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AN INFANT WITH BECKWITH-WIEDEMANN SYNDROME AND CHROMOSOMAL DUPLICATION 11p13→pter.: CORRELATION OF SYMPTOMS BETWEEN 11p TRISOMY AND BECKWITH-WIEDEMANN SYNDROME

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Summary A female infant with partial trisomy 11p(p13→pter) resulting from a paternally inherited balanced translocation is described and compared with 14 previously reported cases of trisomy 11p. The patient had macroglossia, umbilical and inguinal hernias, hypotonia, soft and wrinkled skin, dysmorphic face, high-arched palate, hepatosplenomegaly, intestinal malrotation, Meckel's diverticulum, and mental retardation. The patient's karyotype was 46,XX,−4,+der(4), t(4;11)(q35;p13)pat. Of all 15 patients including our case, the clinical features of 13 patients with duplication of the 11p15 band resembled those of Beckwith-Wiedemann syndrome.

INTRODUCTION

Partial trisomy 11p was first described by Francke (1972) and Falk *et al.* (1973), and at least 14 cases have now been reported. A resemblance between features of trisomy 11p and of Beckwith-Wiedemann syndrome (BWS) was reported by Waziri *et al.* (1983) and Turleau *et al.* (1984). BWS was independently described by Beckwith (1963) and Wiedemann (1964) and more than 200 cases have now been described (Sotelo-Avila *et al.*, 1980). We report here an additional case with partial trisomy 11p, and discuss the relationship between partial trisomy 11p and BWS.

CASE REPORT

The female patient (Fig. 1), the second child of healthy nonconsanguineous parents, was born with asphyxia (Apgar score 5) at 39 week's gestation. At the

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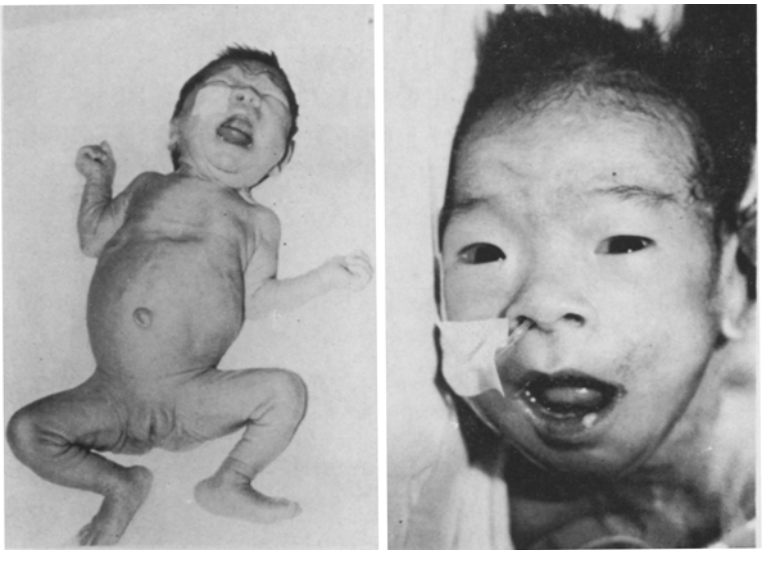

Fig. 1. The patient at 32 days.

Table 1. Dermatoglyphic analysis of the proband.

	Digit					Thenar	Hypothenar	Interdigital pattern		
	1	2	3	4	5			2	3	4
Right	Lu	Lu	W	W	W	—	Lu	—	—	Ld
Left	W	W	W	W	W	—	Lu	—	—	Ld

	Triradius					Main line				Simian line
	a	b	c	d	t	A	B	C	D	
Right	+	+	+	+	t″	1	1	5	7	—
Left	+	+	+	+	t″	1	1	5	7	—

time of her birth, her brother was healthy; the mother was 27 and the father 28 years old. The birth weight was 3,100 g, crown-heel length 49.5 cm, and head circumference 34 cm. She was admitted to our hospital on the second day after birth. She did not have hypoglycemia and neurological examination revealed weak sucking and generalized hypotonia. The craniofacial dysmorphism included macroglossia, large anterior fontanelle prominent occiput, flat forehead, antimongoloid slant, epicanthal folds, hypertelorism, broad flat nasal bridge, high-arched palate, and micrognathia. Other malformations were short neck, hypertrichosis, rocker-bottom feet and soft wrinkled skin. During her hospitalization, the patient demonstrated hepatosplenomegaly, mental retardation, and umbilical and bilateral inguinal

hernias. An intravenous pyelogram revealed a duplication of the right renal pelvis and ureter. On the 69th day after birth, she developed an incarcerated ileus due to intestinal malrotation and Meckel's diverticulum; they were surgically corrected. The patient died at 108 days of age. Dermatoglyphics did not reveal any abnormal patterns except for palmar axial triradii in the t'' position bilaterally. The digital and palmar patterns are described in Table 1.

