Case reports

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46,XX/47,XX,+14 mosaicism in a liveborn infant¹

SUMMARY A liveborn infant with the complement 46,XX/47,XX,+14 shared certain features in common with the following previously reported cases: (1) the one previously reported possible case of trisomy 14, (2) cases in which individuals had at least some portion of chromosome No. 14 in triplicate, and (3) cases of atypical D trisomy (Snodgrass category II). The common features include developmental retardation, wide flat nose with bulbous or wide tip, large mouth with turned down corners (some with protruding lips), short neck (some with redundant skin folds), low-set ears, retrognathia, digital anomalies (usually contractions and deviations), palatal anomalies, and cryptorchidism.

Trisomy for certain autosomes—notably nos. 8, 13, 18, and 21—has been detected not only in liveborn infants, but also among spontaneous abortuses (Carr, 1971; Kajii *et al.*, 1973; Boué and Boué, 1974). By contrast, other trisomies are usually detected only in abortuses, or they have not been reported at all. Though trisomy 14 has been detected among spontaneous abortuses (Kajii *et al.*, 1972, 1973; Boué and Boué, 1974), its occurrence in liveborn infants has not been confirmed by chromosome banding techniques. One possible case was studied with autoradiographic techniques (Murken *et al.*, 1970). We report here a liveborn infant whose complement was 46,XX/47,XX,+14, the first such case reported to our knowledge.

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Case report

S.B. was born after 42 weeks' gestation to a 32-year-old father of German descent and a 26-year-old mother of German-Bohemian-Polish descent. The pregnancy was characterized by polyhydramnios, but it was normal otherwise. Both parents are in good health. Their two previous pregnancies resulted in healthy, well-developed children, a 7-year-old girl and a 4-year-old boy.

At birth S.B. weighed 3260 g, was 49 cm long, and had a head circumference of 33 cm. The following abnormalities were present: frontal bossing, asymmetrical palpebral fissures, eversion of the lower eyelids, a fissure of the right inner canthus, proptosis, an unusual translucent film over the eyes that disappeared several days after birth, a wide flat nasal bridge, a protruding upper lip, a protruding tongue, a recessed chin, a highly arched palate, a short neck, a grade 3/6 systolic heart murmur that was not further characterised, bilateral clinodactyly V, and hypotonia. Though S.B. appeared healthy when discharged from the hospital at 4 days of age, she subsequently ate poorly and gained weight slowly. Intolerance to cow's milk was suspected, and soy bean formula was administered; however, she still failed to gain weight. At 8 months of age she developed *H. influenza* meningitis that responded to antimicrobial therapy. At that time both her height and weight were below the 3rd centile. Her head circumference was 44 cm (50th centile). The following clinical tests were normal: routine haematological and urinary studies, x-ray films of the skull and cervical spine, urinary chromatogram for amino acids, serum thyroxine, and serum immunoglobulins. Cytogenetic findings are described below.

At 1 year of age S.B. weighed 6945 g. She could sit unassisted, utter unrecognizable sounds, and walk

Fig. 1 D group chromosomes from a 47,XX,+14 lymphocyte of S.B. (G-banding technique).

both in a 'walker' and with assistance. During an examination at 16 months of age she was docile and co-operative, but still could not talk coherently. She walks and runs freely with the assistance of a canvas-sling-type walker; however, she only takes a few steps without the walker. She eats only strained foods, and gags on table foods. Her first year molars have recently erupted. Compared to her normal sibs, S.B. appears developmentally retarded.

CYTOGENETIC ANALYSIS

One hundred and twenty-five lymphocytes in metaphase were analysed from 2 blood samples obtained 4 months apart. Trypsin-Giemsa banding was produced by modification of the Seabright technique (1971). Ten cells showed a 47,XX,+14 complement (Fig. 1). These 47,XX,+14 cells were detected in 6 different cultures, 3 from each sample; therefore, it seems unlikely that trisomic cells arose *in vitro*. In addition, 59 cells derived from skin fibroblasts (fourth passage) were also examined. Two cells showed trisomy 14; both were detected in the same culture. Only 2 other aneuploid cells were detected, 1 in a blood culture and 1 in a culture of skin fibroblasts. The first was a broken cell with 42 chromosomes. Interestingly, 3 No. 14 chromosomes were present. The second cell had 45 chromosomes.

