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GAPO Syndrome in Three Relatives in a Turkish Kindred

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GAPO syndrome in 2 sibs (brother and sister) and in a first cousin presented slight variations in the clinical picture. These include presence of some body hair, white eyelashes, deep furrows on sternum and back, disproportional body build, and minor skeletal abnormalities. It has been suggested that the athletic appearance of affected individuals is most likely due to the excessive amount of connective tissue. © 1993 Wiley-Liss, Inc.

KEY WORDS: GAPO syndrome, growth retardation, alopecia, pseudoanodontia, autosomal recessive inheritance, glaucoma

INTRODUCTION

Until mid-1990, GAPO syndrome [McKusick 230740] was reported in twelve individuals from 7 different families, the last one being the case of Manouvrier-Hanu et al. in 1987 [Andersen and Pindborg, 1947; Epps et al., 1977; Fuks et al., 1978; Gorlin et al., 1978; Shapira et al., 1982; Wajntal et al., 1982, 1990; Gagliardi et al., 1984; Silva, 1984; Tipton and Gorlin, 1984; Manouvrier-Hanu et al., 1987; Dellac et al., 1990]. We report on 3 additional cases, two sibs and a paternal cousin from Türkiye. They are the first patients reported from this country.

CLINICAL REPORTS

Propositus, M.C. (Fig. 1, IV-6), male, was born in 1971 in Samsun at the Black Sea. He came to our attention because he was called to military duty (no male being exempted from military service in Türkiye). He was referred to Gülhane Military Medical Academy Hospital in Ankara for a thorough examination and consultation. However, he himself and his family were familiar with the abnormalities not only because these were present from early months of life but also because 2 other relatives, one sister and a cousin had the same condition (Fig. 1, IV-1 and -10). The family is a Turkish native of the Black Sea shore.

On physical examination, he was a short, stocky man with an unusual and characteristic appearance (Fig. 2). Height was 144 cm and weight 47 kg. There was no scalp hair, except for a few loose tufts on the back of the lower scalp, pale brown in color, rather long, but very thin in texture (Fig. 2). He described his hair as abundant as that of his younger sister, both having normal hair in the first 2 to 3 months of life. Four small irregular telangiectatic plaques lying side-by-side were also noted on the occiput. Hypotrichosis also affected the face; he has never shaved (Fig. 2). He had a large, slightly protruding forehead with prominent supraorbital ridges and globes. Eyebrows were barely indicated as a few thin hairs, eyelids were thick, eyelashes were present but white, and irises light blue. The teeth were unerupted, although they were present on a panoramic roentgenogram; thus he had pseudoanodontia (Fig. 3). There were 3 remnants of enamel of the maxillary teeth. He had midface hypoplasia, a striking facial appearance and grossly wrinkled skin with deep furrows particularly on the forehead and periorbital regions because of an excess of subcutaneous tissue. The distance between eyebrows and eyes were enlarged. The palate was rather shallow, the philtrum was long, and both lips, especially the lower one, were conspicuously thick but the chin was small. Yet as a whole, the expression of the face seemed child-like. His speech was low-pitched.

The neck was long and enlarged with a little tuft of hair at the back as mentioned above, and minimally webbed. The chest was asymmetrical and on the left the sternal furrow was enlarged. There also was abundant body hair, brownish in color (contrasting with scalp and face), increasing inferiorly and merging with that of the pubis. On the back, another furrow just over the vertebral column from the lower ends of both scapulae to the middle of the sacrum was present. Increased lordosis and umbilical hernia were noted. The genitalia seemed to be enlarged, most probably because of sub-

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The cases were reported with a heading "Progeroid Syndrome with the Excess of Connective Tissue Fibers—A new Entity?" as a poster in 24th Annual Meeting of the European Society of Human Genetics held on 29 May–1 June 1992 in Elsinore, Denmark.

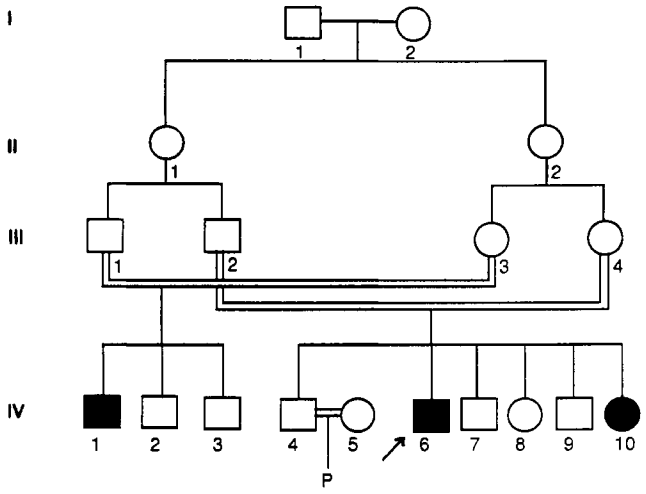

Fig. 1. Partial pedigree. Only relevant individuals are shown.

cutaneous tissue abundancy, as on other parts of the body. Both pubic and axillary hair were scanty. He described his sexual behavior as normal; however, he failed to ejaculate.

