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Brief Clinical Report

A Child With Multiple Congenital Anomalies and Karyotype 46,XY,del(14)(q31q32.3): Further Delineation of Chromosome 14 Interstitial Deletion Syndrome

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We report on an infant with a multiple congenital anomaly syndrome and severe developmental delay in association with a previously undescribed de novo interstitial deletion of chromosome 14 [karyotype: 46,XY,del(14)(q31q32.3)]. Comparison of the presented patient with previously reported cases of interstitial and terminal chromosome 14q deletions provides a group of patients monosomic for various overlapping portions of the distal half of chromosome 14q and suggests a limited similarity in phenotype among patients with common deleted 14q segments. All patients with distal 14q deletions were developmentally delayed, most were microcephalic and failed to thrive. Most of the patient's anomalies were limited to the face and head. Few major internal congenital anomalies were observed. These comparisons serve to further clarify possible associations of subchromosomal aberrations with specific phenotypes.

KEY WORDS: **human chromosome 14, chromosome deletion, chromosomal aberration, aneuploidy, mental retardation, multiple congenital anomalies**

INTRODUCTION

Isolated de novo deletions of chromosome 14 are rare and deletions resulting from the formation of ring chromosome 14's account for most reported cases [Schinzel, 1984]. We present a previously unrecognized de novo interstitial deletion of chromosome 14 with a karyotype 46,XY,del(14)(q31q32.3) in an infant with developmental delay and multiple congenital anomalies. Comparison of the patient's phenotype with 6 previously reported patients with chromosome 14q deletions [Nielsen et al., 1978; Hreidarsson and Stamberg 1983; Turleau et al., 1984; Kawamura et al., 1985; Yamamoto et al., 1986] suggests that monosomy for subregion 14q31.1q32.1 may be associated with a limited number of facial characteristics.

CLINICAL REPORT

A.S. was the 3841 g male infant of a 43 week pregnancy and was delivered by an uncomplicated repeat cesarean section to a 26-year-old mother and a 27-year-old father. His mother had one previous uncomplicated pregnancy resulting in a normal infant. Pregnancy, delivery, and neonatal course were normal. No known exposures to recognized teratogens were noted. There was no family history of consanguinity, spontaneous abortions, congenital anomalies, or mental retardation.

Developmental delay was apparent at 10 months at which time the patient could not crawl, sit unsupported, or pull to a stand. He crawled at 15 months and stood at 18 months. At 22 months he cruised, used a single word and knew three body parts.

On physical examination at 22 months, all growth parameters were below the 3rd centile with a head circumference (OFC) of 45.9 cm, length of 76.5 cm, and weight of 9340 g. Physical manifestations included fine sparse hair; bushy eyebrows with wide, medially flaring margins; bilateral epicanthal folds; prominent, bilaterally cupped, apparently low-set ears with thick overfolded helices and small dermal pits below the tragii bilaterally; a broad, depressed nasal bridge; an upturned nose; full cheeks; a long well formed philtrum; a bow-shaped, thin upper lip; a highly arched palate; a bifid uvula; bilaterally dystrophic maxillary incisors; a tongue with a depressed midline crease and septated tip; micrognathia; diastasis recti; coronal hypospadias with

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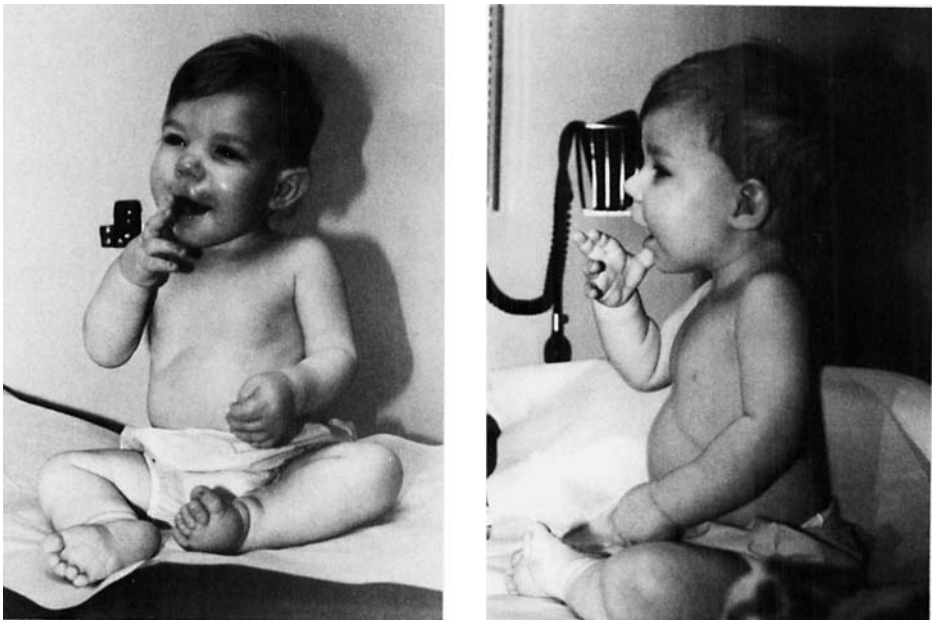

