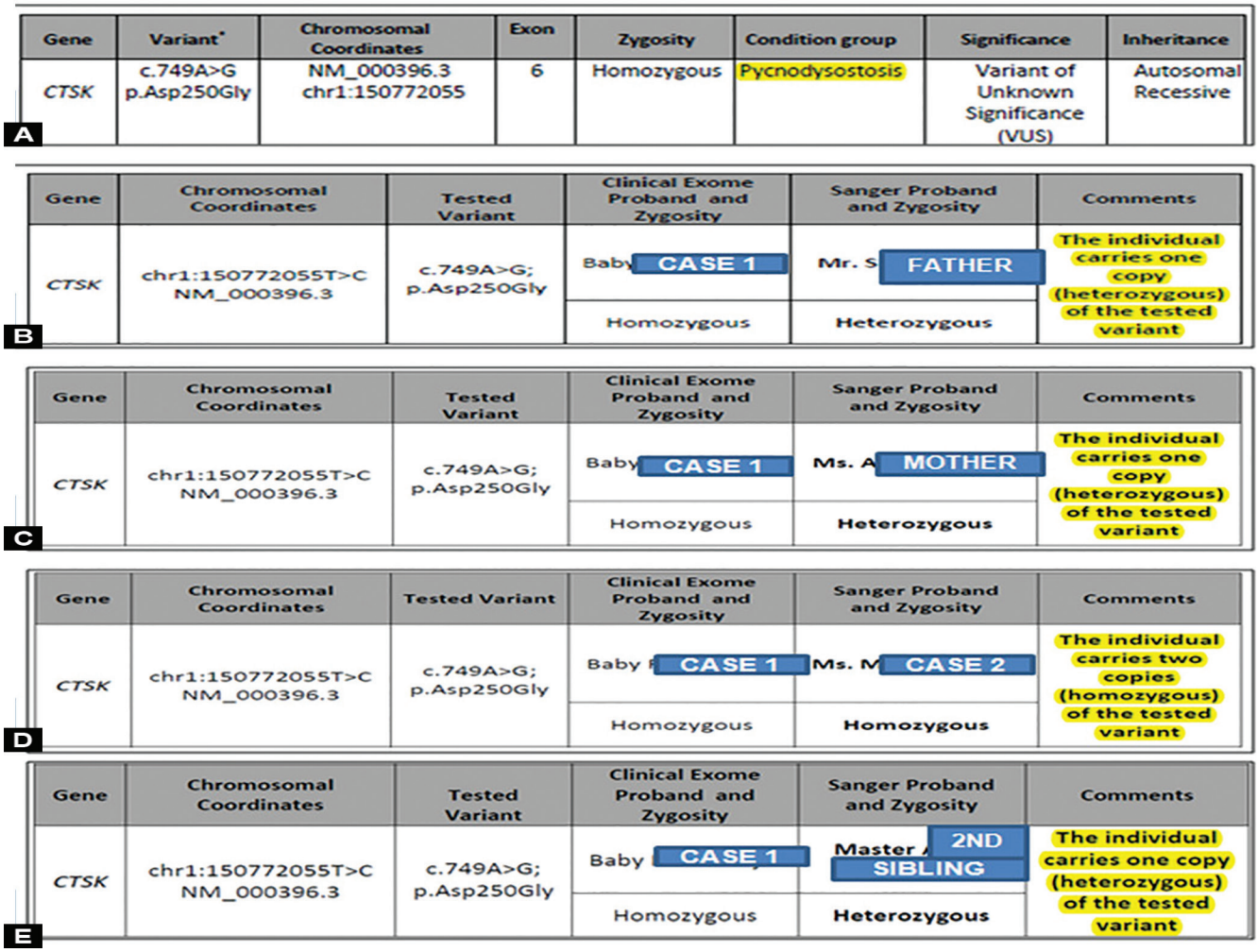


Fig. 4: PSG report



Figs 5A to E: Sanger sequencing test report, (A) Case 1; (B and C) Parents of case 1 and case 2 heterozygous for CTSK gene variant; (D) Case 2, the younger sibling; (E) The youngest sibling heterozygous for CTSK gene variant