He had short arms and forearms relative to chest and abdomen, short broad hands, and hypermobile joints with hyperconvex finger nails. Lower limbs also were proportionately short, the feet being broad. Muscles were conspicuous in almost all parts of the body in an athletic manner. He stated his sweating is normal. In addition to the hemangiomatous plaques over the occiput, there was a hypopigmented area about 2 × 2 cm. His psychomental development was normal, yet he appeared somewhat slow in motor activities.

Results of all laboratory tests, including hormone profiles, were normal. Audiometric analysis showed a slight bilateral conductive type of hearing loss and eye examination showed left scotomas; measurement of tension was 28 and 37 mm Hg (appl) on the right and left eye, respectively. X-ray examination documented thickened long bones of the limbs with some tubular disarrangement, medial exostoses on the upper tibiae, square pelvis, osteoacrolysis of both hands, vertebral abnormalities, localized kyphosis, and scythe-like ribs (Fig. 4). Muscle hypertrophy was also evident.

Skin biopsy specimens processed as usual showed a thin epidermis, slight hyperkeratosis, increased amounts of collagenous fiber, and either absent or sparse hair follicles in different parts of the specimen.

Other Relatives

F.C. is the younger sister of the propositus (Fig. 1, IV-10), 9 years old. She was an exact but smaller copy of her brother. She too had slightly disproportionate short stature. Her height was 108 cm and weight 18 kg. Her arms just reach the upper one-third of the legs. She also had the characteristic facial appearance without any further malformation, and seemed healthy and of normal psychomental development; in some respects she probably was superior in mental abilities.

The head appeared larger than normal and protruded forward from frontal bones, making the forehead conspicuous anteriorly and superiorly. The veins were superficial. On top of the scalp there was a hypopigmented spot 2 × 2 cm with irregular boundaries, and a telangiectatic plaque of about 2 × 3 cm in diameter on her neck. The scalp was completely devoid of hair, except for a loose tuft of dull-colored long hair spreading from the occiput down to neck. She had a full head of hair until

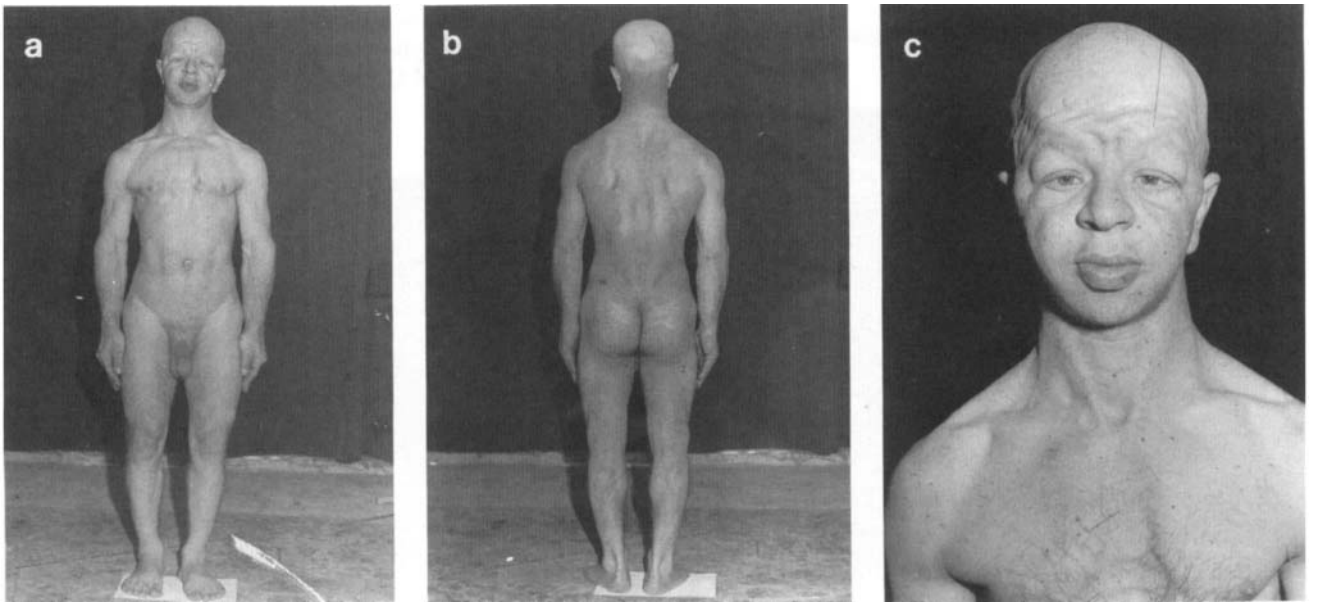

Fig. 2. **a–c:** M.C., the propositus; front and back views. Note the tuft of hair over the neck and furrowed back, and hairs over the body.

