

## GAPO syndrome – Report of a rare case and review

**Malarmathi Eswaramoorthy<sup>1</sup>, Murali Gopika Manoharan<sup>2</sup>**

*From <sup>1</sup>Post Graduate, <sup>2</sup>Professor and Head, Department of Oral Medicine and Radiology, Tamil Nadu Government Dental College and Hospital, Chennai, Tamil Nadu, India*

### ABSTRACT

A typical case of GAPO syndrome is an autosomal recessive disorder caused by biallelic mutations in the anthrax toxin receptor 1 gene. GAPO is the acronym for the syndrome characterized by a pattern of growth retardation, alopecia, pseudoanodontia, and progressive optic atrophy. Until now, approximately 60 cases have been reported. Herewith, we report the case of a 16-year-old male patient with GAPO syndrome who reported with the chief complaint of missing teeth in the front and back region in both the upper and lower jaw and wanted replacement of teeth. On examination, he had alopecia, short stature along with blindness. The dental findings were unerupted primary and permanent dentitions, which seemed clinically to be a total anodontia and the dental X-rays showed multiple impacted teeth. Based on the clinical and radiographic features, the case was diagnosed as GAPO syndrome.

**Key words:** Anthrax toxin receptor 1, Autosomal recessive inheritance, GAPO syndrome, Pseudoanodontia

**A**mong various rare diseases, GAPO syndrome stands out as a distinctive and unique syndrome characterized by growth retardation (G), alopecia (A), pseudoanodontia (P), and optic atrophy (O). This condition was first described by Andersen and Pindborg in 1947 [1]. Tripton and Gorlin in 1984 named this condition as GAPO syndrome (OMIM230740) [2]. It is a very rare hereditary disease having an autosomal recessive mode of inheritance. It has an estimated incidence of one in 1 million live births with no apparent sex, ethnic, or geographic predilection [3]. Homozygous nonsense or splicing mutations in the anthrax toxin receptor 1 (ANTXR1) gene (2p13.3) cause GAPO syndrome. Until now, approximately 60 cases have been reported [4]. Individuals with GAPO syndrome may exhibit a range of abnormalities including wide anterior fontanelle, bossed forehead, prominent scalp veins, hypertelorism, micrognathia, protruding lips and auricles, saddle and depressed nasal bridge, premature aging appearance, skin redundancy, absence of eyebrows, eyelashes, and scalp hair, umbilical hernia, delayed bone maturation, hepatomegaly, and cardiomyopathy [5].

In this paper, we report the case of a 16-year-old male patient with GAPO syndrome because of its rarity in occurrence and to emphasize the significance of including this condition in the differential diagnosis of complete anodontia. Furthermore, it highlights the multidisciplinary approach needed in the

management to enhance the delivery of good care for patients affected by GAPO syndrome.

### CASE REPORT

A 16-year-old male patient came to the Department of Oral Medicine and Radiology with the chief complaint of missing teeth in the front and back region in both the upper and lower jaw since childhood and wanted replacement of teeth. The patient was diagnosed with GAPO syndrome during his 2<sup>nd</sup> year of life, and the parents were aware of this condition. Family history revealed that he was born as a second child to consanguineous parents delivered by elective cesarean section. The elder sibling is normal. There was no family history of a similar condition. At birth, his weight was 3 kg, and height was 48 cm, and he was noticed to have dysmorphic craniofacial features. Parents noticed there was a diminished growth and failure of primary teeth eruption. The mother gave a history that the child was born with adequate hair and then he developed alopecia at the age of 6 months, gradual reduction in eyesight at the age of 4½ years. He had normal sweating and was without any history of associated medical ailment. Past medical history revealed that he has obstructive sleep apnea for the past 4 years.

On general examination, the patient showed a short stature (144 cm) and a weight of 64 kg. Examination of the head-neck and face revealed oxycephaly, alopecia, wide anterior

Access this article online

Received - 13 April 2024  
Initial Review - 26 April 2024  
Accepted - 05 June 2024

Quick Response code



DOI: 10.32677/ijcr.v10i7.4590

**Correspondence to:** Malarmathi Eswaramoorthy, Department of Oral Medicine and Radiology, Tamil Nadu Government Dental College and Hospital, Chennai - 600 003, Tamil Nadu, India. E-mail: malar2113@gmail.com

© 2024 Creative Commons Attribution-NonCommercial 4.0 International License (CC BY-NC-ND 4.0).

fontanelle, saddle nose with depressed nasal bridge, low-set ears, micrognathia, thick protruding lower lip with normal upper lip (Fig. 1), sparse eyebrows and eyelashes, hypertelorism, and thickened eyelids (Fig. 2a). Ocular manifestations revealed strabismus, ptosis, and blindness. Ocular manifestations revealed strabismus, ptosis, and blindness (Fig. 2a). The fingers of the hands and legs were short and stubby, and the nails were normal (Fig. 2b and c). His skin appeared redundant hyperplastic with unusual wrinkles. The intellectual quotient was good.

