Sibs With Growth Deficiency, Delayed Bone Age, Congenital Hip Dislocation, and Iridocorneal Abnormalities With Glaucoma

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We report on a brother and sister with short stature, delayed bone age, developmental delay, congenital hip dislocation, and iridocorneal abnormalities with onset of glaucoma at or soon after birth. Results of endocrine evaluation were normal. To our knowledge, no similar pattern of defects has been reported previously.

KEY WORDS: short stature, developmental delay, autosomal recessive, familial occurrence

INTRODUCTION

Iridocorneal dysplasia has been reported in combination with short stature and delayed osseous maturation as part of the SHORT syndrome [Gorlin et al., 1975; Sensenbrenner et al., 1975; Toriell et al., 1985]. We report on a brother and sister with a unique combination of iridocorneal abnormalities and congenital glaucoma, short stature with delayed osseous maturation, congenital dislocation of the hips, developmental delay, high umbilicus, and minor foot anomalies, but lacking the triangular face and lipoatrophy of the SHORT syndrome.

CLINICAL REPORT

Patient 1 was the first child of healthy, nonconsanguineous parents. There was no toxin exposure or known diabetes mellitus. The mother had a 4-day febrile gastroenteritis in the third gestational month and was treated for a urinary tract infection in the sixth month. Delivery was at term, with birthweight of 2,159 g (−3.5 SD) and length of 47 cm (15th centile). OFC was not recorded. He was seen elsewhere neonatally with the possible diagnoses of Donohue or Seckel syndrome. Bilateral hip dislocation was treated with triple diapers with apparent resolution.

When seen by us at 27 months, he had already undergone bilateral goniotomy for glaucoma. His length was 82 cm (−6 SD), weight was 9.0 kg (−4 SD), and OFC was 47 cm (5th centile). Pertinent physical findings (Fig. 1) included a posteriorly sloping skull with prominent occiput, mild micrognathia, slightly downslanted palpebral fissures with prominent globes and enlarged corneas, measuring 13.5 mm horizontally OU. Inner canthal, interpupillary, and outer canthal distances were all at the 10th centile. The nasal bridge was prominent with somewhat small nasal alae. The teeth appeared normally configured. The umbilicus was high (Fig. 2). Genitalia were normal. Total hand length was 5.7 cm (10th centile). Fingertip dermatoglyphics included 8 whorls and 2 ulnar loops. There was pes planus with prominent heels and dorsally placed left 2nd and 5th and right 2nd toes. The metacarpophalangeal joints were hyperextensible, but no large joints were involved. Bone age on hemiskeleton at 27 months should have 32 + 12 epiphyseal ossification centers. Our patient had 5, all of which appeared radiographically normal.

At age 36 months, his height was 78.7 cm with an arm span of 73 cm. Upper to lower segment ratio was 1.23 (normal value for a 4-year-old male). Total T4 was 11.3 (upper limit of normal) with a normal TSH of 5.3. Serum electrolytes, calcium phosphorus, SGOT, alkaline phosphatase, iron, TIBC, and ferritin were all normal. Baseline growth hormone was 10.4 and somatomedin C was 20 μg/ml. Chromosome analysis was 46,XY.

The mother's second pregnancy was monitored by serial ultrasound examinations, with normal intrauterine growth of patient 2, who was delivered at term. Birth length was 48 cm and weight 3,268 g. The corneal diameters were 11 mm in the newborn period, with intraocular pressures of 14–16 mm Hg. Radiologic skeletal survey showed no ossified epiphyses, and bilateral hip dislocation. The optic discs were abnormal, with large cups.
Progressive changes prompted bilateral goniotomy at age 2 months.

Congestive heart failure developed, and a ventricular septal defect (VSD) was diagnosed by catheterization. She was initially treated with digoxin and diuretics, but continued poor weight gain and continuing heart failure prompted surgical repair at age 3 months. She then developed respiratory syncytial virus pneumonia requiring 6 days of respirator support.

