

Parental consanguinity in the blepharophimosis, heart defect, hypothyroidism, mental retardation syndrome (Young-Simpson syndrome)

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Abstract

In 1987 Young and Simpson reported a child with hypothyroidism, congenital heart disease, severe mental retardation, and striking facial dysmorphism. Two subsequent reports have described patients sharing some of the features of their case, although in both there were enough discordant features to make it uncertain that the same entity was being described. Here we present a female infant with virtually identical features to Young and Simpson's original case. Her Caucasian parents are first cousins, raising the possibility of autosomal recessive inheritance of this new syndrome.

(*J Med Genet* 1993;30:255-6)

Case report

The healthy, rubella immune mother, aged 21, smoked three cigarettes a day. A urinary tract infection at three months' gestation was treated with an unidentified antibiotic. Caesarean section was performed at 41 weeks for failure to progress in labour. Apgar scores were 2 at one minute, 4 at five minutes, and 6 at 10 minutes; the baby was hypotonic and required resuscitation. Birth weight was 4120 g (90th to 97th centile), length 53 cm (75th to 90th centile), and OFC 38 cm (97th centile). The father, aged 31, and mother are first cousins (through their father and mother respectively). The family is of Caucasian (Scottish/Irish) extraction.

Clinical examination at 7 months showed micrognathia and a posterior cleft of the hard and soft palate, ending just behind the anterior alveolar ridge. The feet had a postural calca-neovalgus deformity. There was truncal hypotonia and dystonia, with stereotyped extension of the upper limbs (mainly right) accompanied by extreme forearm pronation. There were also persistent purposeless trunk and head movements with roving eyes but no nystagmus. The skull showed occipital and frontal prominence and large anterior (75 × 58 mm) and posterior fontanelles. The ears were low set, with prominent antihelices and malformed lobules (figure). The palpebral fissures were short (18 mm, <<3rd centile). There was a prominent nasal bridge, flattened nasal tip, and triangular 'carp shaped' mouth, with a prominent but short philtrum and a deep mid-line groove arising from the lower end of the nasal columella (figure). There was a single

palmar crease on the left and bilateral single crease of the fifth fingers with clinodactyly. OFC was 43.5 cm (50th centile), weight 7.2 kg (10th to 50th centile). Developmentally, there was almost complete head lag; there was visual fixation and following through 180°, but no hand-eye coordination; objects were held and brought to the mouth. Overall, performance was delayed to approximately a 3 month level.

Chest x ray showed 11 pairs of ribs, with widening of the anterior ends. Echocardiogram indicated an atrioventricular canal. Karyotype was normal (46,XX) on two examinations. Cranial ultrasound was unremarkable. Urine and blood screen for amino and organic acids and TORCH serology were normal. Hypothyroidism was detected by the neonatal screening programme; at 13 days of age, free T4 was 10.5 pmol/l (normal 10 to 25) and TSH 146 IU/l (0.15 to 3.3). TSH was suppressed into the normal range by treatment with 40 µg thyroxine daily.

Discussion

Features shared by this case and the case of Young and Simpson¹ are: early hypotonia, developmental retardation, craniofacial dysmorphism (prominent occiput, short palpebral fissures, triangular mouth with short philtrum, micrognathia, prominent nasal bridge with flattened nasal tip), 11 pairs of ribs, congenital heart disease, and congenital hypothyroidism. Indeed, the only major discordant features are the cleft palate and absence of nystagmus in our case. The former might be expected to be variable if it is secondary to the mandibular hypoplasia (Pierre-Robin sequence). Our patient's weight and OFC at birth were large compared to the patient of Young and Simpson,¹ but, like the latter, have fallen away relative to the centiles. The presence of parental consanguinity in our family (of Caucasian northern European origin) suggests that this new syndrome may be an autosomal recessive single gene disorder, for which the eponym 'Young-Simpson syndrome' seems appropriate.

The present case is the only reported one exhibiting virtually all the features of the case of Young and Simpson.¹ However, there have been three other reports of patients with overlapping clinical features. A male infant who died shortly after delivery is the most convincing other case of this syndrome, although there was no congenital heart disease.² The thyroid was absent at necropsy. The sibs reported by

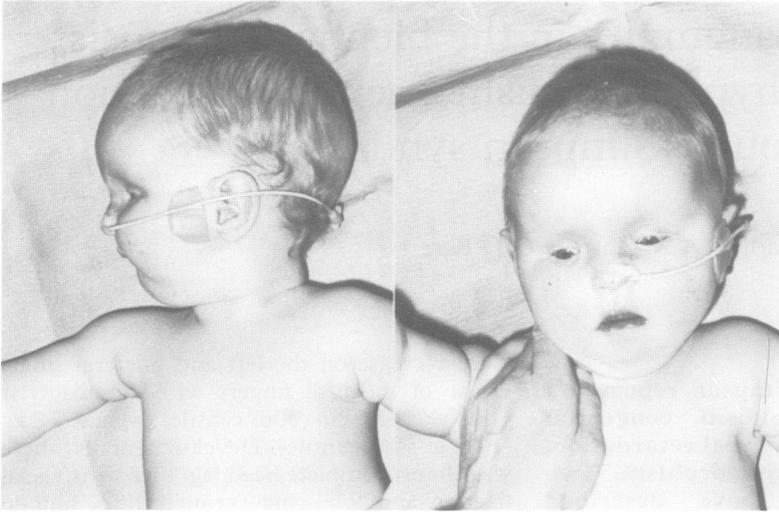
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Received 29 June 1992.
Accepted 13 July 1992.



The patient at 7 months showing prominent occiput and forehead, micrognathia, flat nasal tip, prominent nasal bridge, blepharophimosis (with epicanthus inversus on the left), short, prominent philtrum, and 'carp shaped' mouth.

Holmes and Schimke³ had mild hypothyroidism and congenital heart disease but very different facial dysmorphism and additional minor skeletal anomalies; the authors felt the syndrome was distinct. In a further possible case⁴ the facial dysmorphism again appeared rather different (philtrum long and prominent, rather than short; mouth small, and not carp shaped; nasal bridge flat, not prominent). In addition, there was postaxial polydactyly and no congenital heart disease. It is unclear whether this patient should be classified with that of Young and Simpson¹ and our own.

- 1 Young ID, Simpson K. Unknown syndrome: abnormal facies, congenital heart defects, hypothyroidism, and severe retardation. *J Med Genet* 1987;24:715-6.
- 2 Fryns JP, Moerman P. Unknown syndrome: abnormal facies, hypothyroidism, and severe retardation: a second patient. *J Med Genet* 1988;25:498-9.
- 3 Holmes GE, Schimke RN. Unknown syndrome in sibs: microcephaly, seizures, mental retardation, congenital heart disease, and skeletal abnormalities. *J Med Genet* 1989;26:665-6.
- 4 Cavalcanti DP. Unknown syndrome: abnormal facies, hypothyroidism, postaxial polydactyly, and severe retardation: a third patient. *J Med Genet* 1989;26:785-9.