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Ophthalmic Findings in GAPO Syndrome

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Background: The main manifestations of GAPO syndrome are growth retardation (G), alopecia (A), pseudoanodontia (P), and optic atrophy (O).

Cases: This syndrome has been described in 21 patients from 16 different families. Four cases are from Turkey and have been presented by Saylı and Gül. The purpose of our study is to document the cases from Turkey and discuss the ophthalmological and neuro-ophthalmolgical findings of these and other reported GAPO cases.

Observations: All patients in the literature and our 4 cases have severe growth retardation with delayed bone age in infancy, characteristic facial appearance (high and bossed forehead, midface hypoplasia), alopecia or severe hypotrichosis, and pseudoanodontia. Optic atrophy was present in 1 of our cases and in 5 previous cases. Glaucoma was present in 5 cases, including 2 of ours. Buphthalmia and keratopathy secondary to glaucoma were also observed. White eyelashes, seen only in our cases, may be a sign of "early senility."

Conclusions: Optic atrophy is not a constant finding in GAPO syndrome. Glaucoma may accompany the ocular findings. This syndrome has been attributed to either ectodermal dysplasia or the accumulation of extracellular connective tissue matrix, due to an enzyme deficiency involved in its metabolism. Current studies show that an elastin defect and secondary changes in collagen may be important in the pathogenesis of the disease. **Jpn J Ophthalmol 1999;43:48–52**

Key Words: Alopecia, GAPO syndrome, glaucoma, growth retardation, pseudoanodontia.

Introduction

GAPO syndrome is a developmental disorder with main manifestations of growth retardation (G), alopecia (A), pseudoanodontia (P), and optic atrophy (O). This syndrome was first described by Andersen and Pindborg in 1947.[1] Twenty-one patients from 16 different families have been reported.[1–20] The ophthalmological findings and the pathophysiology of this autosomal recessive disorder have been discussed previously in only one report of a patient.[12]

In this article, we give a detailed ophthalmological and neuro-ophthalmological description and discuss the ophthalmological findings in 4 patients from two Turkish families previously reported by Saylı and Gül in 1993 and in 1996.[14,15]

Clinical Reports

Three of the patients mentioned here are relatives; two are siblings and one is a paternal cousin (Figure 1). The members of this Turkish family are natives of the Black Sea Shore. The fourth patient is from Antakya, Hatay, an eastern Mediterranean city on the Syrian border.

Received: October 27, 1997.
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Written permission has been given by the father of Cases 1 and 2, who is also the uncle of Case 3, for publication of these photographs of his family members for medical purposes.

0021-5155/99/$–see front matter
PII S0021-5155(98)00058-6

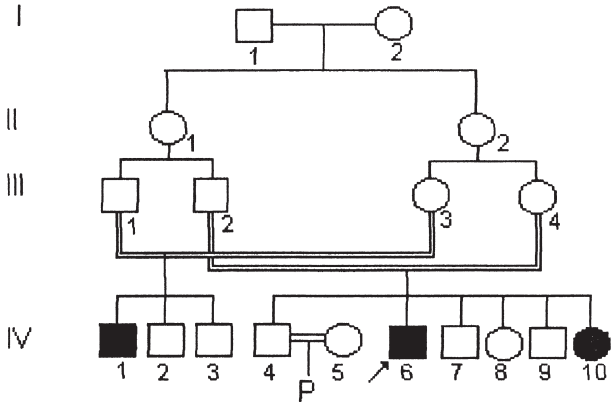

Figure 1. Pedigree of first family.

Table 1. Ophthalmic Findings in Our GAPO Cases

	Case Number			
	1	2	3	4(B)
Optic atrophy	−	−	−	+
Glaucoma	+(B)	−	+(B)	−
Papilla edema	−	+(B)	−	−
Keratopathy	−	−	+	−
Bossed forehead	+	+	+	+
Sparse eyebrows	+	+	+	+
Sparse eyelashes	+	+	+	+
White eyelashes	+	+	+	−
Hypertelorism	+	+	−	−
Prominent globes	+	+	+	−
Swollen eyelids	+	+	+	+

B: bilaterally.

