International Journal of Contemporary Pediatrics
Tyagi R et al. Int J Contemp Pediatr. 2024 Oct;11(10):1453-1458
http://www.ijpediatrics.com
pISSN 2349-3283 | eISSN 2349-3291

DOI: https://dx.doi.org/10.18203/2349-3291.ijcp20242663

Case Report

Overhauling dental implications in a child with rare craniofrontonasal syndrome: a case report

Rishi Tyagi, Amit Khatri, Namita Kalra, Deepak Khandelwal, Neetu Garg*, Padma Yangdol, Shruti Kulkarni

Department of Paedodontics and Preventive Dentistry, University College of Medical Sciences and GTBH, Delhi, India

Received: 10 August 2024
Accepted: 31 August 2024

***Correspondence:**
Dr. Neetu Garg,
E-mail: neetugarg11@gmail.com

ABSTRACT

Craniofrontonasal syndrome is an extremely rare X-linked dominant genetic disorder characterized by features such as hypertelorism, craniosynostosis, ocular anomalies, a bifid nasal tip, and longitudinal ridging with splitting of the nails. Heterozygous females are more severely affected, presenting frontonasal dysplasia and coronal craniosynostosis (fusion of the coronal sutures), while males typically only exhibit hypertelorism. This case report describes the dental management of a 9-year-old female with craniofrontonasal syndrome who was referred to the department of paediatric and preventive dentistry for pain in the lower right and left back tooth region. The patient exhibited a clinical spectrum including microcephaly, short neck, axillary pterygium, clinodactyly of the toes, longitudinal ridging with split nails, pectus excavatum, and underdeveloped female genitalia. Extraoral examination revealed hypertelorism, flat nasal bridge, low-set ears, strabismus, antimongoloid slant, and an indistinct philtrum. Intraoral examination showed a high palatal vault, crowding of the upper and lower arches during the mixed dentition period, multiple dental caries, and poor oral hygiene. An orthopantomogram confirmed delayed dental development. Dental treatment was carried out on a dental chair system using adequate behaviour management techniques with short appointments, keeping in mind the reduced cooperative ability of the child. The importance of this report stems from the limited dental literature available on the syndrome. Preventive measures along with home care instructions were emphasized to support professional care.

Keywords: Frontonasal dysplasia, Craniosynostosis, Hypertelorism, Tooth crowding, Dental caries

INTRODUCTION

Craniofrontonasal syndrome (CFNS, OMIM 304110) is a rare yet distinguishable disorder. It has a birth prevalence of 1 in 120,000, and it is characterised by features such as unilateral or bilateral coronal synostosis, hypertelorism, a grooved nose, "frizzy" hair, and abnormalities of the shoulder girdle, hands, and feet.[1] Cohen, the same researcher who came up with the term craniofrontonasal dysplasia (CFND), identified CFNS as a subpopulation of frontonasal dysplasia patients.[2] An earlier report of the condition was made by Reich et al and Slover and Sujansky made their observation at the same time as Cohen.[2-4] Other authors, including Cohen, Young, Grutzner and Gorlin, have written reviews of the craniofrontonasal syndrome.[5-7]

Craniofacial characteristics include brachycephaly, coronal synostosis, craniofacial asymmetry, frontal bossing, dry curly or frizzy hair, coronal ocular hypertelorism, broad nasal bridge, bifid nose, pterygium colli, and longitudinally grooved nails. Additional findings include hyperextensible joints, mild syndactyly of the soft tissues, clinodactyly of the fifth fingers, and scoliosis. Malocclusion, ear anomalies, broad toes and hallucal duplication, minor vertebral anomalies, unusual

dermatoglyphics, developmental delay, short clavicles, down-sloping shoulders, pectus excavatum, and unilateral breast hypoplasia are all characteristics that have been observed in affected individuals.[8,9]

Pedigrees that show vertical transmission have been recorded, even though the vast majority of cases are sporadic and occur in females, who are typically more severely affected than the few males who have been reported to have the condition.[2,10] Although male-to-male transmission has not been observed in any published studies to this day, Reich et al did note 2 instances of it in an abstract of a publication under review.[11] X-linked dominant inheritance, metabolic interference, and a semi-lethal mutation with similarities to the T-locus in mouse are just some of hypotheses that have been proposed.[12-14] The demonstration of mutations in EFNB1 gene in 2004, which had previously been mapped to Xq13.1 region, provided evidence that confirmed these findings.[15]

