Case Report

A Rare Indian Case of GAPO Syndrome with Dental and Other Findings

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Abstract

GAPO syndrome is an entity with multiple congenital anomalies syndrome involving connective tissue characterized by growth retardation, alopecia, pseudoanodontia, and optic atrophy (GAPO) syndrome. To date, only approximately 45 cases of this extremely rare syndrome have been reported. We present thee case of a 9-year Indian male patient with GAPO syndrome in association with craniosynostosis along with degenerating optic nerve, short stature, partial anodontia, abnormally thick maxillary buccal and lingual frenum, born first to parents showing consanguineous marriage; however, the intelligence quotient of the child was good.

Keywords: Anodontia, buccal, frenum, GAPO syndrome, lingual

Introduction

Rare diseases (RD) are defined as diseases affecting no more than 1:2000 individuals in the European Union and no more than approximately 1:1250 individuals in the USA.[1,2] Among numerous RD, GAPO Syndrome is one such entity that has derived its name from acronymic designation for a complex of growth retardation, alopecia, pseudoanodontia, and optic atrophy (GAPO) syndrome.[3] The syndrome was first reported by Andersen and Pindborg in 1947, and based on four similar cases reported from Brazil and Israel, as well as one from the U.S., along with the symptoms of optic atrophy, Tipton and Gorlin in 1984 established the term GAPO syndrome (OMIM230740) as a distinct entity.[3] We present the case of a 9-year Indian male patient with GAPO syndrome in association with craniosynostosis along with degenerating optic nerve, short stature, and born second to parents showing consanguineous marriage; however, the intelligence quotient of the child was good.

Epidemiology

GAPO syndrome is having an autosomal recessive mode of inheritance for genetic transmission through generations, and since its first description from 1947, only 45 patients are reported approximately till now worldwide in the literature.[4] The differential diagnosis for GAPO syndrome includes Hutchinson-Gilford (Progeria), Werner syndrome (Pangeria), Acrogeria (Gottron type), Rothmund–Thomson syndrome, cartilage-hair hypoplasia, and the tricho-dento-osseous syndrome and Ellis–van Creveld syndrome.[5,6] The life expectancy of patients with GAPO syndrome is reduced, and it is observed that they usually die in their third or fourth decade of life due to generalized interstitial fibrosis and atherosclerosis.[7]

Etiology

A basic underlying molecular defect in GAPO syndrome is yet to be defined clearly as the candidate gene is yet unclear; however, it is thought to be due to homozygous nonsense or splicing mutations in the anthrax toxin receptor 1 (ANTXR1) gene previously known as tumor endothelial marker 8 (TEM8), resulting in truncated isoform of the ANTXR1 protein.[7,8]

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Clinical Features of Case

A 9-year-old male child reported to the department of pediatric and preventive dentistry, after referral from pediatrician for oral and dental abnormalities. The child was diagnosed with GAPO syndrome from the 3rd year of his life, and parents were aware of the condition. On asking about the relationship between parents, father revealed that they had consanguineous marriage in close relation. The child was born as a first child to them. Mother did not face any prenatal, antenatal, or postnatal complications during the course of pregnancy, and her delivery was normal. The child looked normal till 2 years of life, and then, parents observed diminished increase in height. Parents further observed no eruption of teeth and gradual reduction in eye sight of child. They investigated the child in detailed about the present condition through genetic mapping and other sophisticated investigations and was diagnosed as GAPO syndrome.

The clinical examination of the patient revealed having a peculiar geriatric look. Child was showing a short stature with a height of 110 cm and weight of 19 kg, which was less than normal parameter due to postnatal growth retardation. Examination of the hand and leg joints revealed hyperextensible joints, and osseous anomalies like short length of long bones. Fingers of hands and legs were short, and nails were showing koilonychia. Examination of face and head–neck region revealed typical facies of GAPO syndrome with high and bossing forehead, prominent scalp veins, hypertelorism, puffy eyelids, and midfacial hypoplasia. Scalp hairs, eyebrows, and eyelashes were sparse showing partial alopecia [Figure 1]. Ears were low set, and premature aging appearance was evident mainly due to redundant hyperelastic skin with unusual wrinkles [Figure 2]. Nasal bridge was depressed with anteverted wide nostrils and long philtrum. The upper lip was normal; however, the lower lip was thick and everted. Ocular manifestations revealed progressive optic atrophy, ptosis, glaucoma, and strabismus [Figure 1]. Parents also reported gradual loss of hearing acuity and deafness. Contrary to the findings of mild intellectual deficits mentioned in previous cases, this patient was having a good intellectual quotient that was evident from his school performance.

