Case reports

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Ring chromosome 14: a distinct clinical entity*

SUMMARY An infant girl with ring chromosome 14 is presented. The findings in this patient and in six previously reported cases of a ring 14 suggest that a characteristic clinical syndrome is associated with this chromosome aberration. The major features of the ring chromosome 14 syndrome include mental retardation, a disorder of skin pigmentation, seizures, and dysmorphic features, including flat occiput, epicanthal folds, downward slanting eyes, flat nasal bridge, upturned nostrils, short neck, and large low set ears.

In 1971 Gilgenkrantz *et al*[1] reported a 21-month-old retarded girl with dysmorphic features, microcephaly, and epileptic seizures. Cytogenetic studies revealed a ring chromosome. Subsequently a pair of monozygotic female twins[2 3] and two other cases of the 14 ring chromosome abnormality with similar features were reported.[4 5] Valera and Sternberg[6] reported two cases with a 'D' ring chromosome abnormality. While their first case conforms to the clinical entity of the ring 14 syndrome, their second case probably represents a case of a ring 13 abnormality.[7]

The purpose of this report is to describe another child with the ring chromosome 14 abnormality and to outline the clinical features associated with this cytogenetic aberration. The similarity of this clinical syndrome to the features of tuberous sclerosis is stressed.

Case report

A female of Puerto Rican descent was first seen at the age of 8 months because of poor activity, excessive recurrent respiratory infections, and delayed development. She was the product of her mother's only pregnancy. Both parents were healthy and young (16 and 20 years, respectively). Pregnancy, delivery, and the neonatal period were uneventful and the birthweight was 2835 g.

Physical examination revealed a retarded infant with a high forehead, narrow biparietal diameter, flat occiput, flat nasal bridge, hypertelorism and downward slanting eyes, epicanthal folds, short thick eyebrows, low set ears with large lobes, and a narrow high arched palate (fig 1). The upper lip was downturned with a marked cupid bow contour. Length and weight corresponded to the 3rd centile. Redundant skin resembling a buffalo hump was noted over the nape of her neck and multiple depigmented spots were present on the thigh, right leg, lower abdomen, and buttock. There was a linear café-au-lait spot on the left lower abdomen and one on the left buttock. The liver was palpable at 4 cm and the tip of the spleen was felt. The infant did not smile and had staring spells. A greyish pigmentation around the macula was noted in the fundi. Head control was poor for age with marked head titubation. Muscle tone was increased and deep tendon reflexes were symmetrical and hyperactive with a crossed adductor response, bilateral withdrawal reflexes, and unsustained ankle clonus. Severe metatarsus adductus was noted bilaterally, more prominent on the left. Later the infant developed generalised tonic clonic seizures and myoclonic jerks (infant spasms) poorly controlled with anticonvulsive treatment. In view of the vitiliginous

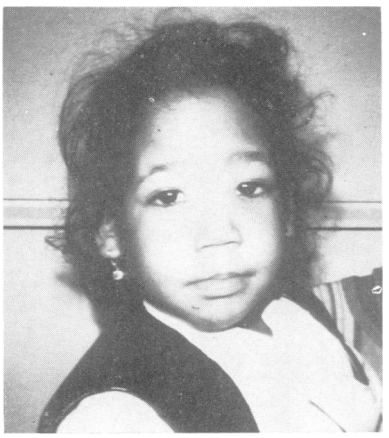

FIG 1 *Proband at the age of 2 years. Note flat nasal bridge, hypertelorism, downward slanting eyes, epicanthal folds, thick eyebrows.*

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spots, delayed development, and recurrent seizures, a diagnosis of tuberous sclerosis was entertained.

The infant's development remained very slow. At 35 months of age her height, weight, and head circumference were just below the 3rd centile. She could stand and walk with support with little titubation. There was very little speech development and her mental capacity was in the range of moderate to severe retardation.

The results of routine laboratory tests, including CBC, urine analysis, sickle cell prep, glucose, urea, uric acid cholesterol, calcium phosphate, alkaline phosphatase, total protein, albumin, globulin, bilirubin SGOT, LDH, sodium potassium, chloride, CO_2, TORCH titres, serum hexosaminidase and β-galactosidase, blood and urine amino-acids, spinal fluid chemistry, and skull *x*-ray were all within normal limits. Serum immunoglobulins revealed IgG 5·8 and IgA 0·3 g/l (normal 0·35 to 0·75 g/l). A spinal tap yielded clear fluid under normal pressure and normal chemistries. Electroencephalogram showed multifocal spike and wave discharges arising from multiple independent foci and becoming generalised at times. At 10 months computerised tomography showed mildly dilated ventricles, subarachnoid space, and subarachnoid sulci, consistent with mild cerebral atrophy. Electroretinograms were normal.

