VOLUME - 10, ISSUE - 10, OCTOBER - 2021 • PRINT ISSN No. 2277 - 8160 • DOI : 10.36106/gjra

Original Research Paper

Paediatrics

GAPO SYNDROME- A VERY RARE ENTITY

Dr. Malavika B G Consultant Pediatrician, Department of Pediatrics. RJN Apollo Spectra Hospitals, Gwalior – 474002

Dr. Abhas Kumar* HOD & Consultant Neurologist, Department of Neurology, RJN Apollo Spectra Hospitals, Gwalior – 474002. *Corresponding Author

ABSTRACT GAPO syndrome is an extremely rare entity, where GAPO is an acronym which stands for Growth retardation, Alopecia, Pseudoanodontia, and Optic atrophy (GAPO) syndrome. Approximately 46 patients have been reported in literature. We present a case of a 10-year old Indian male child with GAPO syndrome in association with cranisynostosis along with bilateral glaucoma, short stature, complete anodontia and abnormally thickened lingual frenulum, born to parents of non-consanguineous marriage with history of similar features in younger sister; however, the intelligence quotient, motor development and social domains of the child were appropriate for the age.

KEYWORDS : GAPO, Pseudoanodontia, alopecia, optic atrophy.

INTRODUCTION:

Among numerous rare diseases, GAPO Syndrome is an entity that has derived its name from acronymic designation for a complex of **G**rowth retardation, **A**lopecia, **P**seudoanodontia, and **O**ptic atrophy (GAPO) syndrome [1]. The syndrome was first reported by Andersen and Pindborg in 1947.

Epidemiology:

GAPO syndrome has 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 [2].

Pathogenesis:

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 non-sense 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 [3,4].

Case Report:

A 10-year-old male child presented to the department of ophthalmology for blurring of vision and was later referred to department of pediatrics for pediatric evaluation. The child was born as a first child of non-consanguineous marriage. 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. Child also had delayed motor skills in the early years of life. Parents further observed no eruption of teeth and gradual reduction in eye sight of child.

Child's younger sister had similar illness and had loss of vision for the past 1 year and has similar morphological features. The clinical examination of the patient revealed having a peculiar geriatric look. Child was showing a short stature with a height of 122 cm and weight of 23.4 kg, which was less than normal parameter due to postnatal growth retardation.

Examination of face and head–neck region revealed typical facies of GAPO syndrome with high and bossing forehead, prominent scalp veins, sparse scalp hairs, eyebrows, and eyelashes, low set ears [Figure 1].

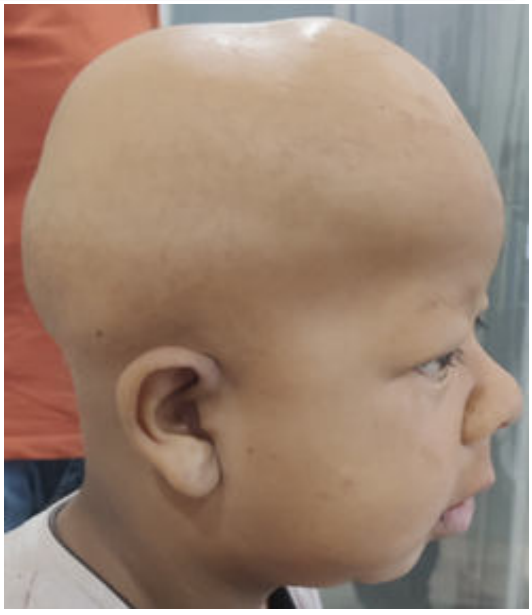

Figure 1. Image Showing Alopecia, Sparse Eye Brows, Frontal Bossing With Prominent Scalp Veins, Low Set Ears.

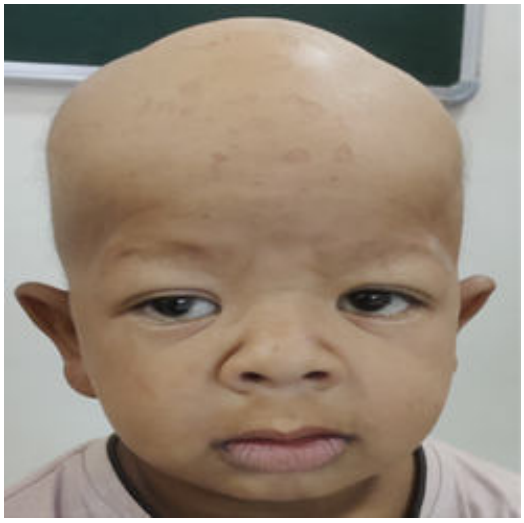

Figure 2. Image Showing Hypertelorism, Mid Facial Hypoplasia, Puffy Eyelids, And Midfacial Hypoplasia. Scalp Hairs, Eyebrows, And Eyelashes Were Sparse Showing Partial Alopecia.

