RING 14 SYNDROME WITH DECREASED BONE MINERAL CONTENT IN TWO PUBERTAL GIRLS

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Summary Two female cases with r(14) syndrome, aged 14 and 16, were reported. Both cases had mental retardation, microcephaly, growth retardation, epilepsy and ataxia. But craniofacial dysmorphic features, typical to r(14) syndrome, were rarely observed. Bone mineral content was decreased in one of the cases. The cataracta and abnormal pigmentation of the retinae was observed in one of the cases.

INTRODUCTION

Fourteen cases with ring chromosome 14, identified by autoradiography or banding techniques, have been reported so far (Gilgenkrantz *et al.*, 1971; Jalbert *et al.*, 1977; Dzarlieva, 1977; Abe *et al.*, 1978; Vekemans *et al.*, 1979; Amarose *et al.*, 1980; Riley *et al.*, 1981; Schmidt *et al.*, 1981; Iselius *et al.*, 1980; Triolo *et al.*, 1981; Lippe and Sparkes, 1981).

The characteristic features of the r(14) syndrome include dolichocephaly, epicanthic fold, downward slanting eyes, large low-set ears, short neck, psychomotor retardation, seizures and recurrent respiratory infections (Schmidt *et al.*, 1981).

Most of the reported cases, however, were infants or young children. This is the reason why we reported two r(14) cases in pubertal age.

CASE REPORT

Casel. H.T.

The proposita HT, female, was born to unrelated parents, following 39 weeks of gestation complicated by severe emesis and toxicemia of pregnancy. Her father and mother were 34 and 22 years old, respectively and, were in good health. Her burth weight was 2,140 g, length 43 cm, and head circumference 30 cm. She had respiratory distress and feeding difficulty during neonatal period. She developed normally until 16 months of age, when intractable generalized convulsion occurred.

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Fig. 1. a, The case 1 (HT) at 14 years old; b, The case 2 (KW) at 16 years old. Note broadnasal bridge, narrow and downward palpebral fissures, and microcephaly.

She was referred to our clinic because of intractable convulsion and delayed psychomotor development at 6 years of age. She showed microcephaly (-5 SD), small stature (-1.4 SD), narrow palpebral fissure, broad nasal bridge, high-arched palate, bilateral preauricular pits, hypertrichosis over the back, short fifth-fingers and mental retardation (2 year-old level) (Fig. 1). She had generalized convulsions once or twice a month after antiepileptic therapy (phenobarbital and phenytoin). Ataxic gait was noted at 8 years of age, but any other cerebellar signs were noticed. Her pubertal development at the age of 14 years was normal.

Dermatoglyphic findings of the proposita and the mother were slightly abnormal (Fig. 2 and Table 1). The dermatoglyphic studies of her father were not available.

Radiological examination revealed hypoplastic midphalanges of fifth-fingers. There was no abnormal findings in the computed tomography (CT) of the head, electroencephalogram, blood sugar and serum electrolytes.

Case 2. K.W.

The proposita KW, female, was born to unrelated 31-year-old father and 28-year-old mother following 38 weeks gestation complicated by severe emesis. There were no miscarriages, congenital malformations, or psychomotor retardation in the pedigree. Her birth weight was 2,350 g. Though her perinatal period was uneventful, her physical growth and psychomotor development was retarded. She began to sit alone at 8 months of age, to walk at 2 years and to speak a word at 3 years.

Fig. 2. Dermatoglyphics of case 1 and case 2.

At 3 years and 5 months old, her weight was 9.5 kg (-2.9 SD), Body length 87.5 cm (-1.8 SD), head circumference 43.5 cm (-4.2 SD). She had generalized tonic-clonic convulsions five times a day at 8 months of age. This grand mal seizures were intractable and continued once a month or once several months until 10 years old. She had myoclonic absence or atypical absence attack several times a day at 11 years of age. She was treated with many drugs (phenytoin, phenobarbital, sodium valproate, carbamazepin, primidon, trimethadione, nitrazepam, sultiame, clonazepam and acetazolamide). Since an ataxic gait was observed, she was referred to our clinic at 16 years of age. She had short stature (-2.7 SD), microcephaly (-4.7 SD), severe mental retardation (2 or 3 year-old level), scoliosis and pes contortus. Downward slanting eyes, broad nasal bridge and flat occiput were noted (Fig. 3).

Dermatoglyphic studies revealed abnormal (Fig. 2 and Table 1). Dermatoglyphics of her parents were shown in Table 1.

Ophthalmoscopic examination revealed retropolar opacification of the lens in the bilateral eyes and greyish drusen-like pigmentations around the macula. The electroretinogram was normal.