Fig. 1. The patient at 15 months.

a cordae; right cryptorchidism; puffy, nonpitting edematous distal extremities; a unilateral Simian crease; short thin convex nails on all digits; and metatarsus adductus bilaterally (Fig. 1). No focal neurological abnormalities or pathological reflexes were noted during repeated examinations. Medical problems have been limited to eczema, managed with topical steroids, and recurrent bilateral otitis media necessitating bilateral tympanostomies. Repeated ophthalmologic examinations have been normal.

Laboratory investigations have included a normal T4, TSH, creatinine, glucose, BUN, and urine amino and organic acids. An echocardiogram was normal. Brainstem auditory evoked potentials were normal. Renal ultrasonography showed mild right hydronephrosis. Patient and parents were unavailable for α_1-antitrypsin levels.

Cytogenetic Studies

The chromosomes of 20 cells were analyzed. The modal chromosome number was 46. Prometaphase trypsin-Giemsa and R banding chromosome analysis performed on the patient's cultured peripheral lymphocytes and Epstein–Barr virus transformed lymphoblasts showed an interstitial deletion of chromosome 14q (Fig. 2); karyotype: 46,XY,del(14)(q31q32.3) with no other apparent chromosome rearrangements. His parents' chromosomes were normal.

DISCUSSION

This patient has a multiple congenital anomaly syndrome and severe developmental delay in association with a heretofore unrecognized de novo interstitial deletion of chromosome 14q31q32.3. We are aware of only 6 other reports of patients with isolated interstitial or terminal 14q deletions [Nielson et al., 1978; Hreidarsson and Stamberg, 1983; Turleau et al., 1984; Kawamura et al., 1985; Yamamoto et al., 1986]. The cytological and clinical characteristics common to 2 or more of our patient and those previously reported with isolated 14q deletions are summarized for comparison in Table I with the patient with the most proximal breakpoint to the left. As illustrated in Figure 3, collectively, these 7 patients are monosomic for various segments of the distal half of chromosome 14q. At least 2 patients are apparently monosomic for any given subregion of distal 14q. The segment of 14q monosomic in any patient varies from approximately 6% for the 14q terminal deletion [Hreidarsson and Stamberg, 1983] to 33% for the patient with deletion 14q23q32 [Turleau et al., 1984]. Additionally, there is an apparent nonrandomness of chromosome breakpoints among the deleted chromosomes. As summarized in Table I, two patients have breakpoints at 14q23, 14q24.3, 14q31, 14q32.1, and 14q32.3. The significance of the apparent clustering of 14q breakpoints is uncertain.

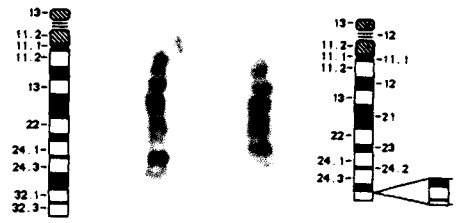

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Fig. 2. Partial karyotype of patient showing a schematic diagram of the normal (left) and deleted (right) chromosome 14 bracketing the patient's Giemsa-trypsin banded normal chromosome 14 (left) and the patient's Giemsa-trypsin banded deleted chromosome 14q31q32.3 (right).