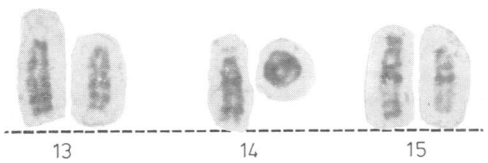

FIG 2 *Partial karyotype of proband, 46,XX,r(14). Breakpoints at bands p12 and q24.*

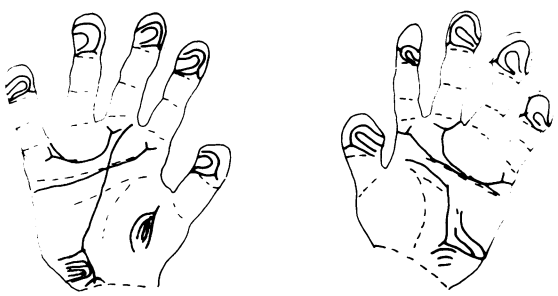

FIG 3 *Hand prints of proband.*

Cytogenetic studies from peripheral blood and skin biopsy revealed a 46,XX,r(14) karyotype using Giesma, quinacrine, and R staining. The breakpoints were at bands p12 and q24 (fig 2). Some instability of the ring chromosome was reflected in its size and in its absence in some of the metaphases in the fibroblast cultures.

Dermatoglyphic analysis revealed normal palmar creases, ten ulnar loops on the fingertips, and an absence of the triradius *c* on both hands. A radial loop occupied the right hypothenar area and an ulnar loop the left. In the left thenar region a palmar loop was present (fig 3). The plantar patterns were not unusual.

The parents' dermatoglyphs and karyotypes were normal. The mother had two pigmented naevi.

Discussion

A ring chromosome 14 aberration has been described in six girls, including a pair of monozygotic twins. The clinical features of the six patients and of our patient are summarised in tables 1 and 2. The very detailed description by Gilgenkrantz *et al*[1] provides a good summary of the morphological features characteristic of this syndrome. Indeed, similar manifestations were found in our patient, and these are recognisable in the photographs of the monozygotic twins reported by Jalbert *et al*,[2] the cases described by Abe *et al*,[4] Amarose *et al*,[5] and case 1 of Varela and Sternberg,[6] although this last patient was studied before the availability of banding techniques. Apart from the patient of Abe *et al*,[4] who had a complex chromosome rearrangement involving chromosomes 13 and 14, all the children were microcephalic and featured moderate to severe psychomotor and growth retardation, dolichocephaly with biparietal narrowing, high forehead, downward slanting eyes, epicanthi, a short neck, seizures and neurological abnormalities including tremor, athetosis, hypotonia, and hypertonia. They all suffered from recurrent respiratory infections and four[1 4–6] had congenital heart defects. Like our patient, two other children[4 6] had vitiliginous and café-au-lait spots.

The mothers' ages at the time of birth ranged from 36 to 16 years. The birthweight was generally low, from 1480 to 3650 g (table 2).

The dermatoglyphic features generally showed an increased number of ulnar loops on the fingertips, while the twins described by Jalbert *et al*[2] had a radial loop on the second finger and four whorls and three whorls, respectively, on other fingers. Simian creases were reported by Gilgenkrantz *et al*.[1]

Thus, the characteristic features of the ring

TABLE 1 *Ring chromosome 14: dysmorphic features*

	Valera and Sternberg[6]	*Gilgenkrantz et al*[1]	*Jalbert et al*[2]	*Abe et al*[4]	*Amarose et al*[5]	*Present case*
Microcephaly	+	+	+	−	+	±
Flat occiput	?	+	+	+	+	+
Dolichocephaly	?	+	+	+	+	+
Epicanthal folds	?	+	+	+	+	+
Downward slanting eyes	+	+	+	+	+	+
Flat nasal bridge	?	+	+	+	+	+
Anteverted nostrils	?	+	?	+	+	+
Downturned lips	?	+	?	+	+	+
High arched palate	?	+	−	−	+	+
Low set ears	?	+	−	+	+	+
Short neck	?	+	−	+	+	+
Dyspigmentation	+	−	−	+	−	+
Growth retardation	+	+	+	+	+	±