Table 1. Dermatoglyphic findings of the proposita and their parents.

	Finger patterns										TFRC
	L					R					
	5	4	3	2	1	1	2	3	4	5	
Case 1 (HT)	U	U	U	R	U	U	U	U	U	U	75
Mother	U	W	W	W	U	U	R	W	W	U	111
Case 2 (KW)	W	W	W	W	W	W	W	W	W	W	157
Father	W	W	W	W	W	W	W	W	W	W	143
Mother	U	U	U	R	U	U	U	U	U	U	67
Palm formula											
Case 1 (HT)	L	7. 5". 5'. 3. 13". -t-O.O/O.O.O.L.									
	R	11. 9. 7. 5". 13'. -t-O.O/O.O.O.L.O.									
Mother	L	7. 9. 5'. 3. 13'. -t-O.O/O.O.L.L/L.									
	R	7. 5". 5'. 3. 13'. -t-O.O/O.O.O.L.									
Case 2 (KW)	L	9. 9. 5". 3. 13'. -t-O.O/O.O.L.O.									
	R	9. 9. 5'. 3. 13'. -t-O.O/O.O.L.O.									
Father	L	11. 9. 7. 5'. 13". -t-O.O/O.O.L.O.									
	R	11. 9. 7. 5'. 13". -t-O.O/O.O.L.O.									
Mother	L	7. 5". 5'. 3. 13". -t-O.O/O.O.O.L.									
	R	7. 5". 5'. 3. 13". -t-O.O/O.O.O.L.									

The electroencephalogram showed diffuse synchronous irregular spike-wave and polyspike-wave patterns. Radiological examination revealed mild rachitis and delayed bone age (Fig. 4). Serum calcium was 4.4 mEq/liter, serum phosphate 2.8 mg/dl, magnesium 1.8 mEq/liter, alkaliphosphatase 24 U (K-Au). Bone mineral content was decreased (0.259 g/cm²). Serum IgA, IgG and IgM were normal. The cranial CT was normal.

CYTOGENETICS

Cytogenetic studies from peripheral blood culture of the patients are shown in Table 2. We analyzed 200 randomly selected metaphases after 48-hr-culture. Most of cells observed a monocentric ring, but 3 had double rings in both cases. Forty-five chromosomes missing chromosome 14 were observed in 1 cell (case 1) and in 12 cells (case 2). Satellite association of ring chromosome 14 were observed in case 1, but not in case 2.

Fig. 3. Radiogram of the Knee of case 2. Note numerous transverse lines, and poor mineralization of the bone.

Figure 4 shows partial karyotypes of D group chromosomes. The karyotype of case 1 was confirmed to be 46,XX,r(14) (p13q32) by G-banded and Ag-stain techniques (Bloom and Goodpasture, 1976). The G-banded karyotype of her mother was normal. The chromosome analysis of her father was not available. The karyotype of case 2 showed negative Ag-stain of ring chromosome 14, and her karyotype was decided as 46,XX,r(14) (p11q32). G-Banded karyotypes of her parents were normal.

DISCUSSION

Our 2 female cases showed low-birth weight, mental retardation, growth retardation, microcephaly, intractable epilepsy, ataxia and several minor anomalies such as broad nasal bridge, narrow and downward palpebral fissures, and flat occiput. One case had cataracta and abnormal pigmentation of the retinae.

The main clinical features of r(14) syndrome were convulsion (16/16), growth retardation (10/16), ataxia +/- intention tremor (8/16), repeated respiratory infection (7/16) and dysmorphic features; consisting of downward slanting eyes (10/16),

Case 1 H.T.

Case 2 K.W.

Fig. 4. Partial karyotypes of the proposita.

Table 2. Cytogenetic findings (Blood culture, 48 hr).

	Case 1 (HT)	Case 2 (KW)
45,XX,-14	1	12
46,XX,r(14)*	196	185
46,XX,r(14)**	3	3
Total	200	200

r(14)*, monocentric ring chromosome 14; r(14)**, dicentric ring chromosome 14.

Table 3. Clinical features of r(14) subjects.

