Case Report

GAPO syndrome: first Egyptian case with ultrastructural changes in the gingiva


We report on a 3-year-old boy with growth retardation, alopecia, pseudoanodontia, and optic atrophy. This is the 18th known and the first Egyptian case of GAPO syndrome. Electron microscopic examination of gingival biopsy showed excessive collagen fibres and endothelial vacuolisation, suggesting involvement of extracellular pathological collagenosis.

The GAPO syndrome (MIM 230740) is the acronymic designation for a complex of growth retardation (G), alopecia (A), pseudoanodontia (P), and optic atrophy (O). Main characteristic facies are frontal bossing, high forehead, midfacial hypoplasia and wide-open anterior fontanelle. This peculiar phenotype makes diagnosis possible in most cases by the age of 6 months. This syndrome was first reported by Anderson & Pindborg (1947). To date, 17 cases from 11 families have been reported: two Danish girls from different families (Anderson & Pindborg, Sandgren 1995), one Jewish girl of Moroccan origin (Fuks et al. 1978, Shapira 1982), one American girl (Tipton & Gorlin 1984), six Brazilians (four males and two females) from three different families (Da Silva 1984, Gagliardi et al. 1984, Wajntal et al. 1990), one Algerian girl (Manouvrier-Hanu et al. 1987, Dellac 1990), three Turks (two males and one female) from the same family (Sayli & Gul 1993), two Indian girls from the same family (Phadke et al. 1994), and one Japanese girl (Moriya et al. 1995). Skin biopsy and/or autopsy have been performed on a few cases of GAPO syndrome. We report on the first Egyptian case with GAPO syndrome with special emphasis on its pathogenesis.

Clinical report

A 3-year-old boy was referred, because of deterioration of vision and alopecia. He had two older normal sibs. His parents were healthy first-cousins from Menia city, in upper Egypt. They were 33 years old at the time of his birth. Pregnancy was uneventful and delivery was induced. There was a 2-week delay with respect to the expected term. Birth weight was 5000 g (+3 SD). The boy had a somewhat peculiar facies and some dark scalp hair.

At the age of 3 months he underwent circumcision and had bleeding from the site, which necessitated stitches. When he was 5 months old he manifested signs of facial palsy, which responded to treatment and resolved within a few days. Another similar attack of facial palsy occurred at 18 months of age. Within 1 year, he became virtually bald with sparse fair-colored, brittle hair. By the age of 2.5 years, he started to complain of progressive deterioration of vision and developed horizontal nystagmus. He sat at 6 months and walked at 15 months, indicating normal psychomotor developmental milestones. There was no similar condition in the family.

On examination, his weight was 12.5 kg (−2 SD), height 87 cm (−2 SD), and head circumference (OFC) 47 cm (−2 SD). His head had an irregular configuration (plagiocephaly) with two midline bony prominences, one posteriorly measuring 2×3 cm, and the other anteriorly around the anterior fontanelle measuring 4×1.5 cm. The anterior fontanelle was still open. He had alopecia with only a few light-colored hairs distributed over
the scalp. His peculiar facial appearance (Fig. 1 and 2) included telecanthus, bilateral proptosis bulbi, puffiness of the upper eyelids, esotropia, fair-colored sparse eyebrows and eyelashes, depressed nasal bridge, anteverted wide nostrils, thick everted lower lip, long prominent philtrum and large ear lobules. His hands were square with moderately hyperextensible joints. Palmar dermatoglyphics showed 8 whorls, one double whorl and one ulnar loop. He had bilateral high axial triradii (t'). His chest, heart, abdominal, genital and neurological examinations were normal.

Dental examination revealed edentulous jaws and thick alveolar ridges (Fig. 3). Panoramic X-ray film of the patient showed that the mandible was crowded with deciduous and permanent teeth, neither of which were erupted. The periapical roentgenogram of the lower anterior teeth (Fig. 4) showed unerupted deciduous and permanent teeth. Skull radiographs showed open anterior fontanelle and patent sutures (Fig. 5). CT brain scan was normal, but magnetic resonance imaging (MRI) of the brain showed bilateral and rather symmetrical hypersignals at the deep parietal and occipital periventricular region and around the optic nerves (Fig. 6 and 7), during T2WI. These patches had strict white matter distribution suggestive of demyelinating lesions. Fundus examination showed bilat-

Fig. 1. Frontal view of the patient showing alopecia, telecanthus, bilateral puffiness of upper eyelids, sparse eyebrows, depressed nasal bridge, anteverted wide nostrils, thick everted lower lip, long philtrum and large ears.

Fig. 2. Lateral view of the patient showing prominence over anterior fontanelle and the same facies as Fig. 1.
Fig. 3. Upper and lower edentulous thick alveolar ridges.

Fig. 4. Periapical film of the lower anterior teeth showing unerupted deciduous and permanent teeth.

eral optic atrophy. Visual evoked potential using flash stimulation revealed absent response on binocular stimulation and on stimulation of each eye separately, which indicated impairment of the visual pathway. Abdominal ultrasound revealed minute cystic spaces in the right kidney, but renal computed tomography (CT) and renal function tests were normal. His thyroid profile was normal, but his bone age was delayed. Ultrastructural examination of a mucosal biopsy from gingiva revealed dense bundles of thin collagen fibres in the subepithelial layer, and hypertrophied, vacuolated endothelial cells lining the numerous venous capillaries (Fig. 8).

