J Med Genet 1995;32:668–672

LETTERS TO THE EDITOR

Anophthalmia with cleft palate and micrognathia: a new syndrome or an unusual presentation of Rubinstein-Taybi syndrome?

In the December 1994 issue of this journal I read with interest the brief paper "Anophthalmia with cleft palate and micrognathia: a new syndrome?" by Phadke *et al.*[1] The authors described a male neonate with bilateral anophthalmos in association with Pierre-Robin anomaly, abnormal genitalia, and normal chromosomes. They discussed the differential diagnosis of X linked Lenz syndrome, and proposed that their patient "represents a new syndrome of anophthalmia, cleft palate, and micrognathia". They also considered the possibility of a microdeletion of 14q as two patients with 14q22q23 deletions reported by Bennett *et al*[2] and Elliott *et al*[3] presented similar clinical manifestations.

During the past few years an increasing number of other syndromes with clefting and microphthalmia/anophthalmia/coloboma have been reported.[4–10] The syndrome of macrosomia, microphthalmia ± cleft palate, and early infant death delineated by Teebi *et al*[7] is an autosomal recessive multiple congenital anomalies syndrome. The association of uveal colobomata, cleft lip and palate, and mental retardation described by Kingston *et al*[4] is apparently inherited as an autosomal dominant trait, and also Edwards *et al*[5] documented vertical transmission of ocular defects, clefting, and dysmorphic features in a family.

In the past we have had the occasion to examine two unrelated male newborns shortly after their birth with an identical pattern of malformations (bilateral anophthalmos, Pierre-Robin sequence, hypospadias grade II-III). They were referred with the possible diagnosis of X linked Lenz syndrome and caused us serious difficulties in final diagnosis and genetic counselling. Both were first children of healthy, unrelated parents and were born after normal, term pregnancies. Birth weights were 2100 g and 2200 g, lengths 46 cm and 44 cm, and head circumferences 33 cm and 33·5 cm, respectively. CT scans of the brain confirmed the clinical suspicion of true anophthalmos without associated CNS malformations. High resolution chromosome studies showed a normal 46,XY male karyotype in both boys. We were not able to establish a final diagnosis in the neonatal period and followed them at regular intervals. Only after the age of 1 year did it become evident that both boys represented a somewhat unusual manifestation of Rubinstein-Taybi syndrome. Now, at their respective ages of 14 and 8 years, they still show significant postnatal growth retardation with growth parameters far below the 3rd centiles for age. The typical Rubinstein-Taybi symptoms (beaked nose with nasal septum extending below the alae nasi, a typical mouth with flat philtrum and thin upper lip, broad proximally implanted thumbs and halluces, fetal pads on short and broad terminal phalanges) became only clearly evident several months after birth.

Looking at the clinical photographs of the proband reported by Phadke *et al*,[1] several additional facial symptoms not discussed by the authors could be in favour of the diagnosis of Rubinstein-Taybi syndrome in this male newborn: low frontal and temporal hair implantation, broad forehead, bushy eyebrows, broad nasal bridge, nasal septum extending below the alae nasi, and long and smooth philtrum with fine upper lip. Failure to thrive was apparently severe with marked delay in motor development until the boy died at the age of 5 months.

Reviews on Rubinstein-Taybi syndrome describe this MR/MCA syndrome as a condition with pathognomonic symptoms which can be detected in the newborn period by characteristic thumb, hallucal, and facial abnormalities.[11] Our experience in the two male patients, briefly described in this letter, illustrates that the final diagnosis of Rubinstein-Taybi syndrome may be difficult and that follow up over the age of 1 year may be necessary.

Finally, bifid uvula, hypospadias, and ocular anomalies, including coloboma of the iris/retina, exophthalmos or enophthalmos, cataract, congenital glaucoma, and megalocorneae, have been reported as occasional associated findings in individual patients with Rubinstein-Taybi syndrome.[11] It would be of interest to hear whether others have followed Rubinstein-Taybi syndrome patients with the same, apparently rare triad of anophthalmia, Pierre-Robin sequence, and hypospadias grade II-III.

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Pallister-Hall and McKusick-Kaufmann syndromes

In their article Unsinn *et al*[1] describe a patient who, in addition to typical manifestations of Pallister-Hall syndrome (PHS) (hypothalamic hamartoblastoma, "central" polydactyly with Y shaped metacarpals), had hydrocolpos caused by vaginal atresia with vaginourethral fistula. The authors proposed that their patient had McKusick-Kaufmann syndrome (MKKS) and hypothesised that PHS and MKKS might be one entity.

Before genetic testing for verification of the specific diagnosis is available, the analysis of clinical manifestations in familial cases of any syndrome remains the best way for the precise delineation of its phenotype. A study of 43 familial cases of MKKS[2] showed that neither preaxial nor central forms of polydactyly have been reported. I do not remember vaginourethral fistulas in these patients either. These two manifestations in the patient of Unsinn *et al*[1] suggest another syndrome than MKKS.

Although anal atresia is one of the clinical manifestations of MKKS, the data by Reed and Griscom[3] do not confirm this because these authors described 26 patients with hydrometrocolpos, but only one or two of them had MKKS.

Virtually any defect may be a component of different syndromes. Hypothalamic hamartoblastoma, for example, has been described in cases with Varadi, Beemer-Langer, Meckel, distal monosomy 7q, and other syndromes.[4–6] The same is true for hydrocolpos.[2] Some syndromes overlap considerably with PHS, and MKKS is one of these.[5] The patient reported by Unsinn *et al*[1] confirms this overlap, which "reflects similarity in chronology and topography of the primitive event".[6] Although brain investigations in the patients with suspected MKKS should be done, there are no data confirming that MKKS and PHS may be one entity.

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