

only be accurately described using R and Q banding, imply that 4 chromosome breaks occurred: this raises the problem of such complex anomalies frequently reported in association with the 'cri du chat' syndrome (Catti and Schmid, 1971; Taillemite *et al.*, 1973; Berger *et al.*, 1974).

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Erythropoietic protoporphyria, heterozygous cystinuria, and reduced peptidase A activity in a patient with 46,XX/46,XX,18q—mosaicism¹

SUMMARY An interesting patient with a deletion of the long arm of chromosome 18 is presented. Her symptoms are severe in comparison with some other 18q— patients, yet she was found to have a mosaicism with a normal 46,XX karyo-

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type in about 20% of her cultured lymphocytes. In addition, she had erythropoietic protoporphyria, was heterozygous for type II or III cystinuria, and had reduced levels of peptidase A activity. Detailed studies on the patient, her family, and two additional 18q— patients suggest that the association with erythropoietic protoporphyria is coincidental and that the cystinuria gene was inherited from the patient's father. The reduced peptidase A activity, however, supports earlier observations that the peptidase A locus maps in the q22 to terminus region of chromosome 18.

A recognisable syndrome has emerged in association with a deficiency of part of the long arm of chromosome 18 which has been referred to by some as the 'carp-mouth' syndrome (Lejeune *et al.*, 1966). Cytogenetically, the deletion usually involves one-quarter to one-third of the terminal portion of the long arm. Most reported cases have been spontaneous. A few, however, have occurred in families where a balanced translocation involving chromosome 18 is segregating. At least 6 cases have been reported with mosaicism (46,XX/46,XX,18q—). In addition to the more common 18q— syndrome, several cases have been reported with deletions of the short arm of 18 and a few with ring 18 chromosomes.

The following report presents an interesting patient with the 'carp-mouth' syndrome.

Case report

This white female patient (K.B.) was born in 1967 after an uneventful pregnancy and delivery. She was the fifth of six children born to healthy, unrelated parents. The family history was negative, except for a maternal aunt with severe mental retardation of unknown aetiology. Our patient weighed 2.3 kg at birth, and presented a serious feeding problem from the third day of life. In 1966, she was evaluated for developmental retardation. A diagnosis of diffuse brain damage with mental retardation, ocular difficulties, severe hypotonia, and bilateral equinus deformity of the feet was made. Casts were applied to correct a left calcaneus valgus and right tibial torsion and forefoot varus. Her head size was 40 cm (5 cm below expectations). The fundi revealed greyish discs, but there was no hyperplasia of the iris and no Brushfield spots. The lower limbs were held in a frog-leg attitude. The deep tendon reflexes in the lower limbs were absent. There was no Babinski and no Moro reflex. Urine studies were negative for sugar, protein, acetone, and reducing substances. A ferric chloride test was negative. X-ray studies of the skull

and lumbar spine were normal. Routine blood chemistry was normal. An electroencephalogram, electromyogram, spinal tap, and an IVP were normal.

In 1967 she was placed in a home for retarded infants. She was able to move about freely but could not sit up or crawl. She continued to be a serious feeding problem.

In 1972 she became a resident of the West Seneca Developmental Center. Her height was still below the third centile for her age and her head circumference was 46.25 cm. Physical examination in 1974 disclosed profound mental and psychomotor retardation. Height was 105 cm, span 108 cm, symphysis to heel distance 52 cm, and weight 14 kg. She was microcephalic, with the head especially narrow in its lateral diameter. There was considerable generalised hypotonia. While not able to sit, stand, or walk, she was able to roll from prone to supine. Ears were low set with prominent antitragus, antihelix, and stenotic hypoplastic ear canals with impaired hearing. There was coarse bilateral horizontal nystagmus and myopia, but no ocular fundoscopic anomalies. The interpupillary distance was normal but there were median epicanthal folds. There was considerable midface dysplasia, with a prominent flat nasal bridge. The characteristic carp-shaped mouth was present and there was an uneven palate with arching to the right. There was a low hairline, mild pectus excavatum, and widely spaced nipples. There was a mild scoliosis with a convex curve to the right in the lumbothoracic region, and a congenital heart defect consisting of either a bicuspid aortic valve or minimal supra-aortic stenosis. There was hypoplasia of the labia majora. The hands were small with spindle-shaped fingers and proximally implanted thumbs. A simian crease was present on the left palm and all 10 digits showed whorls. The feet showed corrected talipes equinovarus, abnormal implantation of the toes, and lymphangiectatic oedema.