plate (similar to twin block) with auxiliary buttons for attachment of class II elastics to posture mandible in a forward position. However, because of compromised dental support, the appliance lacked stability. Thus, the two acrylic plates were attached, and a monoblock appliance was fabricated with mandible in forwardly advanced position (Fig. 6). Pharmacological approach with mometasone furoate intranasal spray 1 puff (50 µg) twice daily in each nostril for 6 weeks was also prescribed in consultation with the otolaryngologist to regress hypertrophied adenoids. The total duration of oral appliance therapy has been 17 months, and the patient is still on periodic follow-up.

Treatment Results

Currently, at a follow-up period of 1.5 years, there has been a marked improvement in airway (Figs 7 and 8) (Table 2) with considerable reduction in initial symptoms (Video 2). The AHI score reduced from 25.3 to 14.2 with reduction in total obstructive events from 155 to 95 along with the reduction in total snoring time, indicating reduction in the severity of OSA. The treatment is still in progress.

Video 2: Real-time sleep of case 1 at follow-up (Above-mentioned video is available online on the website of www.ijsm.in.)

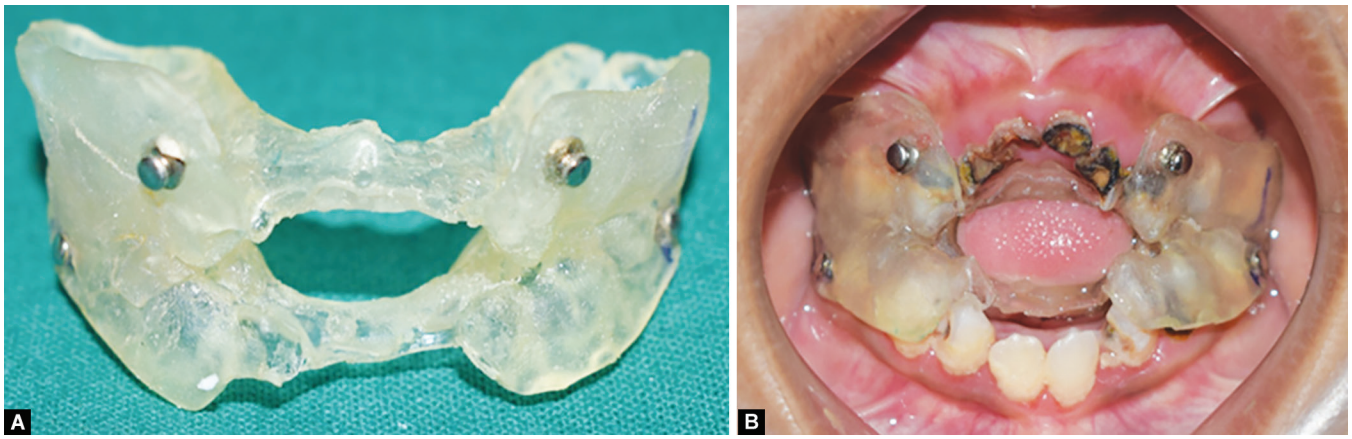
Case 2

A 5-year-2-month-old female patient, younger sibling of the first case, presented with a chief complaint of loud snoring during sleep. However, there was negative history of excessive day sleepiness and forceful awakening during sleep.