The EFNB1 gene is responsible for encoding the transmembrane protein known as ephrin-B1, which functions both as a ligand for Eph receptors and as a receptor for nearby cells that express ephrin-B1. This Eph/ephrin bidirectional signalling system directs cell migration in the frontonasal neural crest, morphogenesis of the palatal shelf, and formation of future coronal sutures.[15] Since the EFNB1 gene is found on the X chromosome, it is susceptible to X-inactivation in females, which happens at random. Random X-inactivation causes a mosaic distribution of the cells carrying mutant and wild-type EFNB1 genes in heterozygous females.[16] Studies that have been reported in the past suggested that the severity of the condition in heterozygous females is associated with a patchy tissue distribution of EFNB1 functional and nonfunctional cells.[15] These studies conducted on animals. Previously described severe phenotype in females may have its origins in a malfunctioning Eph/ephrin signalling system and inhibited communication in boundaries between different tissue patches. According to Wieland et al, Vasudevan et al and Twigg et al this process was referred to as "cellular interference."[16] In hemizygous males, all cells carry mutant EFNB1 gene, there is no generation of a patchy tissue pattern, and there is no formation of disrupted tissue boundaries.[15] Additionally, it is possible that functional redundancy of other ephrins improves milder phenotype. In addition to this, demonstration of more severe phenotype in constitutionally mosaic males lends support to these findings.[17]

It is clear that the vast majority of those affected are females, while males make up a smaller percentage and are typically only mildly afflicted.[18] Manifestations in males are confined to the craniofacial region and consist of ocular hypertelorism, a cleft lip and/or palate in several cases, and malocclusion (cross-bite or posterior open-bite), among other craniofacial abnormalities.[19] Males who are severely affected by the condition are extremely rare. The patient who had been shown by David et al was a male through the correspondence that David et al had with MMC.[20] Natarajan et al reported that there were two brothers who were severely affected.[21]

Craniofrontonasal syndrome can be differentiated from frontonasal dysplasia by clinical examination. The presumed case of frontonasal dysplasia and Klippel-Feil anomaly that was observed in a female patient and reported by Fragoso et al most likely involved CFNS.[22] The patient who was reported to have craniosynostosis and Poland anomaly by Reardon et al is comparable to the patient who was reported by Webster and Deming, and the patient most likely had CFNS, as was suggested by Reardon et al.[23,24] The patient who had CFND, Poland anomaly, and polythelia was described by Erdogan et al and these authors suggested that the patient had a newly recognised syndrome. However, the patient most likely had CFNS instead of this newly recognised syndrome.[25]

CASE REPORT

A 9-year-old female reported to the department of pedodontics and preventive dentistry with the chief complaint of pain in the lower right and left back tooth region. History of present illness was recorded which stated that the patient was apparently alright 10 days back after which she started experiencing pain in the lower right and left back tooth region. Pain was spontaneous, gradual in onset, dull in nature, aggravated by biting, and did not resolve on its own. No history of associated fever or compromised functioning due to pain was recorded.

The medical history of the patient revealed that she had been diagnosed with craniofrontonasal syndrome. Antenatal history confirmed spontaneous conception, folic acid, calcium, and iron supplements were taken by the mother during gestation and no history of tuberculosis, diabetes, blood pressure, or thyroid disorders was observed in the mother. However, a positive history of decreased fetal movements and breech at 9 months was observed in the single scan done. A full-term delivery by caesarean section was performed and the child cried immediately after birth. Although the body weight at birth was not recorded in the patient's medical history, there is no record of NICU / PICU admission. Head circumference showed-3SD indicating microcephaly. The gestational history of the mother showed a healthy male child during first delivery followed by an intrauterine death delivered at term followed by the present child.