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(7)	(8)	(8)	(9)	(10)	(11)	(12)	(13)	(7)
Age at the report	5M	6M	1Y	15M	2Y	2.5Y	2.5Y	3Y	3Y	3Y	3Y	4Y	12Y	15Y	16Y	27Y
Sex	M	F	M	F	F	M	F	F	F	F	F	F	F	F	F	F
Break points	p11q32	...	...	p11q32	p13q24	...	p13q32	p13q32	...	...	p12q24	p11q32	p13q32	p13q32	p11q32	p13q32
Convulsion	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mental retardation	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	±
Microcephaly	+	+	+	+	+	+	+	+	+	+	±	±	+	+	+	—
Growth retardation	+	+	+	+	—	+	+	—	+	+	±	—	—	+	+	—
Ataxia +/- intention tremor	—	—	—	+	—	—	+	—	+	+	+	+	—	+	+	8/16
Abnormal muscle tone	+	+	+	+	+	—	—	—	+	+	+	+	—	—	—	8/16
Repeated respiratory infection	+	+	+	+	+	+	+	+	+	+	+	+	—	—	—	7/16
Pigmented retinae	—	—	—	—	+	+	+	+	+	+	+	+	+	—	+	6/16
Downward slant. eyes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	10/16
Epichathic fold	+	+	+	+	+	+	+	+	+	+	+	+	—	—	—	10/16
Flat occiput	—	+	+	+	+	+	+	+	+	+	+	+	+	+	+	8/16
Broad +/- flat nasal bridge	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	8/16
Dolichocephaly	+	+	+	+	+	+	+	+	+	+	+	+	—	—	—	7/16
High-arched palate	+	+	—	+	+	+	+	—	—	—	+	+	+	+	—	7/16
Short neck	+	+	—	+	+	+	+	—	—	—	+	+	—	—	—	6/16
Low-set ears	+	+	—	+	+	+	+	—	—	—	+	+	—	—	—	5/16
Enlarged lateral ventricles (CT or PEG)	+	+	+	+	+	+	+	+	+	+	+	+	—	—	—	7/16

(1) Triolo *et al.*, 1981, (2) Gilgenkrantz *et al.*, 1971, (3) Lippe and Sparkes, 1981, (4) Amarose *et al.*, 1980, (5) Abe *et al.*, 1978, (6) Dzarlieva *et al.*, 1977, (7) Riley *et al.*, 1981 (familial cases), (8) Jalbert *et al.*, 1977 (twin cases), (9) Schmidt *et al.*, 1981, (10) Vekemans *et al.*, 1979, (11) Iselius *et al.*, 1980, (12) Case 1, (13) Case 2.

epicanthal folds (10/16), flat occiput (8/16), broad $\pm$ flat nasal bridge (8/16), dolichocephaly (7/16), high-arched palate (7/16), short neck (6/16) and low-set ears (5/16) (Table 3). The abnormal pigmentation of the retinae was reported in several cases. This findings may be characteristic in r(14) syndrome. Most cases were females. Most of male cases might be lost in early fetal period. Clinical features of 3 male cases were similar to those of females. Although the younger cases had many minor morphologic abnormalities, the older cases had a few ones. These minor morphologic abnormalities might become obscure with an older age. Main clinical features in older cases were epilepsy, mental retardation, abnormal pigmentation of the retinae and microcephaly.

Ventricular dilatation and cortical atrophy in computed tomography (CT) or pneumoencephalography (PEG) were reported in several cases (7/16). Ataxia, intention tremor and muscle hypotonia may suggest cerebellar dysfunction. There were, however, no cases with cerebellar or brain stem abnormalities in the CT except a case of small cerebellar vermis (Vekemans *et al.*, 1979). Our cases showed ataxia without any other cerebellar signs and normal CT findings. Ataxia in our cases may be due to the intractable epilepsy or anticonvulsants.

Iselius reported a case with mild rachitic changes of the long bones (Iselius *et al.*, 1980). Dzarlieva reported hypoplastic changes of the long bone and delayed bone maturation. Nielsen *et al.* (1978) reported a case of 14q- syndrome with severe rachitis. One of our cases had the same radiological findings and the diminished bone mineral contents. Rachitic changes in our case were thought to be a side effect of epileptic drugs. Thus, the r(14) syndrome may have susceptibility to rickets.

There were no constant dermatoglyphic features in r(14) syndromes. Increased number of ulnar loops on the fingertips were reported by Schmidt *et al.* (8/10). Case 1 had 9 ulnar loops, while case 2 had 10 whorls on the fingertips. Total finger ridge counts were decreased in case 1, but normal in case 2.

In almost cases with r(14) syndrome, the break points were p11-p13 and q32 except for two cases reported by Abe *et al.* and Schmidt *et al.* There were no remarkable variation of the phenotypes in these cases. The phenotype of the r(14) syndrome may be connected with the deletion 14q32-qter or monosomic cell lines derived from ring instability.

A female case with deletion 14q- had psychomotor retardation, epilepsy, repeated respiratory infection and severe rachitis (Nielsen *et al.*, 1978). These features were quite similar to those of r(14) syndrome. Although the ring syndrome shows variable clinical features because of ring instability and different break points (Lejeune, 1968), the r(14) syndrome as well as 14q- syndrome have the characteristic features.

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