Case 1

The propositus was born in 1971 in Samsun on the Black Sea (Figure 2). His younger sister and one of his cousins have the same condition.

On physical examination, he was a short, stocky man with no scalp hair. Hypotrichosis was present on the face. He had prominent globes and a large, slightly protruding forehead with prominent supraorbital ridges (Table 1, Figure 2). The eyebrows were barely visible with only a few thin hairs. The eyelids were swollen due to a subcutaneous infiltration and the tarsus was softer than normal. Eyelashes were present but were white; iris color was light blue. The distance between eyebrows and eyes was unusually great. The eyes were orthophoric, pupils were isocoric, and light reflexes were normal. The corneas were clear and 12 mm in diameter. Iris, lens, and fundus were normal. He had a refractive error of +1.50 diopter (D) at vertical axis for the right eye and +2.50 D at the same axis for the left eye. Visual acuities were 0.9 on the right, 0.8 on the left without correction, and 1.0 with correction for both eyes. Intraocular pressure (IOP) by applanation tonometer was 28 mmHg for the right eye and 37 mmHg for the left eye, without any medication. It was learned that the patient had been under glaucoma therapy for 3 years, but had not taken medication for the previous 2 days. IOP was 17 mmHg with antiglaucoma medication. The iridocorneal angles were found normal by gonioscopy. The visual field was normal for the right eye, but there were relative arcuate scotomas in the left eye. The cup:disc ratio was 3:10 for the right eye and 4:10 for the left. Bilateral pattern visual evoked response (PVER) responses and electroretinogram (ERG) responses were normal.

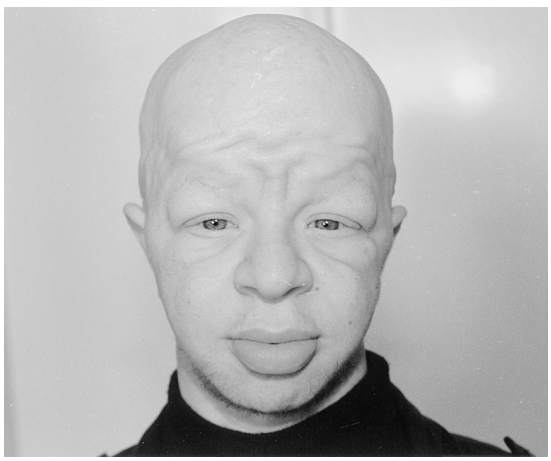

Figure 2. Frontal view of propositus. Note eyebrows are barely visible, eyelids are swollen, eyelashes are white.

Case 2

The younger sister of the propositus was 13 years old when first examined. In physical appearance, she was an exact but smaller version of her brother (Figure 3). She was disproportionately short in stature.

Her head appeared larger than normal and protruded from the frontal bones (Table 1). She was bald except for a tuft of dull-colored long hair spreading from the occiput down to the neck. The skin of her forehead was wrinkled. Her eyebrows were sparse, thin, and short. The eyelashes were sparse and white. The periorbital tissue was abundant and stretchable. The eyelids were swollen due to subcutaneous infiltration and the tarsus was softer than normal. The globes were prominent and the iris color was bright blue, a family trait.

Biomicroscopic findings were normal. Corneas were clear and 12 mm in diameter. By ophthalmos-

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Figure 3. Sister of propositus is a smaller version, physically, of her brother. Her eyebrows are sparse, thin, and short. Eyelashes are white. Iris color is bright blue, a family trait.

copy, the optic nerve heads seemed edematous bilaterally, but there were no hemorrhages or exudates or venous dilatation (Figure 4). Pseudotumor cerebri was considered. The patient refused lumbar puncture. We insisted that she return for routine examination every 2 months. On retinoscopy, there was +1.00 D refractive error in the right eye. The corrected vision was 0.8 in the right and 1.0 in the left eye. IOP was 19 mmHg in each eye by applanation tonometer. The anterior chamber depth and iridocorneal angle were normal. Slight hypertelorism and depressed nasal bridge were other findings. The results of cranial computed tomography (CT) were normal.