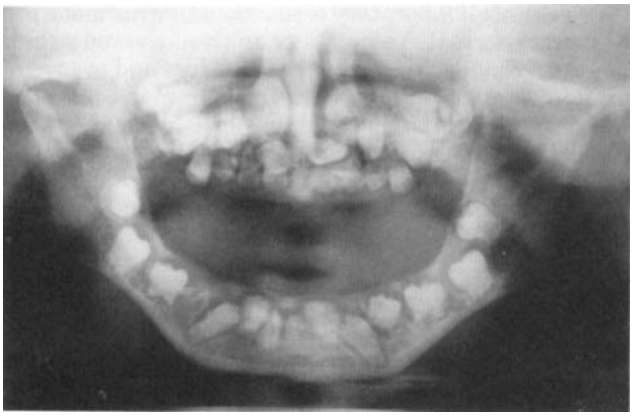

Fig. 3. Panorex film showing unerupted teeth of including incisors, canines and premolars.

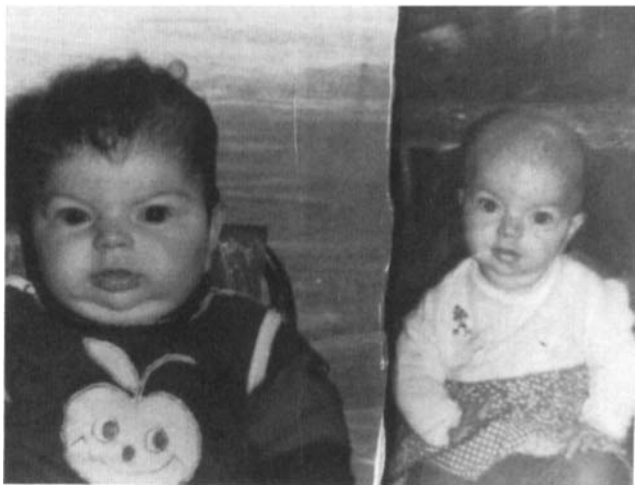

Fig. 5. F.C. before age one year. Note the abundance of scalp hair compared to later hypotrichosis.

about age 3 months; within one year she became virtually bald (Fig. 5).

Skin of the forehead was grossly wrinkled. She had a peer eyebrow hair only on the lateral aspects; eyelashes were scanty with normal intraocular tension. Periorbital tissue was abundant and irises were bright blue, being familial. Slight hypertelorism, depressed nasal bridge, and normal nostrils were other findings. Philtrum was enlarged, more at the base. Both upper and lower lips were thick, the lower being more conspicuous. Lower and upper jaws were somewhat hypoplastic. No permanent teeth were present; however, they were clearly seen in a panoramic roentgenogram.

Her neck appeared long with the deltoid muscles assuming a web-like appearance. Chest was normal though the sternal furrow was enlarged, more in its lower segment. Heart sounds were normal and no organomegaly was present, although the abdomen seemed protruding. An umbilical hernia was noted. On the back, a median deep furrow and increased lordosis were seen. It was interesting that there was a tuft of light-colored hairs in the lumbosacral region. External genitalia appeared normal with no pubic hair at all. No breast development was noted. There was some hair over forearms too.

Distal joints of the fingers were hyperflexible and easily broken hyperconvex nails were noted; she likewise appeared extremely muscular. Results of laboratory tests have so far been normal.

A.R.C. (Fig. 1, IV-1) is the third person with the condition. This man, also born to first-cousin parents, is 17 years old, lives in his native village, and is student in high school. Initially we were unable to examine him, but the condition was so convincingly described by the relatives that no doubt was left about the diagnosis. He then accepted our invitation to be studied and he was found to be an exact copy of M.C. with few variations, if any (Fig. 6). His height is 143 cm and weight 42 kg. Face was hyperemic and covered with acneform lesions, excessive wrinkling of palms and soles and early operations for bilateral glaucoma were differences to be mentioned (Fig. 6). M.C. and A.R.C. had hypermetropic astigmatism.