Other family members could not be tested.

Discussion

This is the first report, to our knowledge, of a liveborn infant with trisomy 14 mosaicism. That the observed

mosaicism did not arise *in vitro* is evident by the detection of 47,XX,+14 cells in two different tissues—skin fibroblasts and lymphocytes, and also cultures initiated from the same tissue on separate occasions.

There have been other reports of individuals with excess chromosome No. 14 material. Murken *et al.* (1970) reported a child with multiple congenital malformations who, on the basis of autoradiographic studies, was said to have trisomy 14. Trisomy 14 with no apparent mosaicism has also been detected among spontaneous abortuses (Kajii *et al.*, 1972; Boué and Boué, 1974). In several other individuals portions of chromosome No. 14 were present in triplicate as result of either segregation from translocation heterozygotes (Allderdice *et al.*, 1971; Reiss *et al.*, 1972; Short *et al.*, 1972; Laurent *et al.*, 1973; Pfeiffer *et al.*, 1973; Fryns *et al.*, 1974), or sporadic structural rearrangements (Muldal *et al.*, 1973).

Trisomy 14 appears to be rarer than trisomy 13, trisomy 18, or trisomy 21. There are several possible reasons for this. First, trisomy 14 might usually be lethal, consistent with observations that this complement is more common among spontaneous abortuses than among liveborn infants. One might also reason that lethality would be expected because chromosome no. 14 has more negative Q- or G-bands than chromosome 13, based upon the hypothesis that negative Q- or G-bands represent regions of genetically active DNA (see Comings, 1974). If this hypothesis is true, one might argue (Hoehn, 1975) that the greater the proportion of negative Q- or G-bands (positive R-bands) in a given chromosome, the more deleterious trisomy for that chromosome. Second, trisomy 14 might originate less often,

Fig. 2 Craniofacial appearances of (a) S.B., whose chromosomal complement is 46,XX/47,XX,+14; and (b) the infant reported by Murken *et al.* (1970) to have the chromosomal complement 47,XY,+14.

though not necessarily be more deleterious than trisomy 13. That is, chromosome No. 14 might be relatively less susceptible to nondisjunction (Therkelsen *et al.*, 1973). A third possibility is that trisomy 14 occurs in livebirths more frequently than generally appreciated, with some cases of trisomy 14 misclassified as cases of trisomy 13. Indeed, phenotypic heterogeneity exists among individuals with the 'trisomy 13 syndrome', and relatively few cases of trisomy 13 have been analysed with chromosomal banding techniques. Thus, some 'atypical' cases of

'trisomy 13 syndrome' (e.g. Snodgrass *et al.*, 1966; Neu *et al.*, 1971; Webb *et al.*, 1971) conceivably could represent cases of trisomy 14. Fourth, trisomy 14 may produce so few phenotypic abnormalities that affected individuals are not necessarily brought for genetic consultation. This would be analogous to trisomy 8, which is detected among older children who show few of the anomalies that usually initiate chromosomal studies (Caspersson *et al.*, 1972). This final possibility would, incidentally, not necessarily be inconsistent with the hypothesis that trisomy 14 is usually lethal.

Fig. 3 Craniofacial appearances of 5 individuals who had portions of chromosome No. 14 in triplicate. Some chromosomal complements have been transformed to the nomenclature recommended by the Paris Conference (1971), based upon published karyotypes and descriptions. (a) 47,XX,+der(14),t(14q-;19+) mat. (From Fryns *et al.*, 1974); (b) 47,XX,+del(14)(q) (From Muldal *et al.*, 1973); (c) 47,XY,+der(14),t(9p+;14q-) mat. (From Short *et al.*, 1972); (d) 46,XY,t(2q+;14q-)/47,XY,-2,+der(2),+der(14),t(2q+;14q-) pat. From Reiss *et al.* (1972); (e) 46,XY,-21,+der(14),t(14;21)(q12;q22) pat. (From Laurent *et al.*, 1973).

For example, fewer than 5% of 45,X conceptuses survive (Boué and Boué, 1974), yet those who do survive usually have no life-threatening anomalies (Simpson, 1976).