General examination of the child exhibited a clinical spectrum of microcephaly, short neck, sloping shoulders, axillary pterygium, clinodactyly of toes, split nails, pectus excavatum, and poorly developed female genitalia (Figure 1 and 2). Radiographic evaluation revealed craniosynostosis with microcephaly and few prominent convolutional markings, bilateral sprengel deformity, pectus excavatum, scoliosis, and narrow thoracic cavity (Figure 3). Optimum vital signs were recorded along with

normal reflexes. Intellectual disability was present. Upon extraoral examination, hypertelorism, flat nasal bridge, low set ears, strabismus, and antimongoloid slant were observed along with indistinct philtrum (Figure 1). Intraoral examination revealed high palatal vault, mild crowding of upper and lower arches in mixed dentition period, ectopically erupted 62, and dental caries with respect to 54, 55, 65, 75, 85, 36, and 46. Pit caries were observed in 74, and 84 (Figure 4). Intra-oral periapical radiograph of 75 and 85 demonstrated caries encroaching pulp along with involvement of furcation area and root resorption (Figure 4). OPG confirms delayed dental age (Figure 5).

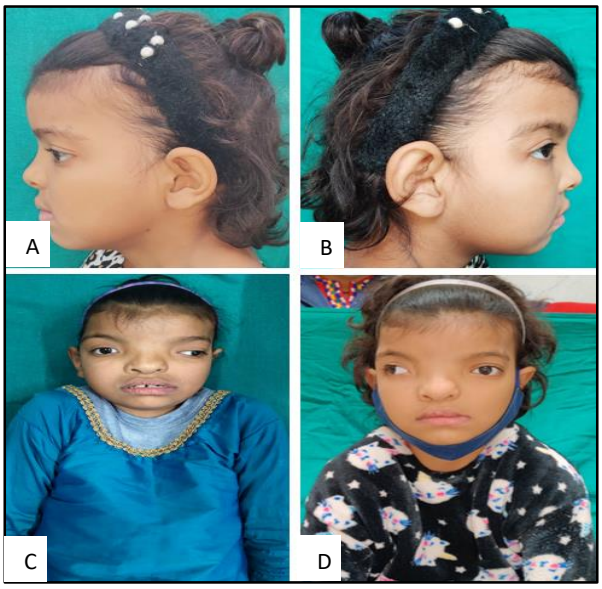

Figure 1 (A-D): Left lateral view, right lateral view and frontal view showing hypertelorism, flat nasal bridge, cleft on tip of nose, low set ears, strabismus, antimongoloid slant, short neck.

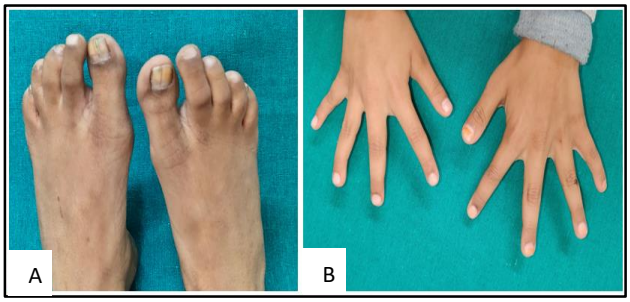

Figure 2 (A and B): Split nails due to longitudinal ridging on B/L toes. Clinodactyly was more pronounced in toe than hands.

The dental management of the patient was first discussed with the parent in a language best understood by the latter. Early morning and short (approximately 15-20 minutes) appointments were scheduled owing to reduced cooperative ability and a single pediatric dentist carried out all procedures for the patient on a dental chair system. Non-pharmacological behavior management techniques including non-verbal communication, modeling on a toy, and were employed during the patient's dental treatment. Extraction of 75 and 85 under local anesthesia 2% lidocaine with 1:100000 adrenaline was carried out. Behaviour rating was done at FR (-) ve (Frankl's behavior rating scale). A papoose board was arranged for, however was not needed during extraction procedure. Caries removal was done using a contrangle handpiece and small round bur at a plodding speed for the patient's comfort followed by glass ionomer cement (GIC) (GC, Tokyo, Japan) restoration for 55, 54, 65, and 46. Pit-fissure sealant (GC, Fuji® VII, Sydney, Australia) was applied in 16, 26, and 36 under controlled isolation. Other pits were also restored with GIC. Casein phosphopeptide-amorphous calcium phosphate-based toothpaste (GC Tooth Mousse, GC Dental, India) was advised to parent for home application (Figure 6). Informed consent obtained from patient's parent for publication.