Intraoral examination revealed micrognathia, and pseudomacroglossia slightly prognathic mandible, partial anodontia [Figure 3]. Teeth seen in the oral cavity were primary only and partially erupted delayed with exfoliation of primary central incisors. More striking feature observed in this patient was widely spaced dentition, and abnormally thickened maxillary buccal and lingual frenum [Figures 3 and 4]. Orthopantomogram [Figure 5] of both the arches show missing 15, 18, 25, 28, 35, 38, 48, and unerupted 55, 65, and 85. However, no caries were seen in any teeth, and oral hygiene maintenance was good. We requested parents to give consent to take skin and gingival biopsy for further investigations, but they denied for any invasive procedures.

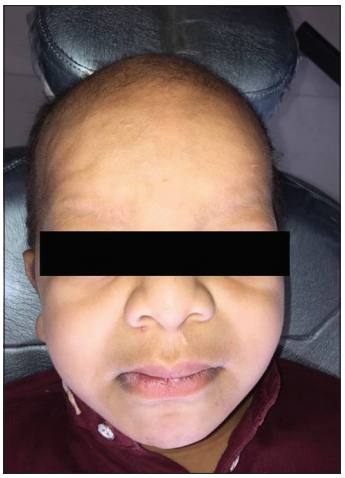

Figure 1: Facial profile of the patient.

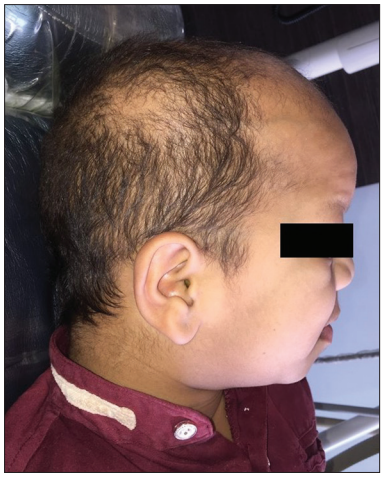

Figure 2: Lateral profile of the patient.

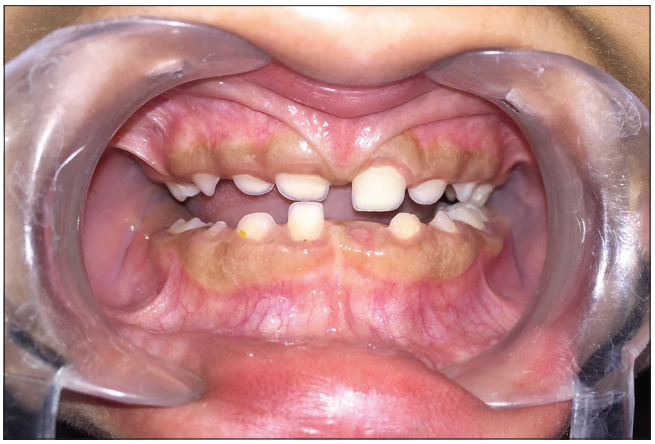

Figure 3: Facial view of maxillary and mandibular arches.

Management and Treatment

There is no curative treatment for this condition. Management mostly relies on ophthalmologic, neurologic, and auditory surveillance with symptomatic treatment of the multiple health problems. As there were no oral and dental pathology

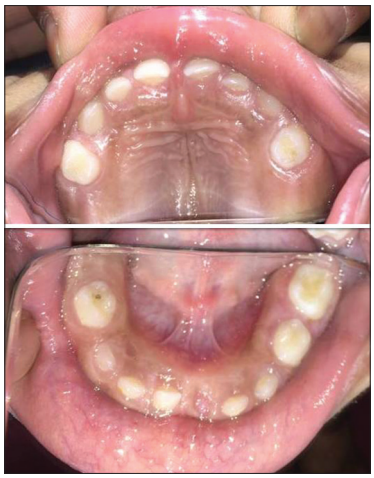

Figure 4: Occlusal view of maxillary and mandibular arches.

observed, we advised the patient for periodic follow-up for eruption status of permanent teeth. The prognosis of patients with GAPO syndrome can be considered fair due to reduced lifespan (until their the 4th to 6th decade of life) if neurological deficits do not dominate in the early age of life.[3]

Discussion

Despite the consistent finding of craniomaxillofacial region and pseudoanodontia as a characteristic component of the syndrome, it has not been widely reported in the dental literature. With this report, the present case becomes the fifth paper to appear in dental literature. All the signs observed in this patient were the characteristic features of the syndrome.