TABLE I. Clinical Traits Common to Two or More Patients with Interstitial 14q Deletions

	Turleau et al. [1984]	Turleau et al. [1984]	Kawamura et al. [1985]	Yamamoto et al. [1986]	Our Patient	Nielsen et al. [1978] Mosaic	Hreidarsson et al. [1983]
Deleted segment	q23q24.2	q23q32	q24.3q32.1	q24.3q32.1	q31q32.3	q31qter	q32.3qter
Gestational age	Term	37 wks	42 wks	37 wks	43 wks	Term	Term
Birth weight (g)	2860	2760	3800	2350	3841	4000	3250
Failure to thrive	+	+	+	−	+	−	+
Psychomotor retardation	+	+	+	+	+	+	+
Microcephaly	+	+	+	+	+	−	−
Seizures	+	−	−	−	−	+	−
Feeding difficulty	−	−	+	+	−	−	−
Small palpebral fissures	−	+	+	+	−	−	−
Epicanthal folds	−	+	−	−	+	−	−
Strabismus	+	+	−	−	−	+	−
Bushy eyebrows	+	+	+	+	+	−	−
Ear abnormalities	+	+	+	−	+	+	+
Small upturned nose	−	+	+	+	+	−	−
Carp mouth	−	+	+	+	+	−	−
Thin upper lip	+	−	−	−	+	−	−
Highly arched palate	−	−	−	−	+	+	+
Abnormal dentition	+	−	+	−	+	−	−
Micrognathia	+	+	+	+	+	+	−
Excess of skin on nape	−	+	−	+	−	−	−
Heart defect	−	+	−	−	−	−	+
Renal anomalies	+	+	−	−	+	−	−
Cryptorchidism	+	+	−	−	+	−	−
Skeletal anomalies	+	+	+	−	+	+	+
Simian crease	−	+	−	+	+	−	−

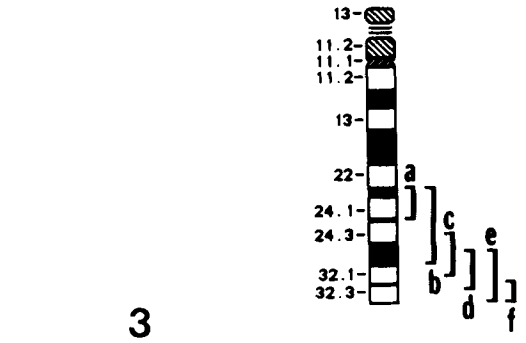

Fig. 3. Schematic diagram showing deleted segments of chromosome 14 in the present and previously reported cases: region a corresponding to del(14)(q23q24.2) [Turleau et al., 1984]; b, del(14)(q23q32) [Turleau et al., 1984]; c, del(14)(q24.3q32.1) [Kawamura et al., 1985; Yamamoto et al., 1986]; d, present case; e, del(14)(q31qter) [Nielson et al., 1978]; f, del(14)(q32.3qter) [Hreidarsson et al., 1983].

Examination of patient phenotypes (Table I) shows that all patients shared many relatively nonspecific manifestations such as psychomotor retardation (7/7), failure to thrive (5/7), micrognathia (6/7), ear abnormalities (6/7), and microcephaly (5/7). In comparison, major internal structural congenital malformations were relatively uncommon. No fatal or life threatening congenital malformations were reported. Observed major internal malformations were limited to congenital heart defects in 2 patients without an apparent common monosomic segment of chromosome 14. The defects consisted of an atrial septal defect (ASD) and bicuspid aortic valve [Turleau et al., 1984] and an ASD with partial anomalous venous return [Hreidarsson and Stamberg, 1983]. Cryptorchidism was reported in 3 patients. Renal anomalies, consisting of isolated findings of renal hypoplasia, or horseshoe kidneys [Turleau et al., 1984] or hydronephrosis (present patient) were observed in 3 patients. Various apparently patient specific skeletal abnormalities were reported in 6 of the 7 patients.

Most of the manifestations found in common among the distal 14q deletion patients were craniofacial and consisted of bushy eyebrows, a small upturned nose, carp shaped mouth, highly arched palate, and abnormal dentition (Table I) and were observed most commonly among the 5 patients monosomic for 14q31q32.1. However, these characteristics were not uniformly observed and some manifestations, such as bushy eyebrows, abnormal dentition, or a highly arched palate, were also observed among the patients monosomic for other portions of distal 14q such as 14q12q24.2 [Turleau et al., 1984] and 14q32.2qter [Hreidarsson and Stamberg, 1983] respectively. Therefore, at this time, we conclude that no definite 14q deletion syndrome is apparent. Analysis of additional patients with distal deletions of chromosome 14q may be helpful in identifying and characterizing specific 14q deletion syndromes.

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