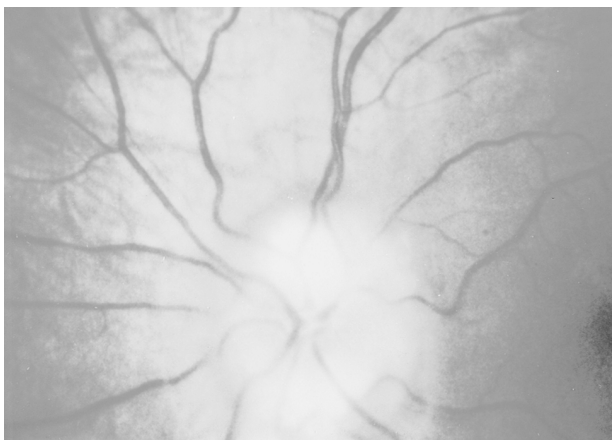

Figure 4. Left eye of case 2. Papilla appear to be edematous bilaterally.

Case 3

This patient was born to first-cousin parents and is a paternal cousin to cases 1 and 2. At the time of examination he was 19 years old and a high school student. He resembled the propositus with a few variations (Figure 5). He was also short in stature. He had excessive wrinkling of his palms and soles.

His eyebrows and eyelashes were sparse, thin, and short, and his eyelashes were white. The supranasal ridges were prominent and the eyelids were swollen (Table 1). His eyes were buphthalmic in appearance and the corneal diameters were 15 mm. There was absolute glaucoma and band keratopathy in the left eye. The fundus could not be observed. There was no light perception in this eye. He had had glaucoma surgery on both eyes at the ages of 7 and 12. In the right eye, the cornea and lens were clear, and surgical scars were observed on the superior conjunctiva near the limbus. There were two peripheral iridectomies. The fundus was normal except for an 8/10 excavation of the papilla. He had a refractive error of +1.50 D at the vertical axis and visual acuity was 0.2 with the Snellen chart. He had a large Bjerrum scotoma connected to the blind spot. IOP was measured as 35 mmHg by applanation tonometer without drug therapy and was lowered to 14 mmHg with the triple drug therapy. Although some peripheral synechias were present, the anterior chamber angle was open. ERGs and PVERs were recorded from the right eye and nearly normal responses were obtained. No sign of optic atrophy was seen.

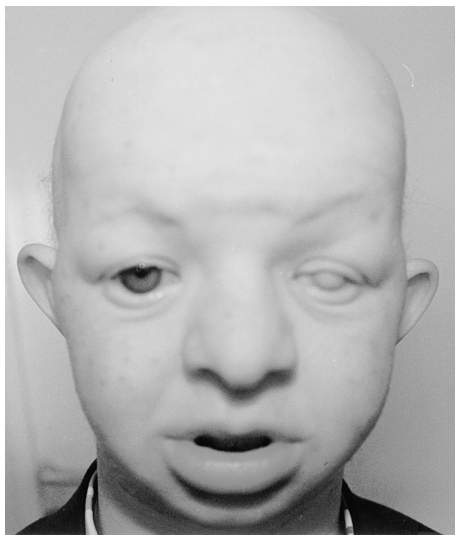

Figure 5. Case 3: Paternal cousin of cases 1 and 2, resembles propositus with a few variations.

Case 4

This case of GAPO was 24 years old when examined and from a different part of Turkey. He was born in Antakya, Hatay, an eastern Mediterranean city. He had all the manifestations of this syndrome. His parents were not related.

His eyebrows and eyelashes were sparse and thin (Table 1), but his eyelashes were black. The palpebral fissures were narrow and the supraorbital ridges were prominent with ptosis of the upper eyelids. The anterior chamber was deep with normal IOP, and the angle was open. Bilateral myopia of −4.00 D, 25 prism diopters of alternating esotropia and bilateral optic atrophy were present. Visual acuities were finger counting at 1 m.

Discussion

The published GAPO cases until now number 21, from 16 different families. All patients in the literature and our 4 cases had severe growth retardation with delayed bone age in infancy and characteristic facial features (high and bossed forehead, mid-face hypoplasia), alopecia or severe hypotrichosis, and pseudoanodontia. The mental state was normal in our cases and in the cases described in the literature.