TABLE 2 *Ring chromosome 14: clinical data*

	Valera and Sternberg[6]	*Gilgenkrantz et al*[1]	*Jalbert et al*[2]		*Abe et al*[4]	*Amarose et al*[5]	*Present case*
Age of mother at birth of child	24	36	28		24	31	16
Age of father at birth of child	?	32	29		28	33	20
Birthweight (g)	2268	2500	1920	1480	3650	2505	2835
Sex	F	F	F	F	F	F	F
Neonatal asphyxia	−	+	+	+	−	−	−
Mental retardation	+	+	+	+	+	+	+
Seizures	−	+	+	+	+	+	+
Intention tremor	?	−	+	+	−	+	+
Abnormal muscle tone	?	+	+	+	+	+	+
Hyperactivity	−	+	+	+	−	?	+
Respiratory infections	+	+	+	+	?	+	+
L^u on fingertips	8	10	5	6	?	2	10
Survival	Died at 5 mth	Died at 3·5 yr	5·5 yr		2 yr	1·5 yr	3 yr

chromosome 14 syndrome include dolichocephaly with high forehead, epicanthic folds and downward slanting eyes, large low set ears and a short neck, psychomotor retardation, seizures, and recurrent respiratory infections. Some patients have congenital heart defects and some have cutaneous pigmentary changes and neurological abnormalities.

Since deletion of both ends of a chromosome accounts for the formation of a ring chromosome, it is understandable that the symptomatology may vary, depending on the amount of material deleted from the chromosome. Nevertheless, a large number of the clinical features are invariably present.

Scattered vitiliginous spots over the legs, buttocks, and abdomen, as well as multiple hyperpigmented spots, in conjunction with psychomotor delay and severe refractory seizures, are characteristic of tuberous sclerosis. However the typical dysmorphic facial features described in this report are not found in patients with tuberous sclerosis and may alert the paediatrician to this particular chromosome abnormality.

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A 5;7, 5;12 double reciprocal translocation in a normal mother and a 5;7 translocation with a recombinant chromosome 5 in her normal child*

SUMMARY A phenotypically normal mother had two apparently balanced translocations involving chromosomes 5, 7, and 12. Her karyotype was 46,XX,t(5;7) (5;12) (p14q34;p14;q21), while her daughter, who was also phenotypically normal, had inherited only one of the translocations. Her karyotype was 46,XX,−5,−7, +rec(5)t(5;7) (q34;p14)mat,+der(7)t(5;7) (q34; p14)mat. The other was lost during a meiotic crossing over, giving the daughter an apparently balanced chromosome complement.

Many cases of single autosomal reciprocal translocations, but only a few double translocations, have been reported.[1–5]

This report concerns a phenotypically normal female with two reciprocal translocations involving three chromosomes and her phenotypically normal daughter who inherited only one of these translocations.

Case report

The proband was a phenotypically normal 29-year-old woman referred to a gynaecological department in 1971 because of three spontaneous abortions in the 12th to 16th weeks of pregnancy.

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Cervical insufficiency was diagnosed and a cerclage applied. Conception occurred and the patient experienced an uncomplicated pregnancy until 8 weeks before term, when a caesarean section was performed owing to premature labour, and a live-born girl of 1500 g was delivered. After treatment in the neonatal department, she thrived well and was described in 1977 by her general practitioner as normally developed, physically as well as mentally.

In 1973 and 1975, a cerclage was again applied. Each time the patient became pregnant, but aborted spontaneously in the 10th and 18th week, respectively.

A chromosome analysis was then performed on the patient, her husband, daughter, and mother. The patient had no contact with her biological father.

CYTOGENETIC STUDIES

Chromosome analysis was carried out on peripheral blood cultures using the GTG, QFQ, and RBA

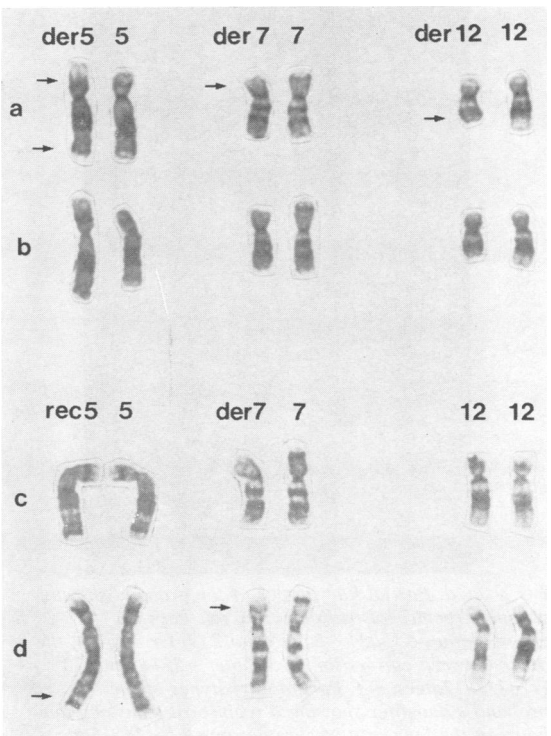

FIG 1 *a, b, partial karyotypes of the proband; c, d, partial karyotypes of the proband's daughter (G banding). The respective breakpoints are indicated on the figure.*