Intraoral examination revealed that the patient had a complete absence of teeth clinically in both arches (Fig. 3a), with abnormally thickened mandibular buccal and lingual frenum (Fig. 3b). Orthopantomogram (OPG) was taken for the patient. OPG revealed multiple impacted primary and permanent teeth (53, 54, 55, 14, 16, 17, 63, 64, 65, 24, 26, 27, 73, 33, 74, 75, 36, 82, 83, 84, 85, 43, 46) with incomplete root formation up to the cervical third of the tooth. It was difficult to ascertain the type of dentition of the impacted tooth. None of the teeth had erupted, indicating pseudoanodontia condition (Fig. 4).

Based on the clinical and radiographic findings, the diagnosis of GAPO syndrome was confirmed. The need for a multidisciplinary approach involving surgery, prosthodontics, and oral rehabilitation was discussed with the patient, and the placement of a complete denture was presented as the best treatment option. Surgical removal of the teeth, even if partial seemed to be complicated. However, the patient refused to undergo the surgical intervention. Hence, the patient was advised of dental rehabilitation using a complete denture without the extraction of impacted teeth.



**Figure 1:** Extraoral images of the patient showing short stature, oxycephaly, alopecia, saddle nose with depressed nasal bridge, low set ears, and protruding lower lip

## DISCUSSION

GAPO syndrome is an entity with multiple congenital anomalies involving connective tissue characterized by growth retardation, alopecia, pseudoanodontia (failure of tooth eruption), and optic atrophy complex. The condition was first described by Andersen and Pindborg in 1947 [1]. Tripton and Gorlin in 1984 named this condition as GAPO syndrome [2]. It is a very rare hereditary disease having an autosomal recessive mode of inheritance. Patient's family history revealed consanguineous marriage which favours the autosomal recessive mode of inheritance. It has an estimated incidence of one in 1 million live births with no apparent sex, ethnic, or geographic predilection. Most of these patients are shown to have a reduced life span or early death in the late fourth decade due to generalized interstitial fibrosis and atherosclerosis [3].

Based on histological and autopsy findings by several authors, the overall clinical manifestation is the consequence of an excessive accumulation of extracellular connective tissue matrix due to homozygous or compound heterozygous mutations in the *ANTXR1* gene, formerly known as tumor endothelial marker 8. *ANTXR1*, a molecule mediating the coupling of extracellular ligands to the actin cytoskeleton, is crucial for actin assembly, and that disruption of the actin network might be a major pathogenetic event leading to altered cell-adhesion properties and progressive extracellular matrix build-up observed in GAPO syndrome [4].

Individuals with GAPO syndrome may exhibit a range of abnormalities including wide anterior fontanelle, bossed forehead, prominent scalp veins, increased intracranial pressure, hypertelorism, micrognathia, protruding lips and auricles, saddle, and depressed nasal bridge, altered ability to sweat, premature aging appearance, skin redundancy, and absence of eyebrows, eyelashes, and scalp hair, hyperextensible joints, hyperconvex nails, umbilical hernia, delayed bone maturation, hypoplasia of the genitalia and mammary glands, and irregular gonadal function. Other manifestations including cardiomyopathy, pulmonary hypertension, hypothyroidism, hepatomegaly, and hearing loss were also reported recently [5]. Wide anterior fontanelle, bossed forehead, prominent scalp veins, hypertelorism, micrognathia, protruding lips, low-set ears, saddle and depressed nasal bridge, premature aging appearance, skin redundancy, and absence of eyebrows, eyelashes, and scalp hair, delayed bone maturation were found in our patient whereas hyperextensible joints, hyperconvex nails, umbilical hernia, hypoplasia of the genitalia and mammary glands, and irregular gonadal function, altered ability to sweat, cardiomyopathy, pulmonary hypertension, hypothyroidism, hepatomegaly, hearing loss were absent in our patient.

The appearance of features such as premature craniosynostosis, premature fusion of calvarial sutures, frontal bossing, and epiphyseal plates can be attributed to the accumulation of excess homogeneous amorphous hyaline material in all organs and in interstitial spaces as well as in serosal membranes. This accumulation may lead to premature fusion of the growing bone ends, contributing to growth retardation, short stature,



Figure 2: (a) Sparse eyebrows and eyelashes, hypertelorism, thickened eyelids; (b and c) short and stubby fingers

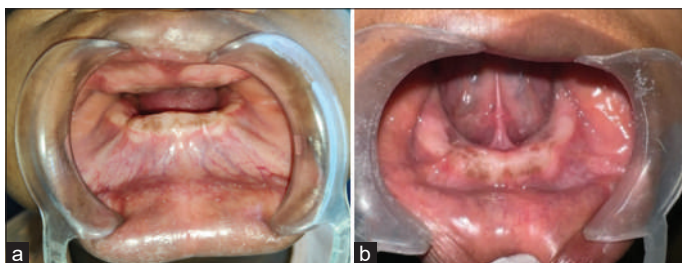


Figure 3: (a) Complete absence of teeth in both the upper and lower arches; (b) abnormally thickened mandibular buccal and lingual frenum



Figure 4: Multiple impacted primary and permanent teeth with incomplete root formation up to the cervical third of the tooth

and dwarfism in affected individuals [6]. Increased vascular endothelial growth factor (VEGF)-A levels are implicated in growth retardation because VEGF-A, expressed by hypertrophic chondrocytes in the growth plates of endochondral bones, induces blood vessels invasion, and stimulates osteoclast/chondroclast differentiation in the growth plates of growing bones. Thus, suggests that agedependent consequences of ANTXR1 loss of function mutations in GAPO syndrome may result from increased VEGF-A expression in the endothelial cells and other cell types within the skin and skeletal tissues [7].