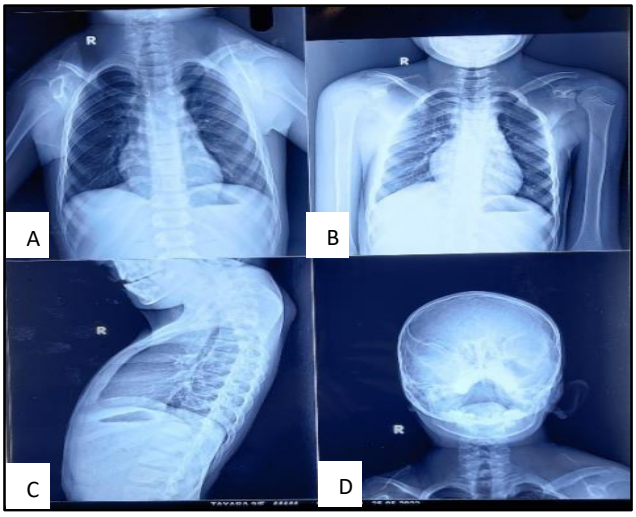

Figure 3 (A-D): Radiograph reveals microcephaly, shoulder pterygium, pectus excavatum, scoliosis, and narrow thoracic cavity.

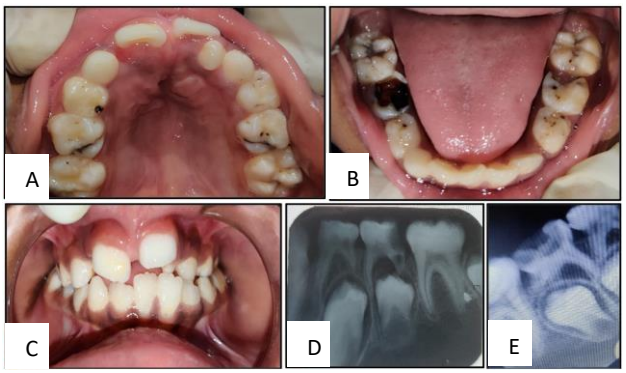

Figure 4 (A-E): Pre-op maxillary occlusal view-caries wrt 55, 65, pit caries wrt 54. pre-op mandibular occlusal view-caries wrt 75, 85, 36, 46, pit caries wrt 74, 84, ectopically placed 62; frontal view, intraoral periapical view wrt 75 and 85.

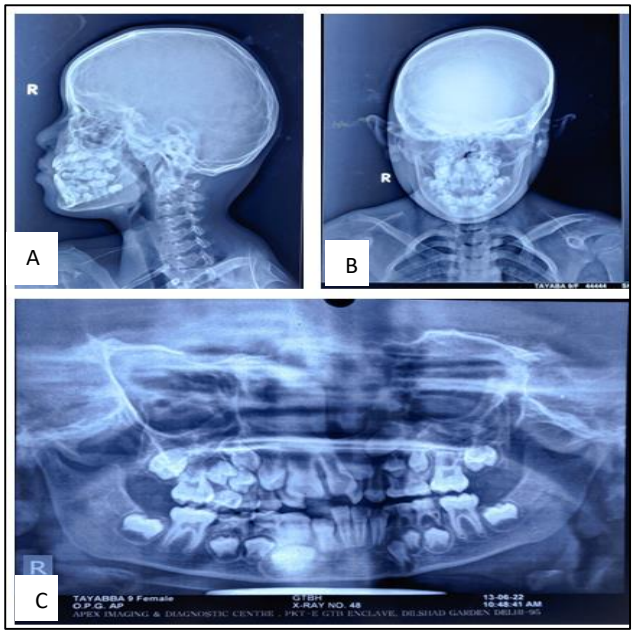

Figure 5 (A-C): Skull lateral view, skull AP view and OPG revealing malaligned teeth, dental caries, and delayed dental age.