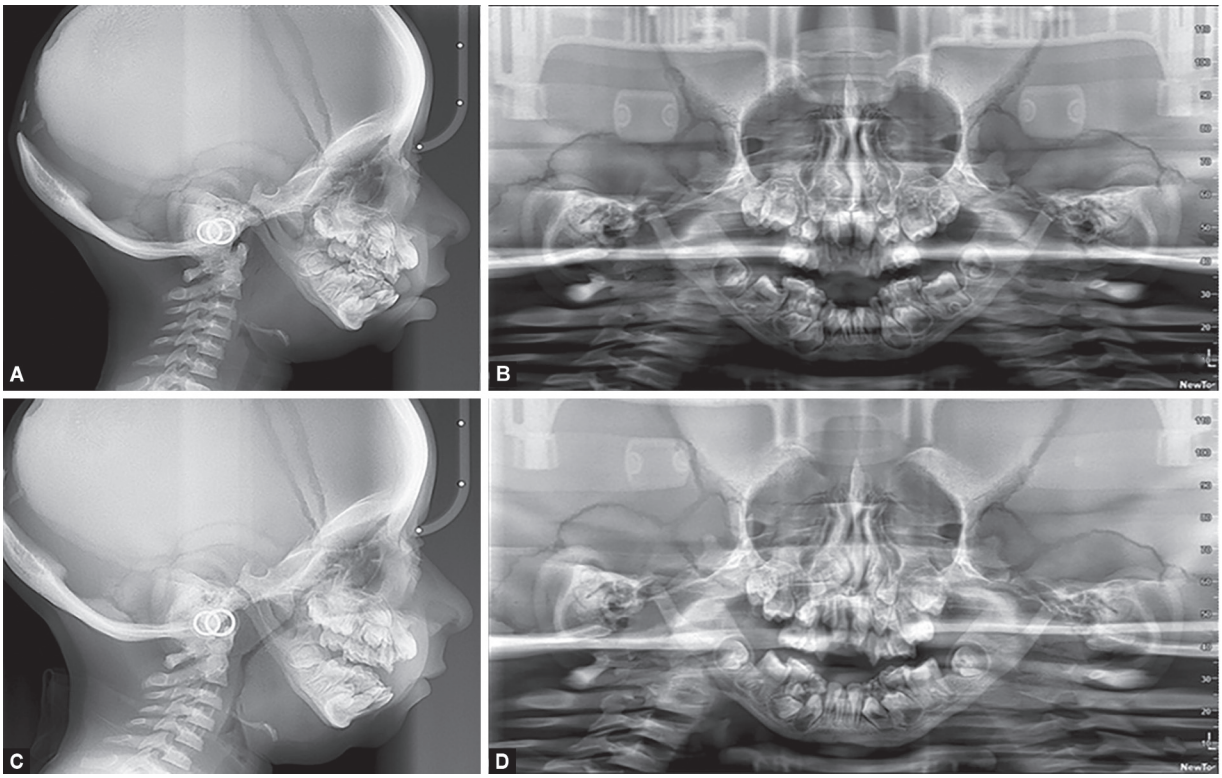
Physical examination and radiographic assessment revealed typical findings of PKND similar to case 1 (Figs 9 and 10), which was confirmed through genetic testing (Fig. 5). Cephalometric findings are presented in Table 1. Airway was compromised though less severe in comparison with case 1. No active intervention other than mometasone furoate intranasal spray (similar to the first case) was prescribed to the patient since she was too young to show compliance with an oral appliance. Currently, at a follow-up of 1.5 years, there has been an improvement in airway (Fig. 11 and Table 3) with considerable improvement in initial symptoms. The patient is still on periodic follow-up.

Discussion

The term "pycnodysostosis" has been derived from Greek words—"pycnos" (dense), "dys" (defect), and "osteon" (bone).[5] It is a rare genetic disorder that has been reported in patients ranging



Figs 6A and B: Oral appliance fabricated for mandibular advancement to enhance oropharyngeal volume



Figs 7A to D: Case 1, radiographs (A and B) Pretreatment; (C and D) At 1.5 years follow-up

from the age of 9 months up to an adult of 77 years of age.[4,10] The prevalence has been estimated to be 1–1.7 per million with equal sex predilection affecting different ethnicities with approximately 200 cases reported till date in the medical literature.[3] Most of the cases have been reported from Asian (39.3%), European (27.7%), and South American (16.6%) continents. Brazil, followed by India and Israel, is the most commonly affected country worldwide.[11]

Parental consanguinity has been recognized as a cause of this autosomal recessive disorder[12] with underlying molecular mutation in the CTSK gene which maps to chromosome 1q21. Commonly occurring mutational hotspots are Arg241 in exon 6 and Ala277 in exon 7, both being located in the mature domain of CTSK. CTSK is a cysteine protease that plays an important role in osteoclast-mediated bone resorption. Impaired enzymatic activity fails to degrade the organic matrix proteins, thereby resulting in increased volume and density of brittle bone with enhanced susceptibility to pathologic fractures.[2]

Currently, there are no specific guidelines in the literature to meet the aesthetic and functional demands of these patients. Since orthodontic and/or orthopedic treatment is entirely based on osteoclastic activity and associated bone remodeling, the efficacy as well as safety of these procedures is an issue of debate.