The patient reported was facing gradual hearing loss. The reasons behind such finding were explained as follows: When auditory loss or deafness is seen in patients with GAPO syndrome, it is mainly due to auditory brainstem responses with cochlear origin of hearing loss or vestibular hypofunction.[9] Another reason cited for deafness is due to defective connexin 26 (GJB2) and 30 (GJB6) genes, which are the most common cause of autosomal recessive deafness worldwide. ANTXR1 mutations have been demonstrated to lead to alterations in actin cytoskeletal microfilaments in fibroblasts of patients with GAPO syndrome. Mutations in gamma actin and beta actin have been reported to cause deafness, presumably by altering the cytoskeleton and affecting gap junction formation by connexin 30.[10]

Decrease in visual acuity seen in patients of GAPO syndrome patient is attributed to optic nerve atrophy, secondary to the nerve constriction, due to thickening and constriction of dura mater surrounding optic nerve, eventually leading to nerve atrophy.[11] Other reasons cited in the literature for such occurrences are interstitial keratitis and ocular inflammation as well as corneal opacity secondary to end-stage congenital glaucoma.[11,12] The appearance of clinical features such as premature craniosynostosis, frontal bossing, premature fusion of calvarial sutures, and epiphyseal plates is accredited to the

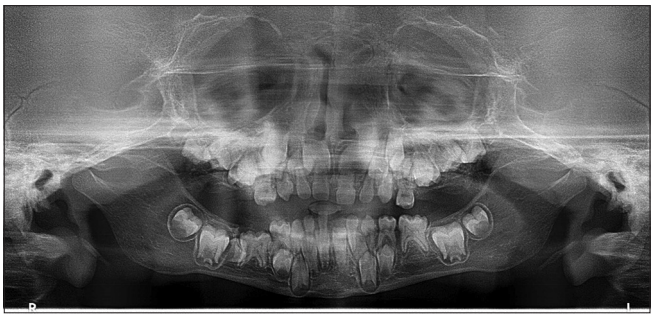

Figure 5: Orthopantomograph of the patient.

presence of excess homogeneous amorphous hyaline material in all organs and interstitial spaces as well as in serosal membranes. The accumulation of excess hyaline material may cause of premature fusion of the growing bone ends. Thus, it can be considered as a causal association for growth retardation, short stature, and dwarfism in such patients.[13]

The dental findings observed in this patient were quite interesting. The teeth were present but failed to erupt in the oral cavity causing pseudoanodontia and resulted increased ridge bone volume.[6,14] Inability of primary and permanent teeth to erupt in the oral cavity causing partial or complete anodontia is related to an excess of extracellular connective tissue matrix that accumulates during life and interferes with the normal functions of all the tissues and organs.[4] One sticking feature that we noticed in this patient was abnormally thick buccal and lingual frenii. An abnormal deposition of collagen fibrils in the connective tissues of gingiva and skin may be related to the abnormal production of collagen. However, the enzymes involved the breakdown of collagen in connective tissues shows diminished activity due to defect in underlying molecule.[8] We could not report other additional findings related to histopathological investigations for skin and gingival tissues due to denial from parents. Keeping their emotional status in mind, we respected their feelings and left that part.

In humans ANTXR 1 gene previously known as TEM8 (RefSeq accession number NM_032208.2) encodes Type I transmembrane protein with a molecular weight of 85 KDa. Von Willebrand factor Type A domain is contained in this amino acid sequence for this receptor protein. This domain is important for protein–protein interaction; an Anthrax receptor extracellular domain (Anth_Ig), and an Anthrax receptor C-terminus region (Ant_C). Two more isoforms have been described: variant 2, which is shorter than variant 1 in the cytoplasmic domain, and variant 3, which is secreted as it does not contain a transmembrane or cytoplasmic domain. This protein is involved in cell attachment and migration and allows the interaction of cells and several components of the extracellular matrix by binding extracellular ligands with the actin of cytoskeleton. ANTXR1 protein is a key player in cell spreading.[8,15]

As extracellular matrix-binding receptors are widely expressed by many cell types in different tissues, ANTXR1 is essential

for the normal development and postnatal homeostasis. Homozygous nonsense mutation (c.505C>T [p. Arg169*]) in ANTXR1 and loss-of-function of the same result in rare GAPO syndrome in humans.[16] Such patients exhibit characteristic clinical features along with additional features, including prominent scalp veins, hemangioma such as vascular anomalies and progressive skin fibrosis.[7] Vascular endothelial growth factor-A (VEGF-A) is likely to play a role in the prominent scalp veins and other vascular anomalies and may contribute to skin fibrosis as well. In addition, because VEGF-A, expressed by hypertrophic chondrocytes in the growth plates of endochondral bones, induces blood vessel invasion, and stimulates osteoclast/chondroclast differentiation in the growth plates of growing bones, one would expect that increased VEGF-A levels play a role in growth retardation in patients with GAPO syndrome.[17,18] Thus, it is possible that some of the age-dependent consequences of ANTXR1 loss-of-function mutations in GAPO syndrome may be due to the increased levels of VEGF-A expression in the endothelial cells and other cell types within the skin and skeletal tissues.[7,17,18]

Conclusion

Although GAPO syndrome has been investigated thoroughly, few dimensions of the syndrome are yet to be explored in the field of science. It is a rare disorder with high morbidity as well as high mortality due to generalized interstitial fibrosis and atherosclerosis. However, proper diagnosis and careful evaluation of such patients are necessary to help them to lead their life with minimum distress.