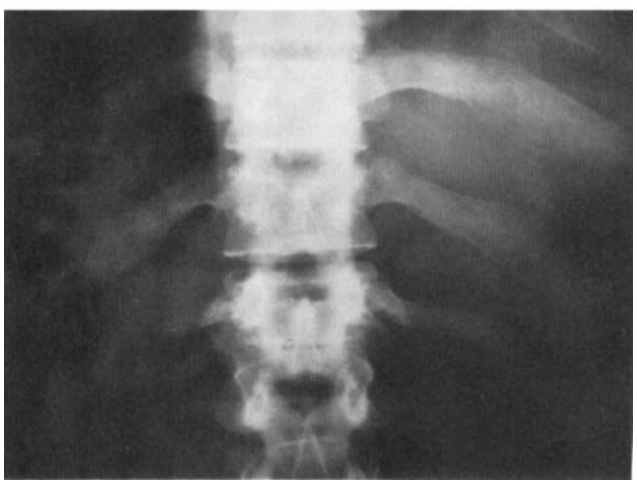

Fig. 4. Roentgenogram of lower thoracic spine of propositus. Note asymmetrical development of 12th pair of ribs with massive increase in width (inferior portion) of proximal portions of ribs.

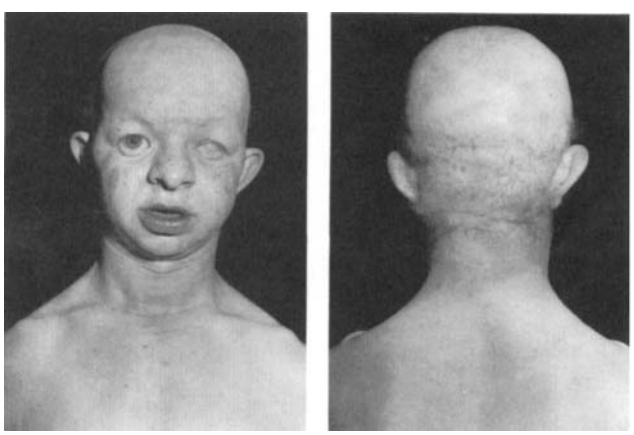

Fig. 6. A.R.C, a paternal cousin, and the third case. Left eye developed severe glaucoma and band keratopathy.

The father of the propositus, aged 41 years, is quite normal as is his wife, aged 40 years (Fig. 1, III-2 and -4). They live in their native village and are first cousins. No other relatives were described as having any of the signs and symptoms of this condition.

DISCUSSION

The patients presented here are typical examples of the GAPO syndrome of growth retardation, alopecia, pseudoanodontia, and optic atrophy, first reported in 1947 by Andersen and Pindborg. The acronym GAPO syndrome was coined in 1984 by Tipton and Gorlin, and the condition is catalogued as No. 230740 by McKusick [1992]. It is clear that this autosomal recessive disorder is extremely rare [Wajntal et al., 1990], and with the present 3 cases, the total number, to the best of our knowledge, is increased to 15.

The clinical picture of the GAPO syndrome is impressively constant. Shortness simulates a rhizomelic type of dwarfism. The body build is generally very muscular and seemingly athletic. All patients have a strikingly characteristic facial appearance. Wajntal et al. [1990] demonstrated the presence of excess homogenous amorphous hyaline material in all organs and interstitia as well as in serosal membranes. These authors attribute such an increase of extracellular components to the decreased breakdown of one or more component(s) rather than its overproduction. However, more work has to be done to elucidate the underlying pathogenetic mechanism. The contribution of such a defect to optic atrophy which is not invariable, as is the case for our patients, remains unknown. None of the cases have optic atrophy, but 2 have glaucoma, making the likelihood that the former is secondary.

While some patients are born with complete alopecia, some, as is the case for the present patients, have apparently normal scalp hair, and while cranial alopecia and facial artrichosis are invariably present, there is some body hair, almost normal in distribution and amount.

In some cases of GAPO syndrome, atrichia was noted at birth [Wajntal et al., 1990] but the authors found no pubic or axillary hair when reexamining their patient at age 27 years. However, his sister was born with scalp hair.

Occurrence of other findings such as white eyelashes, presence of hair on different parts of the body, rhizomelic body build, abnormalities involving costae and tubular bones, deep furrows on sternum and the back, as well as white plaques, suggests that pigment disorder is also involved. We have the impression that the childish appearance of the face has to be taken into consideration in differentiating this from other progeria syndromes.

The thinness of epidermis with the lack of epithelial ridges and residual hair follicles surrounded or filled with homogenous material [Wajntal et al., 1990] might account for alopecia. That our cases additionally exhibited white eyelashes, a finding not mentioned by other investigators, suggests an "aging" event is also in operation. Wajntal et al. [1990] found viscera as well as arachnoid membrane thickened in association with a "coarse" material in gross appearance. Microscopically, there was an increase of an amorphous hyaline substance in all organs and interstitia. Electron microscope studies showed no collagen abnormalities, although small numbers of elastic fibers and thickened collagenous fibers have been noted. Such an organization is compatible with our interpretation that subcutaneous and interstitial collagenous tissue is responsible for the "coarse" appearance of affected individuals.

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