OSA is a common finding in children with PKND, which may occur due to obstruction at three levels, i.e., nasopharynx, oropharynx, and hypopharynx, each of which requires specific treatment.[13] These patients must be diagnosed for OSA during the early childhood, since early intervention results in improved

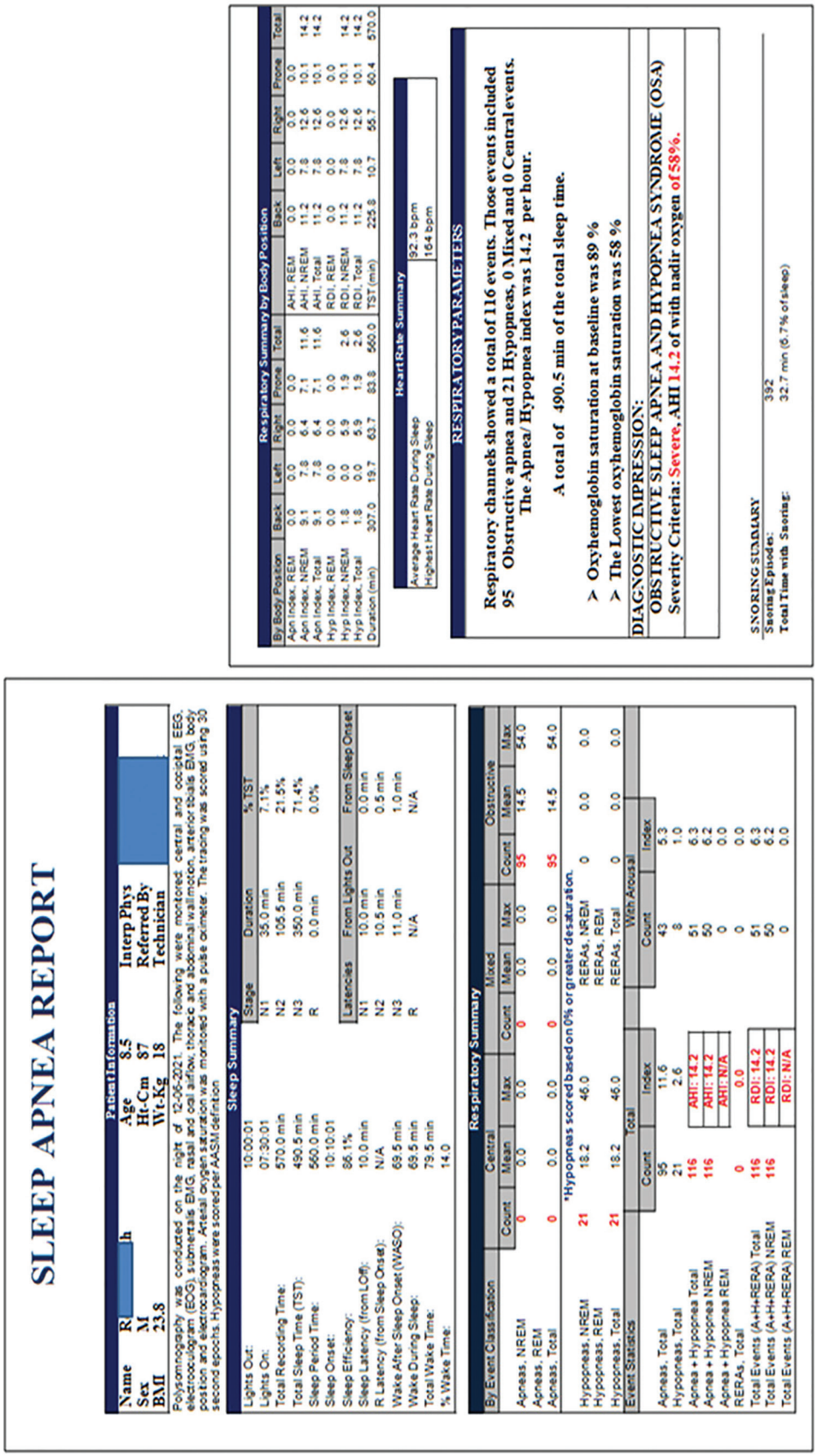
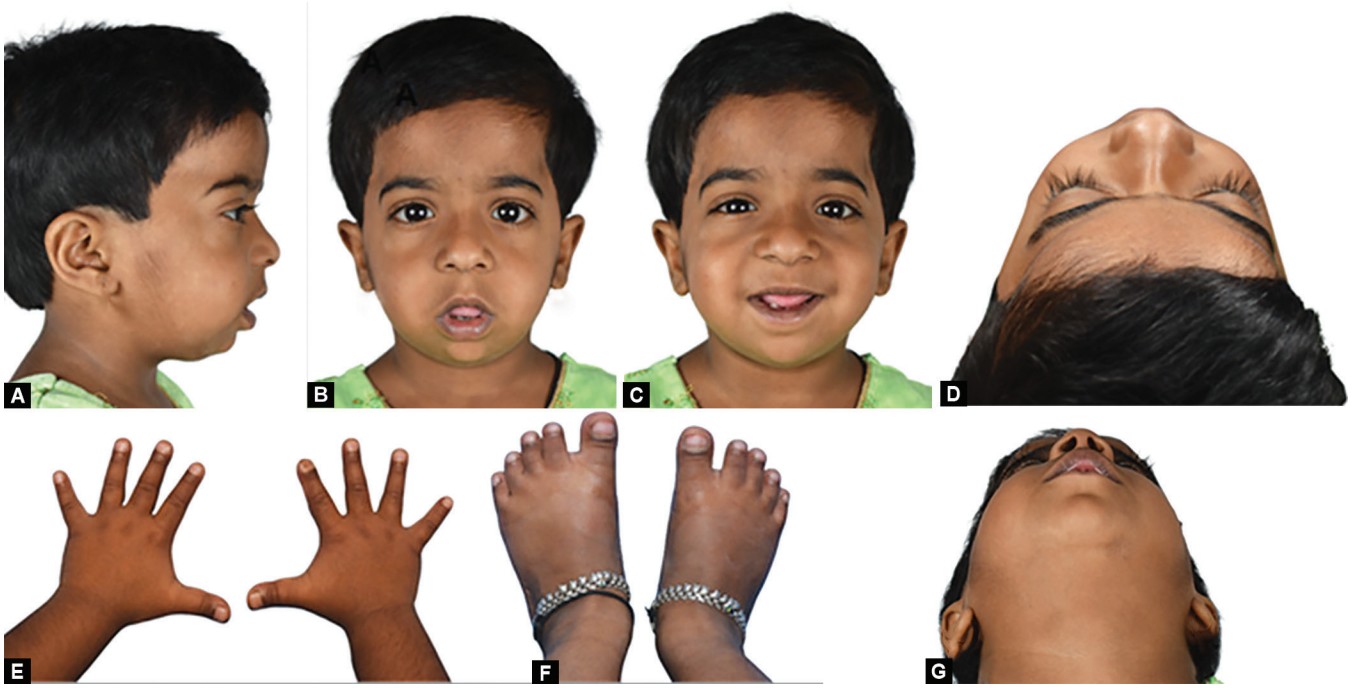