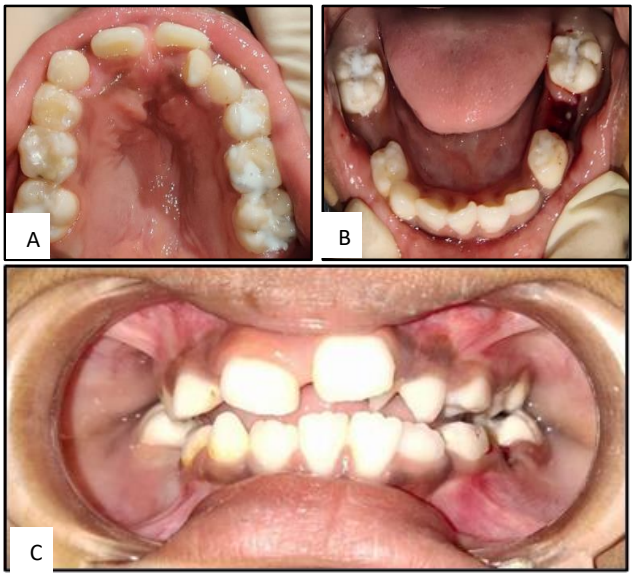

Figure 6 (A-C): Post operative maxillary and mandibular occlusal view, post operative frontal view. Treatment rendered: Extractions 75, 85, Pit fissure sealant, GIC restorations.

DISCUSSION

CFND is an extremely uncommon congenital craniofacial syndrome that is caused by a mutation in the EFNB1 gene. This mutation causes bilateral or unilateral single-suture synostosis (SSS) of the coronal suture, which can affect either side of the face.[2] Patients who have CFND always present hypertelorism (with or without vertical orbital dystopia) and strabismus, which is frequently accompanied by a broad and short nose, as well as a variety of facial features, including a low hairline, a widow's peak, an epicanthic fold, eyelid ptosis, low set ears, a bifid nasal tip, and a high arched palate. In addition, many people who have CFND also have grooves running the length of their nails.[7] Patients suffering from CFND are guaranteed to have SSS, so they mostly possess persistently high intracranial pressure (ICP) as well, which may cause neurocognitive developmental delay. This research was conducted by Renier and colleagues.[26]

Children who have CFNS do not all have the same genetic changes. Because of X inactivation, each individual who has CFNS is one of a kind.[27] Although this syndrome is linked to the X chromosome, EFNB1 heterozygous females are severely affected by it, whereas hemizygous loss of EFNB1 gene function in males appears to be only mildly affected. This is due to a phenomenon that is commonly referred to as "cellular interference," the underlying cause of which is currently unknown.[2] EFNB1 heterozygous females are severely affected by it. The treatment is always surgery, and it is tailored to the particular phenotypic presentation of each individual patient. Between the ages of 6 and 9 months is the window of opportunity for craniosynostosis surgery to be performed successfully. Orbital hypertelorism is not treated until the patient is between the ages of 5 and 8 years old after all permanent teeth have erupted. When the patient is 18 years old and their skeleton has fully matured, only then can they receive treatment for a bifid nose tip.[28] In patients who present late with CFND, it is of the utmost importance to recognise any signs of increased ICP in order to personalise the craniofacial procedure in a way that moves the upper region of the face forward and makes room for the brain.[29]

Genetic counselling or prenatal screening might be recommended in cases where there is reason to suspect that one or both of the parents might be carriers of a genetic condition. A prenatal screening with ultrasound can be attempted by carefully looking for hypertelorism or a bifid nasal tip. This search requires a lot of patience.[28] It would be instructive to determine the levels of the EFNB1 mutation in the father's sperm in cases where the paternal origin has been established. On the other hand, if we know that a mutation is present in levels that are less than 50% in at least one tissue, then the most likely scenario involves their arising post-zygotically. This is because postzygotic mutations are more stable than mutations that occur during zygotic development.[1] Further, use of community or online resources, like parent-to-parent or counsellor-to-parent discussions should be motivated. Home nursing may also be advised if seen fit. Dental home care should include regular oral hygiene practices, quarterly follow up with a pediatric dentist, preventive therapy to avoid any invasive treatments, and orthodontic consultation if the patient qualifies. Surgical interventions may include correction of hypertelorism, fronto-orbital remodelling (FOR), and posterior vault expansion (PVE).