Giemsa banding studies showed a modal number of 46 chromosomes with a deletion of the long arm of chromosome 18 (46,XX,18q-). More recent studies have disclosed a mosaicism with 5 normal cells observed out of 25 total cells karyotyped. As part of a routine lead-screening programme, her free erythrocyte protoporphyrin (FEP) level was measured by the method of Piomelli *et al.* (1973). The result was a level of 250 $\mu\text{g}/100$ ml whole blood (normal < 40 $\mu\text{g}/100$ ml). A repeat specimen three months later showed an FEP level of 286 $\mu\text{g}/100$ ml, together with normal blood lead of 13 $\mu\text{g}/100$ ml, normal red blood cell indices, and normal uroporphyrin and coproporphyrin levels. Thin layer chromatography showed protoporphyrin to be the major component. The faecal protoporphyrin concentration was 237.0 $\mu\text{g}/\text{g}$ dry weight (normal < 30 $\mu\text{g}/\text{g}$), and the coproporphyrin concentration was 34.6 $\mu\text{g}/\text{g}$ dry weight (normal < 20

$\mu\text{g}/\text{g}$) with a P/C ratio of 6.9. These findings indicated that the high FEP was not the result of either iron deficiency anaemia or lead poisoning, but was, in fact, a true erythropoietic protoporphyria. In addition, a rapidly disappearing bright red fluorescence was seen when the erythrocytes were examined microscopically under ultraviolet light.

When urine was analysed, a selective aminoaciduria was found. The levels of two amino acids, lysine and cystine, were found to be very high and ornithine and arginine were in the high-normal range. These data, presented in Table 1, suggested that the patient was heterozygous for type II or type III cystinuria.

Family studies

The unusual association of a deletion of the long arm of chromosome 18, erythropoietic protoporphyria, and heterozygous cystinuria led to special studies being carried out on the patient's family. Cytogenetic studies on the parents revealed normal karyotypes. Blood group genotyping revealed no inconsistency in paternity (Table 2). The FEP levels in the parents and 5 sibs were within normal limits. Additional studies on the parents, including faecal protoporphyrin/coproporphyrin (P/C) ratios and direct microscopical observation of the erythrocytes under ultraviolet light also were normal, with the possible exception of a slightly raised P/C ratio in the father (Table 3).

Analysis of the parents' urinary cystine and lysine levels, summarised in Table 1, showed that the patient's father and all 5 sibs were heterozygous for cystinuria, while the mother's urine was normal.

Special studies

The FEP levels and the urinary amino acid patterns were examined in 2 additional patients with the 18q-

Table 1 *Urinary excretion of cystine and lysine in our patient (K.B.) and her parents, expressed as $\mu\text{mol}/\text{g}$ creatinine*

	Cystine	Lysine
K.B.	176	5096
Mr B.	174	1888
Mrs B.	20	164
Normals	8-89	40-490
Heterozygotes	65-755	390-2990
Homozygotes	1260-4940	2400-21 400

Table 2 *Blood group genotyping on the patient (K.B.) and her parents*

	ABO	Rh	MNS	Kell	Duffy	Kidd	P
K.B.	a ₂ B	R ₁ R ₁	NsNs	kk	Fy ^a /Fy ^b	JK ^a /	P/
Father	A ₁	R ₁ R ₁	MsNs	kk	Fy ^a /Fy ^a	JK ^a /	P/
Mother	B	R ₁ R ₁	NsNs	kk	Fy ^b /Fy ^b	JK ^a /	P/

Table 3 Special studies carried out on the patient (K.B.) and her parents

	Free erythrocyte protoporphyrin ($\mu\text{g}/100\text{ ml RBC}$)	Serum iron ($\mu\text{g}/100\text{ ml}$)	Red blood indices	Blood lead ($\mu\text{g}/100\text{ ml}$)	Faecal P/C ratio
K.B.	400	139	Normal	13	6.9
Father	30	119	Normal	—	4.4
Mother	37	140	Normal	—	3.8
Normals	20–80	60–120	—	0–40	1–4

syndrome. One of these patients was a male born in 1967 and the other was a female born in 1972. Both showed the characteristic clinical features of the syndrome, but were less severely affected than our patient. Neither was a mosaic, neither had erythropoietic protoporphyria, or was heterozygous for cystinuria.

Special studies were also carried out to determine whether hemizyosity (i.e. absence of an allele caused by location of the locus on the deleted segment) could be demonstrated. The Beutler consumption assay for galactose-1-phosphate uridyl transferase (Beutler and Baluda, 1966) gave a normal value of 24.8 enzyme units per g haemoglobin; antibody-crossed electrophoresis to identify the α -1-antitrypsin variant pattern (Federhol, 1969) indicated that the patient was homozygous MM; and the C'1 esterase inhibitor level was 5.1 U/ml (normal range 4.5 to 7.0 U/ml).

Quantitative estimation of the peptidase A activity in red blood cell haemolysates was carried out by the method of Sinha *et al.* (1970) and electrophoresis identification of peptidase A variants by the method of Lewis (1973). Results showed the peptidase A activity in two separate specimens to be 115 and 104 μmol val-leu hydrolysed/hr per g haemoglobin and the electrophoretic phenotype to be A-1. The normal range for A-1 phenotypes is 175 to 728 μmol , with a mean of 369. This relatively low level suggested the possibility of hemizyosity.