Discussion
In 1947, Anderson & Pindborg described the first case of this syndrome. The frontal bossing, high forehead, midface hypoplasia, wide open fontanelle and growth retardation suggested a skeletal dysplasia, while the alopecia and dental anomalies were suggestive of ectodermal dysplasia. Anderson & Pindborg (1947) proposed a new syndrome characterized by ectodermal dysplasia associated with craniofacial dysostosis. Tipton & Gorlin (1984) suggested the name GAPO for this new syndrome. Fifteen other cases have been reported from differ-
GAPO syndrome could be explained by the high inbreeding coefficient in this geographical area (Krieger 1972). Parental consanguinity was present in 10/17 of the GAPO cases. Affected sib(s) or relative(s) were documented in two Brazilian families and in a Turkish one, where the parents were consanguineous (Gagliardi et al. 1984, Wajntal et al. 1990, Sayli & Gul 1993). The parents of our case were first-cousins. The present case had growth retardation, alopecia, pseudoanodontia and optic atrophy, which are characteristics of GAPO syndrome. Review of all published cases showed that growth retardation, alopecia and pseudoanodontia were present in all documented cases. However, optic atrophy was present in only 5/17 cases (Anderson & Pindborg 1947, Shapira 1982, Manouvrier-Hanu et al. 1987, Phadke et al. 1994, Sandgren 1995). Other eye manifestations such as glaucoma, nystagmus, keratoconus, chronic choked optic disks, entropion and papilloedema with dilated retinal veins were documented by various investigators (Gagliardi et al. 1984, Tipton & Gorlin 1984, Wajntal et al. 1990, Sayli & Gul 1993, Moriya et al. 1995). Absent eye manifestations have been reported by Da Silva (1984), Sayli & Gul (1993) and Sandgren (1995). Nystagmus and abnormal visual evoked potential (VEP) were detected in our present case. He has normal genitalia, although hypogenitalism was previously reported (Da Silva 1984, Gagliardi et al. 1984, Wajntal et al. 1990). Computed tomography of the brain showed no abnormality. This finding is similar to that reported by Moriya et al. (1995). However, the MRI showed white matter changes in the parieto-occipital periventricular region and around the optic nerve (Fig. 6 and 7).

Fig. 5. Skull radiography showing open anterior fontanelle.

Fig. 6. MRI of brain showing typical prominent bilateral "increase in signal" at the deep parietal and occipital periventricular region.
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Fig. 7. MRI showing hyperintense signals along the optic nerve.

Fig. 8. Electron microscope picture of gingiva showing dense collagen fibres (CO) in the subepithelial layer. The endothelial cells (END) lining the venous capillaries show hypertrophy and vacuolisation.

Life expectancy seems to be reduced in GAPO syndrome, as the oldest patient died at 39 years (Gagliardi et al. 1984). It was reported that GAPO syndrome is a progeroid syndrome with possible association of various complications, e.g. polycystic kidney (Andersen & Pindborg 1947), increased intracranial tension (Gagliardi et al. 1984) or cerebrovenous circulatory anomalies (Manouvrier-Hanu et al. 1987). Autopsy showed widespread interstitial fibrosis and generalised atherosclerotic changes (Wajntal et al. 1990). Data on skin histology are available in five cases. Wajntal and his co-workers (1990) compared the skin biopsy findings of a patient with GAPO syndrome aged 19 years to another biopsy 8 years later. The first skin biopsy showed preserved epidermis with clumps of homogeneous amorphous hyaline material in the dermis. The second biopsy showed severe atrophy in the epidermis with increased hyaline material and hair follicle atrophy. In another study, microscopic examination of the skin biopsy of a 21-year-old Turkish case showed thin epidermis and increased amounts of collagenous fibres with absent or sparse hair follicles (Sayli & Gul 1993). On the other hand, normal skin biopsies were reported by Tipton & Gorlin (1984) and Phadke et al. (1994). However, their patients were young: 8 years and 5 years old. It seems that the amount of the extracellular collagen material increases with age. The electron microscopic examination of the gingival biopsy of our
3-year-old patient showed excessive collagen fibres and endothelial vacuolisation. Electron microscopic studies of collagen from cultured fibroblasts did not show any collagen abnormalities in a 20-year-old patient studied by Wajntal et al. (1990), although her skin biopsy showed increased collagenous material. Therefore, our findings support the observation by Sayli & Gul (1993) that the increasing deposits of extracellular collagen fibres, together with the decreased number of elastic fibres, are the cause of the coarse and senile appearance of affected GAPO individuals. The basic defect was suggested to be an autosomal recessive defect in an enzyme responsible for breaking down extracellular material (Russell et al. 1992).

In conclusion, we emphasise the importance of studying skin, conjunctival or gingival biopsies using the electron microscope, because the pathogenesis of the GAPO syndrome seems to be associated with an excess of the extracellular collagen material that accumulates during life. This might interfere with the normal function of tissues and organs. Also, we suggest that the letter O in GAPO syndrome should stand for ocular manifestations rather than optic atrophy, as optic atrophy is not a constant feature of the syndrome.

References