CYTOGENETIC STUDY

Chromosomal studies of the proband and the parents were performed on peripheral blood lymphocytes by Trypsin-Giemsa banding. The proband had ex-

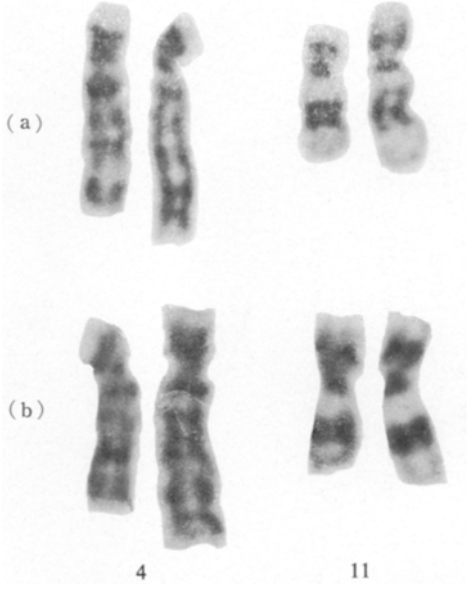

Fig. 2. Partial karyotype of the father (a) and the proband (b) showing the translocation t(4;11)(q35;p13) and partial trisomy 11p13→pter.

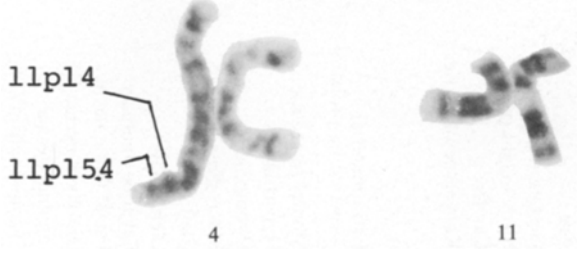

Fig. 3. Partial karyotype of the father 46,XY,t(4;11)(q35;p13).

Table 2. Cytogenetic and clinical features of patients with a partial trisomy 11p.

Authors	Group 1						
	Falk (1973)	Palmer (1976)	Fryns (1981)	Bajolle (1978)	Rethoré (1980)	Waziri (1983) case 1	Waziri (1983) case 2
Sex	M	F	F	F	M	M	F
Age	10 y	3 m	0 d [a]	7 y	15 y	2 m	4 m
Gestational age (wk)	Term	37	30			31.5	39
Birth weight (g)	5,075 [b]	2,440	1,850 [b]	2,270	4,160 [b]	3,600 [b]	4,100 [b]
Carrier	Father	Mother	Father	Father	*de novo*	Father	*de novo*
Karyotype of carrier	t(2;11) (q37;p11.2)	t(3;11;20) (p13;p11; q13)	inv(11) (p11;q25)	t(5;11) (p15;p14)		inv(11) (p13;q23.3)	
Extra material carried by proband	pter→p11.2	pter→p11	pter→p11	pter→p14	pter→p14 p12→q11	pter→p13	p15
Mental retardation	+	+		+	+	+	+
Hypertonia		+		+			
Hypotonia	+					+	
Macroglossia	+			+	+	+	+
Cleft lip		+					
Cleft palate		+			+		
Ear lobe anomaly	+				+	+	+
Facial flame nevus	+					+	
Umbilical hernia		+		+	+	+	+
Inguinal hernia	+	+			+		
Cryptorchidism	+				+	+	
Viscero-abnormality			IM	VSD Mega-ureter			ASD+PS Nephromegaly

Continued (Table 2)

Authors	Group 1						Group 2	
	Turleau (1984) case 1	Turleau (1984) case 2	Journel (1985) Sibling 1	Journel (1985) 2	Aleck (1985)	Our patient	Sanchez (1974)	Strobel (1980)
Sex	F	M	M	M	F	F	F	M
Age	2 y	0 d [a]	16 w [a]	13 w [a]	3 m [a]	3 m [a]	3 y	5 m
Gestational age (wk)	36	32–33	38		Term	39	Term	34
Birth weight (g)	3,400 [b]	2,200 [b]	4,500 [b]	4,450 [b]	3,657	3,100		2,200
Carrier	*de novo*	Father	Father		Father	Father	Mother	Mother
Karyotype of carrier		t(4;11) (q33;p14)	t(11;18) (p15.4;p11.1)		t(5;11) (p15;p12)	t(4;11) (q35;p13)	t(11;12;13) (p12p15q14.1 q23;p11; q24.1;q34)	inv(11) (p14p11q14)
Extra material carried by proband	p15	pter→p14	pter→p15.4		pter→p12	pter→p13	p14→p12	p14.1→p11.3
Mental retardation	+		+	+	+	+	+	+
Hypertonia							+	
Hypotonia	+		+	+	+	+		+
Macroglossia	+	+	+	+	+	+		
Cleft lip							+	+
Cleft palate		+			+		+	+
Ear lobe anomaly			+	+				
Facial flame nevus			+	+				
Umbilical hernia	+		+			+		
Inguinal hernia		+	+			+		
Cryptorchidism		+						
Viscero-abnormality	ASD HS Mega-ureter Ovarian hernia, Diaphragmatic elevation	HS Spina bifida,	Tetralogy of Fallot, Dextrocardia	VSD	Interatrial septal aneurysm	HS IM Meckel's diverticulum, Anomaly of pelvis and ureter	IM Cyst in the septum pellucidum	

