ORIGINAL RESEARCH PAPER

Radiodiagnosis

KEY WORDS: Gapo; Growth Retardation; Alopecia; Pseudo-anodontia; Antxr1 Gene.

GAPO SYNDROME IN TWO SIBLINGS

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ABSTRACT

We report two siblings, born out of a consanguineous marriage, presented with growth retardation, alopecia, unerupted teeth, persistent anterior fontanelle, large cornea and nystagmus. Imaging studies revealed delayed bone age, pseudo-anodontia, patent anterior fontanelle, hydrocephalus and hyperintense periventricular and deep white matter on T2 weighted MRI, pale optic disc on fundoscopy. Genetic tests revealed homozygous mutation in ANTXR1 gene in chromosome 2, confirming a diagnosis of GAPO (growth retardation, alopecia, pseudo-anodontia and optic atrophy) syndrome.

INTRODUCTION

The GAPO (growth retardation, alopecia, pseudoanodontia and optic atrophy) syndrome is a rare congenital anomaly with unique craniofacial features[1]. There are approximately 38 cases described in the literature[Orphanet]. The disease is transmitted by autosomal recessive inheritance [1]. Patients usually present during their early childhood. Diagnosis is suspected based on the characteristic clinical and imaging findings and is confirmed on genetic tests [2]. In this review, we describe two siblings with GAPO syndrome who presented to our tertiary care hospital{Kurnool medical college, Kurnool, Andhra pradesh}.

CASE REPORT

Two siblings - a four-year-old girl and a three-year-old boy, were brought to our hospital by their parents with specific complaints of lack of hair, wide forehead, unerupted teeth and unusual movements of the eyes. Both the children had hair at birth but developed thin, fragile sparse hair following tonsure. The boy had undergone surgery for congenital glaucoma at the age of 2 years. Third-degree consanguinity was noted between the parents.

On examination (Fig 1), both the children demonstrated alopecia, sparse eyebrows and eyelashes, persistent anterior fontanelle, frontal bossing, widely spaced eyes, epicanthus, mega cornea, nystagmus, depressed nasal bridge, anteverted nares, unerupted teeth, thick lower lips, small chin and low set ears. There was growth retardation with short stature. Fundoscopic examination (Fig 2) revealed a pale disc with a cup to disc ratio of 0.6-0.7 in the girl and 0.8-0.9 in the boy. The retinal vessels were dilated.

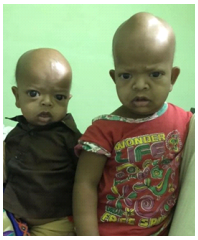

Fig-1 Photograph of affected children with typical facies evident of persistent anterior fontanelle, frontal bossing, widely spaced eyes, epicanthus, mega cornea, depressed nasal bridge, anteverted nares, thick lower lips, small chin and low set ears.

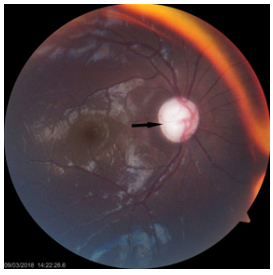

Fig-2 Fundoscopic examination revealed pale optic disc(black arrow) in the four-year-old child

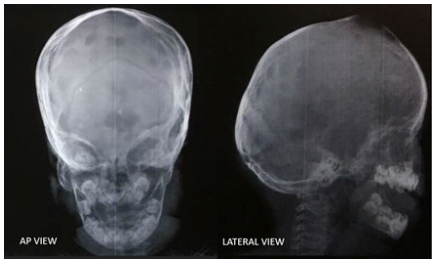

Fig- 4 Plain radiographs of skull anterior and lateral view in a 4 yr old child with evident failure of closure of anterior fontanelle and pseudo anodontia(The permanent teeth may begin to develop but fail to erupt).

Plain radiographs (Fig 3) of the skull, body and extremities revealed patent anterior fontanelle and delayed bone age(Fig 4).

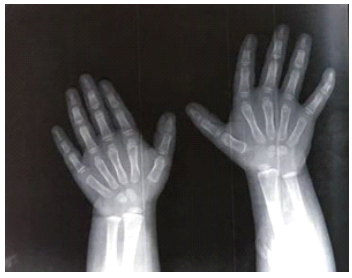

Fig-4 Plain radiographs of hand in a four-year-old child with only two carpal bones suggestive of delayed skeletal maturity.

CT of the brain demonstrated mild hydrocephalus in both the children. MRI of the brain revealed hyperintense foci within the periventricular and deep white matter on T2 weighted and FLAIR sequences.

A clinical exome sequencing genomic analysis was performed using a blood sample in both the siblings. This revealed a homozygous mutation in ANTXR1- anthrax toxin receptor 1 gene (also known as TEM 8 - Tumor endothelial marker 8 genes) confirming the diagnosis of GAPO syndrome in both the children.{Table - 1}

Disease	Gene (Transcript)	Variant (Protein)	Zygosity	Mode of Inheritance	Clinical Significance
GAPO syndrome	*ANTXR1* (ENST00000303714.4)	c.451G>T (p.Gly151Ter)	Homozygous	Autosomal recessive	Likely pathogenic

DISCUSSION

GAPO syndrome represents a complex disorder affecting multiple organs and was first reported in 1947 [1,3]. In addition to the characteristic features described in the case report, the patient can also have midfacial hypoplasia and wrinkles due to hyperelastic skin. In addition to nystagmus, megalocornea and optic atrophy, other ocular manifestations include glaucoma, strabismus, keratoconus and ptosis[4]. Other features include deafness, choanal atresia, umbilical hernia, hyperextensible joints, congenital dislocation of hips, and cutaneous hemangioma. The patient can also have intracranial hypertension, mitral valve disease, cardiom yopathy, renal and liver involvement and altered gonadal function (Orphanet).

In addition to delayed bone age, radiographs may reveal joint dislocations, patent anterior fontanelle, deep furrows on the sternum, maxillary and mandibular hypoplasia, absence of facial pneumatization, enlargement of the metaphases, squared iliac wings, enlargement of proximal clavicles and shortening or arching of long bones. CT and MRI may show enlarged cortical veins, small or absent transverse sinus or sigmoid sinus or left jugular vein. Craniofacial vascular malformations have also been described. A skin biopsy may reveal dermis anomalies including accumulation of hyaline substance and pyoderma vegetans (Orphanet).

Genetic sequencing reveals abnormalities in Chromosome 2 with mutations in ANTXR1 gene that are transmitted in an autosomal recessive fashion, which explains its reported common occurrence with consanguineous marriages. The involvement of multiple organs is related to defects in connective tissue matrix [2,5]. It is suggested that the genetic mutations in ANTXR1 gene result in changes to actin microfilament assembly in fibroblasts resulting in altered cell adhesion and extracellular matrix build up in these patients[2,5].

There is no curative treatment for this condition. Symptomatic treatment of various health problems (lenses for vision correction, antihypertensives for hypertension, surgical correction of mitral valve disease) and surveillance for optic atrophy is recommended. Patient tend have shortened life span with most of them dying in their fourth decade due to multi-organ dysfunction and atherosclerotic disease.

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