Pseudoanodontia is characterized by the clinical but not radiographic, absence of teeth due to failure in their eruption. This phenomenon is linked to the excessive accumulation of extracellular connective tissue matrix, which interferes with normal tissue and organ function, leading to progressive deterioration over time [8]. The alveolar ridges may appear thick, irregular, bulky, and hypoplastic depending on the age of the patient and embedded teeth. In this patient, we noticed the complete absence of teeth clinically in both the upper and lower arches with abnormally thick buccal and lingual frenii. Ultrastructural examination of the gingival mucosa reveals

dense bundles of thin collagen fibers in subepithelial layers and vacuolated endothelial cells lining venous capillaries [9].

Ophthalmic abnormalities include optic atrophy, congenital glaucoma, bilateral papilledema, nystagmus, interstitial keratitis, and ptosis. The decrease in visual acuity is often linked to optic nerve atrophy, secondary to nerve constriction resulting from thickening and constriction of the dura mater surrounding the optic nerve [10]. Our patient's magnetic resonance imaging revealed the features of optic atrophy.

The differential diagnosis of the syndrome includes Hutchinson-Gilford syndrome, characterized by short stature, large open fontanelle, baldness, loss of eyebrows and eyelashes, delayed eruption of teeth, micrognathia, thin, spotty, and wrinkled skin, veins easily seen through the skin, premature aging. The other differential diagnoses include Werner syndrome, cartilage-hair hypoplasia, Rothmund-Thomson syndrome, acrogeria (Gottron type), and the tricho-dento-osseous syndrome [11].

## CONCLUSION

GAPO syndrome is an extremely rare entity. Only a few cases have been reported in the literature worldwide. There is no curative treatment for GAPO syndrome. The oral physician would play a key role in differentiating various conditions presenting complete anodontia. The patient was advised to undergo periodic follow-up examinations to monitor the eruption status of permanent teeth. The prognosis for individuals with GAPO syndrome is relatively fair, with a reduced lifespan (until the 4<sup>th</sup>–6<sup>th</sup> decade of life) if neurological deficits do not dominate at the early age of life.

## REFERENCES

- Andersen TH, Pindborg JJ. Et tilfaelde of total "pseudoanodonti" inforbindelse med kranie deformitet, dvaergvaekst og ektodermal dysplasia. *Odontol Tilster* 1947;55:484-93.
- Tripton RE, Gorlin RJ. Growth retardation, alopecia, pseudoanodontia, and optic atrophy--the GAPO syndrome: Report of a patient and review of the literature. *Am J Med Genet* 1984;19:209-216.
- Dahake PT, Kale YJ, Dadpe MV, Kendre SB. A rare Indian case of GAPO syndrome with dental and other findings. *Int J Pedod Rehabil* 2020;5:25-8.
- Balakrishnan S, Goud I, Teegala ML. Prenatal onset GAPO syndrome with a novel ANTXR1 variant in an Indian child: Expansion of the phenotype and literature review. *Eur J Med Genet* 2024;68:104929
- Dalkiz M, Gul D, Dalkiz AS. Prosthetic rehabilitation and cephalometric evaluation of Gapo syndrome: 29 years follow up. *EC Dent Sci* 2019;18:252-269.
- Golpayegani M, Salari F, Habibi Z, Naderian N, Nejat F. GAPO syndrome with craniosynostosis and intracranial hypertension. *Childs Nerv Syst* 2019;35:1621-4.
- 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.
8. Sciacchitano S, De Francesco GP, Piane M, Savio C, De Vitis C, Petrucci S, *et al.* Complete pseudo-anodontia in an adult woman with pseudo-hypoparathyroidism type 1a: A new additional nonclassical feature? *Diagnostics (Basel)* 2022;12:2997.
  9. Meguid NA, Afifi HH, Ramzy MI, Hindawy A, Temtamy SA. GAPO syndrome: First Egyptian case with ultrastructural changes in the gingiva. *Clin Genet* 1997;52:110-5.
  10. Sethi A, Sethi SS. Growth retardation-alopecia-pseudoanodontia-optic atrophy (GAPO) syndrome: A rare cause of optic atrophy of optic atrophy. *Indian J Ophthalmol Case Rep* 2021;1:588-90.
  11. 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.

*Funding: Nil; Conflicts of interest: Nil.*

**How to cite this article:** Eswaramoorthy M, Manoharan MG. GAPO syndrome – Report of a rare case and review. *Indian J Case Reports.* 2024;10(7):208-211.