Optic atrophy has been reported in only 5 cases.[1,5,11,15,19] There is evidence that thickening of the dura mater surrounding the optic nerve[7,8] may cause optic nerve constriction and eventual optic atrophy. In our second case, the optic discs appeared to be edematous bilaterally, which was thought to be due to pseudotumor cerebri. Appearance of papillaedema[8,10,18] and pallor of the optic disc[11] have been reported in other cases.

Venous dilatation on ophthalmoscopy was mentioned only in 1 case in the literature and was thought to be related to cranial venous dilatation and prominent fontanels.[12] We have not observed venous dilatation in our cases.

ERG and PVER tests in our first and third cases showed nearly normal responses. In Manouvrier-Hanu's case, impairment in the PVER responses was found.[11]

Band keratopathy, seen in our third case, has not been cited in this disorder in the literature. Keratoconus has been mentioned only in Wajntal's cases.[7] In these cases, optic atrophy was absent, instead, the patients had glaucoma.

Glaucoma was present in 5 of all reported cases, including 2 of ours.[7,11,20] All cases, except Mullaney and colleagues', were bilateral. There was no report of glaucoma in the right eye in their description.[20] Increased production, decreased breakdown, or both, of extracellular matrix macromolecules, mainly collagens, were considered to contribute to an excessive deposit, with loss of the trabecular cells during the development of primary open-angle glaucoma (POAG).[21] Marked changes in the distribution and the quantity of elastin in the trabecular meshwork have also been reported in POAG.[22] An excess of extracellular connective tissue matrix,[7] and the presence of abnormally shaped elastic fibrils[23] demonstrated in autopsy and ultrastructural studies may explain the pathogenesis of glaucoma in GAPO.

Although protruding eyes are thought to be due to shallow orbits, prominent globes due to buphthalmia were seen in 2 of our cases. Isolated nystagmus has been reported in this syndrome.[3,5,8]

The other ophthalmological finding in our cases was thinning of hair in the sparse eyebrows. The thickness of the epidermis with epithelial ridges and residual hair follicles surrounded or filled with homogenous material[7] might account for the alopecia. However, Fuchs and Resenman[3] mentioned broad, long, and dense eyelashes. Our cases exhibited white eyelashes, a finding not mentioned by other investigators. This may suggest "early senility." Although the lids seem to be swollen in all cases, in our fourth case and in Wajntal's first case,[7] bilateral ptosis was seen.

An ectodermal dysplasia-like process has been suggested as the pathogenesis of this syndrome,[1,4] and nearly all manifestations have been connected with this. Wajntal et al[7] demonstrated the presence of excess homogenous amorphous hyaline material in all organs and interstitia as well as in the serous membranes. These authors attribute such an increase in extracellular components to decreased breakdown of one or more components rather than their overproduction. The excess extracellular connective tissue matrix that accumulates during a lifetime may interfere with normal functioning of tissues and organs.

Autopsy studies by the same authors showed that the dura mater surrounding the optic nerve may be thickened due to infiltration and may cause a physical compression of the optic nerve.[7] In tomographic studies, an apparent thickening of the optic nerve was evident.[8] The reduction in the number of retinal ganglion cells and optic atrophy may be secondary to the nerve constriction. Hypophoria, retinoschisis, hypermature cataract, and atrophy of the ganglion cells of the retina were reported in autopsy studies in Wajntal's first case,[7] but are not mentioned in other GAPO patients.

Widespread interstitial fibrosis was found in Andersen and Pindborg's patient.[1] On the other

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hand, nothing unusual was noted in an auxillary skin biopsy taken from Gorlin et al's [4] patient, or in the thigh and scalp biopsies from the patient of Phadke et al.[16] The recent ultrastructural work on skin biopsies of our cases showed that the presence of abnormally shaped elastic fibrils and the lack of deposition of elastin may prove significant in pointing to an elastin defect.[23] Excess subcutaneous and interstitial collagenous tissue, either as a result of overproduction or decreased breakdown, might be secondary. These changes may be related to the "coarse" appearance of the affected individuals.

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