Maintaining the visual axis, detecting and treating increased ICP, and other clinical concerns are very important.[30] If the individual also has a cleft, the most pressing concerns are related to feeding and airway obstruction. Surgically, patients with CFND are an exercise in preventing raised ICP and troublesome head shape. This is done while waiting for dental development, which will enable surgery to correct the hypertelorism. Patients who have ophthalmological changes or turricephalic head shapes that indicate the need for vault expansion are managed through our CFA (craniofacial assessment) surveillance programme. Patients diagnosed with unicoronal synostosis frequently undergo FOR, if possible, only on the affected side, before the age of 18 months, and then wait until the maxillary canine has erupted before undergoing additional surgery if the family so desires. Patients with bicoronal keratoconus can choose from one of three different treatment trajectories: early PVE with springs, FOR under 18 months of age, or delaying all surgery until combined hypertelorism correction. Early PVE with springs has a secondary effect that improves the bossing of the upper forehead. If it is at all possible to postpone surgery on the forehead in favour of a single approach, the unoperated approach has a lower risk of complications. The formal surgery, like that of other groups of craniosynostoses, is based on the principles of facial bipartition and box osteotomies, with the latter being chosen for multidimensional hypertelorism. In conjunction with this operation, a dorsal onlay bone graft rhinoplasty as well as extensive soft tissue procedures are carried out on the patient. There may be a need for later refinements in the structures of the nasal tip and canthal region.[31]

CONCLUSION

In conclusion, the presented case of CFNS requires multidisciplinary management approach from birth till adulthood. It is important to understand the genotype-phenotype relationship in every case of CFNS. A pedodontist, oral surgeon, and orthodontist would be an integral part of the overall management team. Communication and timely management can provide excellent prognosis in such cases.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. Twigg SR, Matsumoto K, Kidd AM, Anne G, Indira BT, Richard BF, et al. The origin of EFNB1 mutations in craniofrontonasal syndrome: frequent somatic mosaicism and explanation of the paucity of carrier males. Am J Hum Genet 2006;78(6):999-1010.
2. Cohen MM Jr. Craniofrontonasal dysplasia. Birth Defects. 1979;15(5B):85-9.
3. Reich EW, Cox RP, McCarthy JG. A new heritable syndrome with frontonasal dysplasia and associated extracranial anomalies. (Abstract). In: Fifth International Conference on Birth Defects, Littlefield JW (ed). Excerpta Medica, Amsterdam. 1977.
4. Slover R, Sujansky E. Frontonasal dysplasia with coronal craniosynostosis in three sibs. Birth Defects. 1979;15(5B):75-83.
5. Cohen MM Jr. Craniosynostosis: Diagnosis, Evaluation, and Management. Raven Press, New York. 1986;249-320.
6. Young ID. Craniofrontonasal dysplasia. J Med Genet. 1987;24(4):193-6.
7. Grutzner E, Gorlin RJ. Craniofrontonasal dysplasia. Phenotypic expression in females and males and genetic considerations. Oral Surg Oral Med Oral Pathol. 1988;65(4):436-44.
8. Hunter AGW, Rudd NL. Craniosynostosis. II. Coronalsynostosis: Its familial characteristics and associated clinical findings in 109 patients lacking bilateral polysyndactyly or syndactyly. Teratology. 1977;15(3):301-9.
9. Kere J, Ritvanen A, Marttinen E, Kaitila I. Craniofrontal dysostosis: Variable expression in a three-generation family. Clin Genet. 1990;38(6):441-6.
10. Sax CM, Flannery DB. Craniofrontonasal dysplasia: A semilethal mutation with similarities to the mouse T-locus. Am J Hum Genet Suppl. 1984;29(6):73S.
11. Pagon RA, Beckwith JB, Ward BH. Calvarial hyperostosis: A benign X-linked recessive disorder. Clin Genet. 1986;29(1):73-8.
12. Rollnick B, Day D, Tissot R, Kaye C. A pedigree: Possible evidence for the metabolic interference hypothesis. Am J Hum Genet. 1981;33(5):823-6.
13. Pillat A. Wiener Ophthalmologische Gesellschaft. Epithelsch¨adigung der Hornhaut bei angeborener Trigeminushypoplasie. Wien Klin Wochenschr. 1949;61:605.
14. Reed T, Escobar LF. Dermatoglyphics in the Antley-Bixler syndrome. Dysmorphol Clin Genet. 1988;2(1):6-8.
15. Twigg SR, Kan R, Babbs C, Bochukova EG, Robertson SP, Wall SA, et al. Mutations of ephrin-B1 (EFNB1), a marker of tissue boundary formation, cause craniofrontonasal syndrome. Proc Natl Acad Sci USA. 2004;101(23):8652-7.
16. Wieland I, Reardon W, Jakubiczka S, Franco B, Kress W, Vincent-Delorme C, et al. Twenty-six novel EFNB1 mutations in familial and sporadic craniofrontonasal syndrome (CFNS). Hum Mutat. 2005;26(2):113-8.
17. Twigg SR, Babbs C, van den Elzen ME, Goriely A, Taylor S, McGowan SJ, et al. Cellular interference in craniofrontonasal syndrome: males mosaic for mutations in the X-linked EFNB1 gene are more severely affected than true hemizygotes. Hum Mol Genet. 2013;22(8):1654-62.