Individuals with triplication for at least a portion of chromosome no. 14 share certain features that suggest a clinically recognizable syndrome (Table). The most common features shared by these individuals (features present in at least 5 of 9 cases) are developmental retardation, wide flat nose with bulbous or wide tip, large mouth with turned down corners (some with protruding lips), short neck (some with redundant skin folds), low-set ears, retrognathia, digital anomalies (usually contractions and deviations), palatal anomalies, and cryptorchidism (Murken *et al.*, 1970; Allderice *et al.*, 1971; Reiss *et al.*, 1972; Short *et al.*, 1972; Laurent *et al.*, 1973; Muldal *et al.*, 1973; Pfeiffer *et al.*, 1973; Fryns *et al.*, 1974). Though the infant we report has both 46,XX and 47,XX,+14 cells, she also shows most of the above features. Certain anomalies characteristic of trisomy 13 (e.g. polydactyly, cleft lip and palate, microphthalmia) are present in neither the patient we have described nor are they characteristic of other individuals with triplication for a portion of chromosome No. 14. However, on the basis of cases who show translocations, it may be hazardous to postulate that a clinical pattern is associated with trisomy 14 because (1) the portion of chromosome No. 14 present in excess is not always the same in the reported cases; (2) different regions of chromosome No. 14 are involved in various translocations; and (3) duplications or deficiencies of other chromosomes may influence the phenotype. Finally, some cases of atypical D trisomies (Fig. 4) said to have 'Snodgrass syndrome',

Table Clinical features of 9 individuals with triplication of at least some portion of chromosome no. 14

Feature	No. of Individuals/Total
(1) Developmental retardation	9/9
(2) Electroencephalographic abnormalities	3/9
(3) Seizures	2/9
(4) Hypertonia	2/9
(5) Hypotonia	3/9
(6) Craniofacial	
(a) Microcephaly	4/9
(b) Ears	
Low-set*	5/9
Large	1/9
(c) Forehead with a wide glabella, protruding, or sloping	4/9
(d) Eyes	
Abnormal palpebral fissures	4/9
Microphthalmia	2/9
Hypertelorism	3/9
Hypotelorism	2/9
(e) Nose with a flat nasal bridge and bulbous or wide tip	7/9
(f) Prominent mouth with turned down corners	7/9
(g) Palates	
Highly arched	4/9
Cleft	2/9
(h) Retrognathia	5/9
(7) Short neck†	6/9
(8) Chest	
Cardiac anomalies‡	4/9
Recurrent respiratory infections	4/9
(9) Cryptorchidism	2/3
(10) Skeletal anomalies	
(a) Vertebral	3/9
(b) Digital	5/9
(c) Costal	3/9
(d) Pedal	3/9

*Two of these individuals also had dysplastic ears.
†Two of these individuals also had redundant skin folds.
‡Two of these had murmurs not further characterized.

Fig. 4 Craniofacial appearances of two individuals who would be said to have atypical D trisomy (Snodgrass category II). Chromosomal banding studies were not performed in either case. The chromosomal complements were (a) 47,XX,+D (From Neu *et al.*, 1971), (b) 46,XX/47,XX,+D (Webb *et al.*, 1971).

category II¹ resemble the individuals who have triplication for no. 14 (Fig. 2 and 3); thus, cases of 'Snodgrass syndrome, category II' might represent cases of trisomy 14.

In conclusion, our observation of 46,XX/47,XX,+14 mosaicism indicates that trisomy for no. 14 is compatible with life, at least when associated with a normal diploid cell line. Furthermore, phenotypic similarities among patients with triplication of at least a portion of chromosome 14 suggest an associated clinical pattern.

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- ¹Snodgrass *et al.* (1966) classified cases of D trisomy on the basis of their craniofacial defects. Those in 'category I' were said to have severe prosencephalic defects, e.g. cleft lip, cleft palate, and ocular anomalies. Those in 'category II' were said to be characterized by a large nose with a broad bridge and a bulbous tip, a long upper lip that overhangs the lower lip, an everted lower lip, a large mouth that turns downward at the corners, 'mild' micrognathia, and loose skin folds in the mandibular and periorbital regions.
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45,X/47,XYY mosaicism

SUMMARY This paper describes and discusses the clinical and cytogenetic findings in an infant with an unusual sex chromosome abnormality 45X/47XYY.