[a] Death, [b] Large birth weight. VSD, ventricular septal defect; ASD, atrial septal defect; PS, pulmonary stenosis; IM, intestinal malrotation; HS, hepatosplenomegaly.

trachromosomal material on the long arm of chromosome 4. Her mother had a normal karyotype. Her father had the same abnormality in chromosome 4 as the proband and the distal end of the short arm of chromosome 11 was shortened. The breaking point of the chromosome 11 was at 11p13. These results indicate that the proband's karyotype was 46,XX,−4,+der(4), t(4;11)(q35;p13)pat (Figs. 2 and. 3)

DISCUSSION

The clinical features of 14 previous cases of partial trisomy of the short arm of chromosome 11 as well as ours are compared in Table 2. The chromosomal abnormality in 12 of the 15 patients resulted from rearrangement of parental chromosomes; nine of these 12 patients were given an additional portion of chromosome 11 by a paternal carrier and the rest by a maternal carrier.

With regard to their karyotypes, breaking points on chromosome 11p were found at p11, p12, p13, p14 and p15 bands in each patient. The duplication of 11p15 band, however, was common to all of the patients except for the two cases described by Sanchez *et al.* (1974) and Strobel *et al.* (1980). Since the features of 13 patients with 11p15 trisomy differ from those of the two patients without 11p15, the 13 patients are included in one group and the rest in a second group. The characteristic features of the first group are mental retardation 11/11, macroglossia

Table 3. Frequency of clinical finding in Beckwith-Wiedemann syndrome and trisomy 11p.

Clinical finding	% in BWS[a]	Trisomy 11p	
		Group 1	Group 2
Macroglossia	82.0	11/13	0/2
Umbilial anomalies	75.2	9/13	0/2
Increased birth weight	38.5	9/13	0/2
Ear lobe anomalies	38.0	7/13	0/2
Facial flame nevus	32.1	2/13	0/2
Hepatomegaly	32.1	4/13	0/2
Genitourinary anomalies	24.1	7/13	0/2
Nephromegaly	23.0	3/13	0/2
Cardiac anomalies	15.5	6/13	0/2
Splenomegaly	13.8	4/13	0/2
Gastrointestinal anomalies	13.2	3/13	0/2
Mental retardation	12.0	11/11	2/2
Inguinal herniae	5.7	6/13	0/2
Hypoglycemia	30.4	3/13	0/2

[a] This result is quoted by Sotelo-Avial *et al.* (1980).

11/13, large birth weight 9/13, umbilical hernia 9/13, cryptorchidism 4/6, early death 6/13, and congenital heart disease 6/13. The patients in the second group do not have any of the features like the above mentioned except for mental retardation. They have severe cleft lip and palate, and we are under the impression that their facial dysmorphisms are different from those of patients in the first group (Tables 2 and 3). On the basis of the phenotypic and cytogenetic findings in the first group of patients we suspect that the 11p15 band taking part in the 11p trisomy may constitute a clinically recognizable syndrome.

The four cardinal signs of BWS are umbilical hernia, macroglossia, gigantism and ear lobe grooves (Wiedemann, 1973). Furthermore, a review of the patient literature shows several abnormalities occurring in various combinations (Sotero-Avila *et al.*, 1980). In Table 3, the frequencies of clinical findings in the first group are compared with those in BWS. They are similar except that in the first group higher frequencies of mental retardation, early death and inguinal hernia are found. Furthermore, the two patients in the second group did not show any similarities to BWS. The mode of inheritance in BWS remains uncertain. Although most instances of BWS are sporadic, familial cases are suggested to be autosomal recessive, or autosomal dominant with variable expressivity (Sotero-Avila *et al.*, 1980; Niikawa *et al.*, 1986).

Genes coding for insulin and oncogene HRAS1 were confirmed within the 11p15 band (McKusick #17673 and 19002). Hyperinsulinemia in the fetal period causes neonatal hypoglycemia and gigantism, which are indicative of BWS. The increased frequency of malignant tumors in patients with BWS may be explained by the localization of oncogenic gene on the 11p15. Saal *et al.* (1984) studied the molecular hybridization of DNA probes for the insulin and c-Ha-*ras*-1 genes in two BWS patients and could not find evidence for an increased dosage of either gene. We suggest that the genetic material relating to BWS should be on the 11p15 band since there are a marked phenotypic overlap between the BWS and 11p15 trisomy patients, although further gene dosage studies as well as studies of DNA polymorphisms are needed to clarify the relationship between 11p15 and BWS.

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