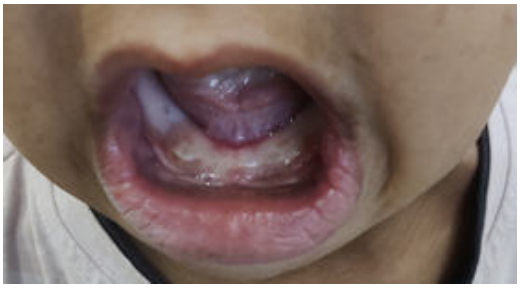

Figure 3. Image Shows Anodontia.

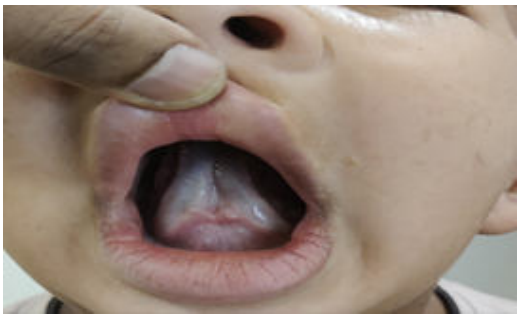

Figure 4. Thickened Frenulum.

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. Contrary to the findings of mild intellectual deficits mentioned in previous cases, this patient was having a good intellectual quotient and had near normal motor skills at par with his age group.

No teeth were seen in the oral cavity, although orthopantomogram showed non-erupted teeth. More striking feature observed in this patient was abnormally thickened maxillary buccal and lingual frenulum [Figure 4].

DISCUSSION:

Despite the consistent finding of cranio-maxillofacial region, decrease in visual acuity and pseudoanodontia as a characteristic component of the syndrome, it has not been widely reported neither in ophthalmology nor pediatrics literature.

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 [5].

Clinical Features:

Patients have a short stature due to post-natal growth retardation and a typical facies with high and bossing forehead, hypertelorism, puffy eyelids, midfacial hypoplasia, depressed nasal bridge, anteverted wide nostrils, thick everted lower lip, micrognathia, low-set ears and premature aging appearance mainly due to redundant hyperelastic skin with unusual wrinkles. Scalp hair may be primarily present but disappears after the first months of life leading to complete or partial alopecia.

The appearance of clinical features such as premature craniosynostosis, frontal bossing, premature fusion of calvarial sutures, and epiphyseal plates is accredited to the 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 [6].

Eyebrows and/or eyelashes are sparse. Primary and permanent teeth are formed but fail to erupt. 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. An abnormal deposition of collagen fibrils in the connective tissues of gingiva and skin may be related to the abnormal production of collagen.

Ocular manifestations may include progressive optic atrophy, glaucoma, strabismus, megalocornea, myelinated retinal nerve fiber layer, bilateral keratoconus, nystagmus and ptosis.

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. 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 [7, 8].

Otorhinolaryngologic features are choanal atresia, deafness and presence of flaccid and pulsatile masses with an audible murmur in the mastoid area associated with dilated and tortuous scalp veins. Patients have a mild intellectual deficit. Some patients have also been reported with umbilical hernia, hyperextensible joints, osseous anomalies (congenital dislocation of hips or delayed bone age) and cutaneous manifestations (hemangioma or depigmented areas). Other manifestations include intracranial hypertension in infancy, hypothyroidism, mitral valve dysfunction or cardiomyopathy, hepatomegaly, renal impairment and altered gonadal functions (irregular periods or amenorrhea, oligo asthenospermia).

Diagnosis:

Diagnosis mostly relies on physical examination. Cerebral angiography and magnetic resonance angiography reveal prominent cortical veins, occluded or absent left transverse sinus, left sigmoid sinus, agenesis of left jugular vein, and enlarged veins underlying the palpable scalp masses. Skin biopsy may reveal dermis anomalies including amorphous hyaline substance and recently reported pyoderma vegetans.

Ante-natal diagnosis is not possible.

Genetic Counselling:

GAPO syndrome follows autosomal recessive inheritance.

Treatment:

There is no curative treatment. Management mostly relies on ophthalmologic surveillance and symptomatic treatment of the multiple health problems.

Prognosis:

GAPO patients are reported to have a reduced lifespan (until their 4th -6th decade of life).

REFERENCES:

1. 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.
2. 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.
3. 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.
4. 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.
5. Aggarwal S, Uttarilli A, Dalal AB. GAPO syndrome with deafness: New

feature or incidental finding? Clin Dysmorphol 2013;22:161-3.
6. 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.
7. 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.
8. 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.