Comments

Erythropoietic protoporphyria (EPP) has not previously been found in association with a deletion of the long arm of chromosome 18. There is a single published report, however, of a pair of sibs with chromosome 18 abnormalities associated with an unusual hepatic porphyria of long standing (Simon *et al.*, 1973). The male sib was mosaic for a deletion of the short arm of chromosome 18 (46,XY/46,XY,-18p-), while his sister was mosaic for trisomy 18 (46,XX/47,XX18+). While the exact type of porphyria was not established in these patients, they did not appear to have EPP and the association with the chromosomal abnormalities were probably fortui-

tous. Whether or not the association of EPP with the 18q- deletion in our patient is significant remains to be determined. Our inability to detect the condition in the parents or two additional 18q- patients suggests that it resulted from a new mutation.

Sinha *et al.* (1970) noted that among subjects with the common electrophoretic phenotype Peptidase A 1, there was considerable variation in the activity of this red cell enzyme. This quantitative variation was found to be the result of a common electrophoretic polymorphism of the enzyme, called peptidase A 8 (Lewis, 1973). In our patient, as well as her parents, the electrophoretic phenotype was shown to be Pep A 1. Therefore, the reduced activity was not caused by the presence of a peptidase A 8 allele.

The structural gene locus for peptidase A has been assigned to chromosome 18 in man through the use of mouse-human somatic cell hybrids, Chinese hamster-human hybrids, and from studies on cultured lymphoblastoid line clones. McAlpine *et al.* (1975) have also presented relevant cytogenetic and biochemical data from a family in which an insertion involving chromosomes 11 and 18 is segregating 46,XX or XY, ins(11;18)(p15;q11q21). Three mentally retarded sibs in this family were found to be hemizygous for the q11 to q21 region. All three were found to have the peptidase A 8-1 phenotype. This provided evidence for the exclusion of the Pep A structural gene locus from the q11 to q21 region. The data from our patient support the idea that the peptidase A locus maps in the q22 to terminus region of chromosome 18.

The demonstration that the cystinuria gene is inherited independently of the 18q- deletion suggests that it is not located on the deleted segment of chromosome 18. The normal galactose-1-phosphate uridyl transferase and C'1 esterase inhibitor levels, and a normal α -1-antitrypsin phenotype, also suggest that the responsible genes are not located on the deleted segment of chromosome 18.

In evaluating future patients with the 18q- syndrome, it is recommended that they be closely examined for possible defects in heme biosynthesis as well as peptidase A activity and electrophoretic phenotype.

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Familial radioulnar synostosis

SUMMARY A family with proximal radioulnar synostosis segregating in three generations is described. Familial radioulnar synostosis is a rare anomaly; however, the sporadic form is a frequent feature in cases of sex chromosome abnormalities and other syndromes. This disorder has been reported in several ethnic groups, but this is apparently the first example from the black population.

Congenital synostosis of the proximal radius and ulna was first described by Sandifort in 1793, with over 265 cases reported since. Though most cases are sporadic, a small number are familial. The first report of familial radioulnar synostosis was by Abbott in 1892, and approximately 18 families have been described to date (Abbott, 1892; Davenport *et al.*, 1924; Fahlstrom, 1932; Hansen and Andersen, 1970; Berant and Berant, 1973). Almost all of these families are of western European origin, several of Jewish descent.

Familial radioulnar synostosis tends to be bilateral, and a majority of the affected are males. The inheritance pattern is autosomal dominant, but incomplete penetrance is common.

This report describes bilateral proximal radioulnar synostosis in three generations of a black American family. The clinical syndrome, its embryology, and treatment are discussed.

Case report

The propositus, a 3-year-old black boy, was the product of an uncomplicated 36-week pregnancy. Birthweight was 2350 g (25-50%), length 46 cm (25-50%), head circumference 32 cm (25-50%), and chest circumference 30 cm (25%). One- and five-minute Apgar scores were 8 and 9, respectively. Bilateral limitation of forearm supination was noted soon after birth. The neonatal period was otherwise uncomplicated, and subsequent growth and development were normal.

When examined at 3 years, the patient was a bright, well-developed boy. Height was 98 cm (75-90%) and weight was 13.2 kg (25%). There was distinct limitation of forearm supination from the vertical bilaterally (left 20°, right 15°). Deep tendon reflexes were depressed. The remainder of the physical examination was normal.

Radiographs revealed bilateral synostosis of the proximal ends of the radius and ulna (Fig. 1). CBC was normal. Buccal smear was 100% chromatin negative.

PEDIGREE

The family pedigree is illustrated in Fig. 2. Affected individuals occur in three successive generations. The patient's mother (III.2) has almost total restriction of forearm motion subsequent to bilateral osteotomies in childhood. A maternal uncle (III.4) and great uncle (II.5) of the patient are also affected with bilateral radioulnar synostosis, but have not been studied. The maternal grandmother (II.2) of the propositus is unaffected, showing incomplete penetrance.

Comment

The kindred illustrates several of the typical features of the familial congenital radioulnar synostosis syndrome, including bilateral involvement, autosomal dominant inheritance, and incomplete penetrance. Though the maternal grandmother of the propositus must carry the abnormal gene, she is unaffected. Males are more often affected than females. Familial radioulnar synostosis tends to be bilateral, but some families tend to exhibit unilateral involvement. Radioulnar synostosis has been associated with