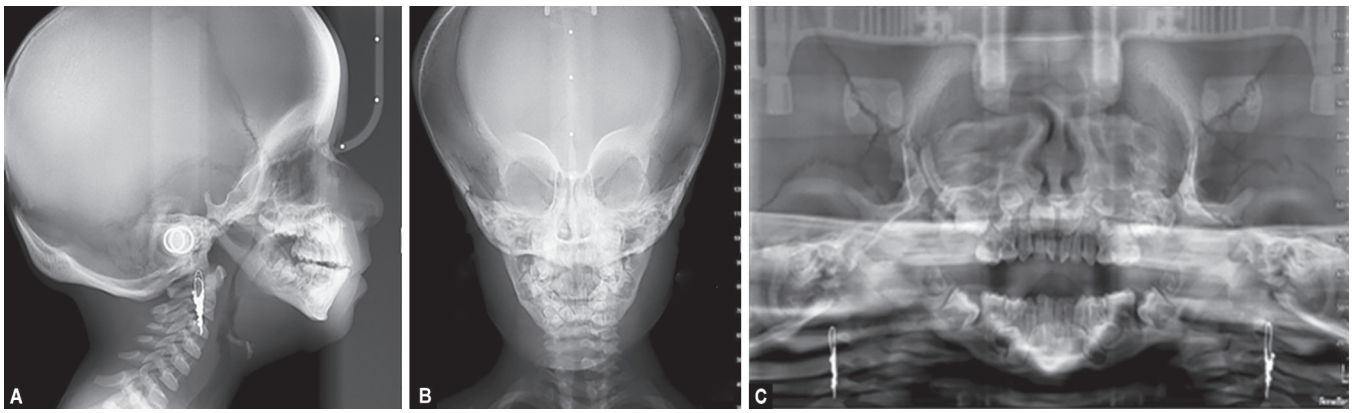
Fig. 8: PSG report at follow-up

Table 2: Airway analysis (lateral cephalogram) for case 1

Airway parameter	*Description*	*Normal value (for male)*	*Pretreatment*	*At follow up*
Nasopharyngeal airway space (NAS)	Measured from PNS to upper pharyngeal wall along palatal plane	25.9 ± 2.6 mm	5.2 mm	6.2 mm
Superior pharyngeal airway space (SAS)	A horizontal distance from the tip of the soft palate to pharyngeal wall	9.9 ± 2.8	5.5 mm	6.4 mm
Oropharyngeal airway space (PAS)	A horizontal distance from the posterior margin of the tongue to pharyngeal wall measured on Go-B line	10.1 ± 3.1	1.7 mm	2.4 mm
Hypopharyngeal airway space (HAS)	Minimum horizontal distance in the hypopharyngeal area measured from point V (intersection of tongue and epiglottis)	18.71 ± 2.6	1 mm	3.2 mm



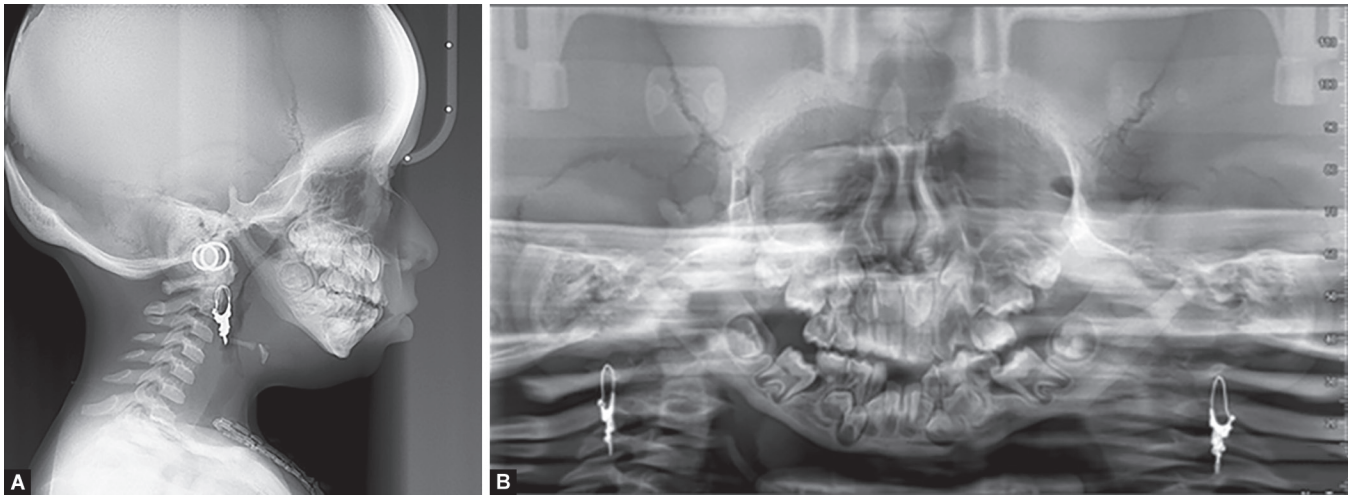
Figs 9A to G: Case 2, (A to E) Facial assessment; (F) Short stubby digits with dysmorphic nails; (G) Sandal foot deformity