Declaration of patient and parents' consent

All the authors certify that they have obtained all appropriate parent's consent forms and patient's consent forms. In the form, parents as well as the patient have given their consent for his images and other clinical information to be reported in the journal. The patient understands 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.

References

1. European Organization for Rare Disorders. Available from: http://www.eurordis.org. [Last accessed on 19 Aug 20].
2. National Organization for Rare Disorders. Available from: http://www.rarediseases.org. [Last accessed on 19 Aug 20].
3. da Silveira HE, Quadros OF, Dalla-Bona RR, da Silveira HL, Fritscher GG. Dental findings in GAPO syndrome: Case report. Braz Dent J 2006;17:259-62.
4. Nanda A, Al-Ateeqi WA, Al-Khawari MA, Alsaleh QA, Anim JT. GAPO syndrome: A report of two siblings and a review of literature. Pediatr Dermatol 2010;27:156-61.
5. Young ID. Cranioectodermal dysplasia (Sensenbrenner's syndrome). J Med Genet 1989;26:393-6.
6. Suri L, Gagari E, Vastardis H. Delayed tooth eruption: Pathogenesis, diagnosis, and treatment. A literature review. Am J Orthod Dentofacial Orthop 2004;126:432-45.
7. Salas-Alanís JC, Scott CA, Fajardo-Ramírez OR, Duran C, Moreno-Treviño MG, Kelsell DP. New ANTXR1 Gene mutation for GAPO syndrome: A case report. Mol Syndromol 2016;7:160-3.
8. Bayram Y, Pehlivan D, Karaca E, Gambin T, Jhangiani SN, Erdin S, *et al*. Whole exome sequencing identifies three novel mutations in ANTXR1 in families with GAPO syndrome. Am J Med Genet A 2014;164A: 2328-34.
9. Rapsomaniki M, Chiarella G, Mascaro I, Ceravolo F, Cassandro E, Strisciuglio P, *et al*. GAPO syndrome associated with vestibular dysfunction and hearing loss. Am J Med Genet A 2013;161A:2102-4.
10. Aggarwal S, Uttarilli A, Dalal AB. GAPO syndrome with deafness: New feature or incidental finding? Clin Dysmorphol 2013;22:161-3.
11. Lei S, Iyengar S, Shan L, Cherwek DH, Murthy S, Wong AM. GAPO syndrome: A case associated with bilateral interstitial keratitis and hypothyroidism. Clin Dysmorphol 2010;19:79-81.
12. Bozkurt B, Yildirim MS, Okka M, Bitirgen G. GAPO syndrome: Four new patients with congenital glaucoma and myelinated retinal nerve fiber layer. Am J Med Genet A 2013;161A: 829-34.
13. Goyal N, Gurjar H, Sharma BS, Tripathi M, Chandra PS. GAPO syndrome with pansutural craniosynostosis leading to intracranial hypertension. BMJ Case Rep 2014;2014:bcr2013201727.
14. Manouvrier-Hanu S, Largilliere C, Benalioua M, Farriaux JP, Fontaine G. The GAPO syndrome. Am J Med Genet 1987;26:683-8.
15. Olsen BR, Berendsen AD, Besschetnova TY, Duan X, Hu K. Fell-Muir lecture: Regulatory mechanisms of skeletal and connective tissue development and homeostasis – Lessons from studies of human disorders. Int J Exp Pathol 2016;97:296-302.
16. Stránecký V, Hoischen A, Hartmannová H, Zaki MS, Chaudhary A, Zudaire E, *et al*. Mutations in ANTXR1 cause GAPO syndrome. Am J Hum Genet 2013;92:792-9.
17. Puranik RS, Puranik SR, Hallur N, Venkatesh D. GAPO syndrome – A rare cause of osteomyelitis of jaws; report of 4 cases with a brief review of the literature. J Oral Maxillofac Surg 2018;76:1216-25.
18. Goloni-Bertollo EM, Ruiz MT, Goloni CB, Muniz MP, Valério NI, Pavarino-Bertelli EC. GAPO syndrome: Three new Brazilian cases, additional osseous manifestations, and review of the literature. Am J Med Genet A 2008;146A: 1523-9.