18. Gorlin RJ. Microtia, absent patellae, short stature, micrognathia syndrome. J Med Genet. 1992;29(7):516-7.
19. Porteus MEM, Cross I, Burn J. VACTERL with hydrocephalus: One end of the Fanconi anemia spectrum of anomalies? Am J Med Genet. 1992;43(6):1032-4.
20. David JD, Poswillo DE, Simpson DA. The Craniosynostoses: Causes, Natural History, and Management. Springer-Verlag, New York, 1982.
21. Natarajan U, Baraitser M, Nicolaides K, Gosden C. Craniofrontonasal dysplasia in two male sibs. Clin Dysmorphol. 1993;2(4):360-64.
22. Fragoso R, Cid-García A, Hernández A, Nazará Z, Cantú JM. Frontonasal dysplasia in the Klippel-Feil syndrome: A new assorted malformation. Clin Genet 1982;22(5):270-3.
23. Reardon W, Temple IK, Jones B, Baraitser M. Frontonasal dysplasia or craniofrontonasal dysplasia and the Poland anomaly? Clin Genet 1990;38(3):233-6.
24. Webster JP, Deming EG. The surgical treatment of bifid nose. Plast Reconstr Surg. 1950;6(1):1-37.
25. Erdogan B, Aköz T, Görgü M, Kutlay R, Dağ F, et al. Possibly new multiple congenital anomaly syndrome: Craniofronto-nasal dysplasia with Poland anomaly. Am J Med Genet. 1996;65(3):222-5.
26. Renier D, Sainte-Rose C, Marchac D, Hirsch JF. Intracranial pressure in craniostenosis. J Neurosurg. 1982;57(3):370-7.
27. Dupré S, Care H, Gordon Z, Wall SA, Wilkie AOM, Johnson D, et al. Implications for the Multi-Disciplinary Management of Children with Craniofrontonasal Syndrome. J Craniofac Surg. 2020;31(4):e362-8.
28. Biswas B, Mondal M, Roy A, Das R. Craniofrontonasal dysplasia syndrome: A rare case. Med J DY Patil Univ 2015;8(5):672-4.
29. Raposo-Amaral CE, Resende G, Denadai R, Ghizoni E, Raposo-Amaral CA. Craniofrontonasal dysplasia: hypertelorism correction in late presenting patients. Childs Nerv Syst. 2021;37(9):2873-8.
30. Tay T, Martin F, Rowe N, Johnson K, Poole M, Tan K, et al. Prevalence and causes of visual impairment in craniosynostotic syndromes. Clin Exp Ophthalmol. 2006;34(5):434-40.
31. O'Hara J, Ruggiero F, Wilson L, James G, Glass G, Jeelani O, et al. Syndromic Craniosynostosis: Complexities of Clinical Care. Mol Syndromol. 2019;10(1-2):83-97.

Cite this article as: Tyagi R, Khatri A, Kalra N, Khandelwal D, Garg N, Yangdol P, et al. Overhauling dental implications in a child with rare craniofrontonasal syndrome: a case report. Int J Contemp Pediatr 2024;11:1453-8.