Figs 10A to C: Case 2, pretreatment radiographs (A) Lateral cephalogram; (B) Posteroanterior cephalogram; (C) Orthopantomogram

ventilation, which has a positive influence on the growth and development of craniofacial complex. Muto et al.[14] suggested respiratory insufficiencies in forms of snoring or OSA as a common and underappreciated feature of PKND due to retrognathia leading to glossoptosis and consequently narrowing of the airway space. Similar findings have been reported by various other authors.[15,16]

OSA resulting from nasal obstruction may be due to nasal polyp, deviated nasal septum, or hypertrophied inferior turbinates.[13]



Figs 11A and B: Case 2, radiographs at 1.5 years-follow-up (A) Lateral cephalogram; (B) Orthopantomogram

Table 3: Airway analysis (lateral cephalogram) for case 2

Airway parameter	*Description*	*Normal value (for female)*	*Pretreatment*	*At follow up*
Nasopharyngeal airway space (NAS)	Measured from PNS to upper pharyngeal wall along palatal plane	24.1 ± 2.3 mm	6.8 mm	7.2 mm
Superior pharyngeal airway space (SAS)	A horizontal distance from the tip of the soft palate to pharyngeal wall	9.9 ± 2.4 mm	4.5 mm	5.4 mm
Oropharyngeal airway space (PAS)	A horizontal distance from the posterior margin of the tongue to pharyngeal wall measured on Go-B line	10.0 ± 2.8 mm	2.8 mm	3.9 mm
Hypopharyngeal airway space (HAS)	Minimum horizontal distance in the hypopharyngeal area measured from point V (intersection of tongue and epiglottis)	16.5 ± 3.1 mm	12.3 mm	12.5 mm

Adenoid hypertrophy, being relatively more common in children, can be managed with adenoidectomy or conservatively with a pharmacological approach, which was in both of our cases. Oropharyngeal obstruction resulting from tonsillar hypertrophy can be managed with tonsillectomy,[13] while the problem of long soft palate can be catered with uvulopalatopharyngoplasty,[17] laser-assisted uvulopalatoplasty,[18] or radiofrequency tissue ablation.[19]

Based on the severity of skeletal malocclusion, respiratory insufficiency due to hypoplastic maxilla and mandible can be managed with DO. However, due to frequently associated risk factors, such as pathologic fractures and maxillary osteomyelitis,[20] oral appliance therapy, which advances the mandible and tongue thereby increasing the oropharyngeal volume, was adopted in our first case. Both the patients are on periodic follow-up of every 3 months.

Besides the interceptive approach, special emphasis must be given to preventive dentistry since most of the PKND children present with poor oral hygiene, extensive dental caries, and generalized gingivitis or periodontitis. Periodic dental visits for topical fluoride application and enforcement of good oral hygiene are extremely important.

Conclusion

Respiratory needs are the primary determinants of an individual since the first day of life, which has a great influence on craniofacial growth and development as well as systemic wellbeing of an individual. Although PKND is a rare genetic disorder, many case reports are available in the literature highlighting the different aspects of the medical and dental condition. Although OSA is a frequently encountered feature among patients with PKND, the same has not been highlighted and addressed in the literature. Altered bone physiology among these patients along with poor oral hygiene and compromised dental condition poses great challenge to an orthodontist. A multidisciplinary approach with emphasis on preventive care is advocated, and a long-term follow-up is required for these patients.

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