At 4 months she had a length of 54 cm (−4 SD), weight of 3.63 kg (−4 SD), and OFC of 39.2 cm (<50th centile). Facial appearance was similar to that of her brother (Fig. 3). She also had a high umbilicus (Fig. 4), anteriorly placed anus, hypoplasia of the labia majora, right simian and left bridged palmar creases, dorsally placed 2nd toes, and prominent heels. Skeletal survey showed only ossification of the distal femoral epiphysis (normal for 36 weeks gestation). Because of the patient’s medical problems and normal laboratory results in her brother, the parents have been resistant to allow extensive endocrine evaluation.

A neurodevelopmental evaluation was performed by a multidisciplinary team using the Bayley Scales of Infant Development, Early Learning Activity Profile, Clinical Linguistic and Auditory Milestone Scale, and Zimmerman’s Preschool Language Scale. Both patients demonstrated mild to moderate delay in all areas.

Minimal scatter within each skill level was noted except for expressive language in patient 1, which was at the 36 month level. He was neurologically normal, however, his severe impulsivity and easy distractability was atypical of a 44-month-old even when his mild cognitive delays were taken into account. Patient 2 had mild hypotonia, normal DTR’s, and delayed protective reflexes.

**DISCUSSION**

These sibs present with a unique combination of defects. Both had iridocorneal abnormalities, dislocating hips, high umbilicus, minor foot abnormalities, delayed skeletal maturation with short stature, and developmental delay.

The eye abnormalities consisted of bilateral dysgenesis involving the anterior segment, megalocorneae, and secondary glaucoma, with large optic nerve cups. Each child appears to have had an initially favorable response to goniotomy.
which include both the Axenfeld and Rieger anomalies. The corneas of both children show a peripheral ring which represents a prominent, anteriorly displaced Schwalbe's line (posterior embryotoxon). Examination of the angle structures shows that patient 1 had many fine strands of iris tissue fused to the posterior embryotoxon. This finding was absent in patient 2. Both sibs have stromal iris hypoplasia and diffuse iris transillumination.

Hypothyroidism can cause a delayed skeletal maturation and short stature, but its effects are not seen until after birth. Patient 1 was short at birth, and high normal levels of thyroid hormone and normal thyroid stimulating hormone make thyroid deficiency unlikely. Growth hormone (GH) deficiency may also cause short stature and delayed skeletal maturation. Its action is also postnatal. Isolated GH deficiency has been reported to occur with the Rieger syndrome (iridocorneal defect with characteristic face, umbilicus and abnormal teeth) [Sadeghi-Nejad and Senior, 1974]; however, not all of their patients with Rieger's syndrome had GH deficiency. Only one child in the family with Rieger syndrome reported by Feingold et al. [1969] had low GH levels. Our patients lacked the typical facial, dental, and umbilical findings of this syndrome. The SHORT syndrome, which includes Rieger anomaly of the eye and delayed bone age, was reported in brothers [Gorlin et al., 1975], and as 2 isolated cases [Sensenbrenner et al., 1975; Toriello et al., 1985]. We know of an unreported family with SHORT syndrome in at least 2 generations [Jorgenson, 1987]. Our patients lacked the triangular face and lipoatrophy seen in this syndrome, and the similar syndrome reported by Aarskog et al. [1983].

Iris hypoplasia with glaucoma has been described as an isolated defect [Weatherill and Hart, 1969]. De Hauwere et al. [1973] described a mother and her 2 children with iridocorneal dysplasia consistent with Rieger anomaly, developmental delay, and dislocated hips. They also had hypotonia, laxity of joints, and hypertelorism. The son had a bone age of one year at age 3½ years. The sister's length was at the 90th centile for age and sex at 9 months.

The megalocornea and mental retardation (MMR) syndrome [Neuhauser et al., 1975; Del Giudice et al., 1987] may also include short stature as a variable finding. None of these patients had reported bone age delay or high umbilicus.

In summary, we present a brother and sister with short stature, delayed skeletal maturation without evidence of an endocrine cause, developmental delay, high umbilicus, minor foot anomalies, and iridocorneal abnormalities with glaucoma. The presence of a VSD in patient 2 may be a variable part of their syndrome or a manifestation of a multifactorial trait expressed coincidently. To date, no similar constellation of abnormalities has been reported. Because both parents are free of any minor manifestations of their children's syndrome, we believe this is a previously unreported autosomal recessive syndrome, although gonadal mosaicism for an autosomal dominant syndrome cannot be ruled out.

REFERENCES

Fig. 4. Patient 2: age 10 months.