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CHROMOSOME ABNORMALITIES AND EPILEPTIC SEIZURES

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Summary A cytogenetic survey was performed on 172 patients with mental retardation and epileptic seizures. Chromosome abnormalities were detected in 27 patients consisting of 18 out of 36 patients with more than 3 dysmorphic features (MCA group) and 9 out of 136 patients with less than 2 dysmorphisms (non-MCA group). Chromosome abnormalities were frequently found in cases with neonatal seizures, West syndrome, Lennox syndrome and Grand mal seizures, but not in partial seizure or pure absence seizures. It is significant that 9 chromosome abnormalities including 4 rings were unexpectedly detected, and 6 of these cases developed intractable seizures. The incidences of seizures in the patients with various types of chromosome abnormalities were presented along with a review of the literatures. The incidence of seizures in each chromosome abnormality varied from 100% to 0% and was not correlated with the degree of dysmorphism or lethality. Therefore, a specific chromosome site closely related with epileptogenesis may be supposed.

INTRODUCTION

Epilepsy, a symptom of underlying brain dysfunction, is probably caused by various etiologies. The genetic basis of epilepsy has been studied and epileptic genes have been investigated by molecular genetic studies (Delgado-Escueta *et al.*, 1986). To study the epileptic gene, one must find the specific chromosomal site of epileptic seizures. However, the chromosomal location of specific epilepsy is unknown as yet. It is important to delineate the relationship between chromosome anomalies (chromosomal sites) and seizures. Numerous chromosome abnormalities, delineated by banding techniques, have been reported to complicate epileptic seizures (Kunze, 1980). Complications of seizures are important in the management of patients with chromosome abnormalities. The incidence of epileptic seizures has

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been reported for a few chromosome abnormalities such as trisomy 21 and trisomy 18 (Nielsen and Pedersen, 1969; Taylor, 1970; Hodes *et al.*, 1978; Tatsuno *et al.*, 1984), but little is known about most chromosome abnormalities because of their rareness. Also, we have little knowledge as to the incidence of chromosomal anomalies in individuals with mental retardation and epileptic seizures. We performed chromosome analyses and investigated the frequencies of chromosome abnormalities and the characteristics of seizures including types, onset, complications and prognosis in such patients. Furthermore, we examined the incidence of epileptic seizures in chromosome abnormalities by means of a review of the literatures and our own cases.

SUBJECTS AND METHODS

A cytogenetic study was performed from January, 1979 to December, 1985, on 172 mentally retarded patients with associated seizures in the Division of Child Neurology, Tottori University School of Medicine in Yonago and the residential institutions for mentally retarded (Kaisei Gakuen, Kurayoshi and Mominoki-En, Yonago). Patients with genetic diseases, obvious perinatal or postnatal brain damage, or simple febrile convulsions were excluded. The patients were divided into two groups according to the number of major and/or minor dysmorphisms. A major congenital anomaly was defined as a morphological abnormality with a functional defect present at birth. A minor anomaly was defined as minor morphological abnormalities without a functional defect. Thirty-six patients (18 males and 18 females) showing more than 3 major and minor anomalies comprised the multiple congenital anomaly (MCA) group. A hundred thirty-six patients (68 males and 68 females) showing less than 2 major and/or minor anomalies made up the non-MCA group. The age at examination ranged from 0 to 26 years (Table 1).

Table 1. Age at the time of chromosome analysis in mentally retarded individuals with associated seizures.

Age	MCA group		Non-MCA group		Total		
	Male	Female	Male	Female	Male	Female	Total
0- 5 M	6	5	6	3	12	8	20
6-11 M	2	4	5	11	7	17	22
1- 4 Y	2	4	9	17	11	21	32
5- 9 Y	3	3	17	13	20	16	36
10-14 Y	2	1	10	15	12	16	28
15-19 Y	2	0	12	4	14	4	18
20-26 Y	1	1	9	5	10	6	16
Total	18	18	68	68	86	86	172

MCA, multiple congenital anomalies (more than 3 major or minor anomalies); M, months; Y, years.

The degree of mental retardation ranged from moderate to severe. Patients of under 4 years of age exhibited severe developmental delay or mental retardation diagnosed on follow-up examinations. Chromosome analyses using peripheral lymphocytes were carried out by the conventional Giemsa method in 40 cases and by banding methods (R and/or G-banding) in 132 cases (Ieshima *et al.*, 1984). The incidence and characteristics of the seizures were studied. Cranial CT scanning was performed for patients with chromosome abnormalities.

RESULTS

Chromosome abnormalities were observed in 27 of the 172 patients; that is, 18 of the 36 patients (50%) in MCA group and 9 of the 136 patients (6.6%) in non-MCA group. The 18 patients with MCA were suspected to have chromosome abnormalities clinically. However, the other 9 with chromosome abnormalities, including 2 with inversions, were referred to our clinic because of intractable seizures and severe mental retardation without MCA. The clinical features of the chromosome abnormalities are presented in Table 2. In MCA group (Table 2a), chromosome abnormalities consist of the 13 cases with trisomy or partial trisomy, and the 5 with monosomy or ring chromosome. As to seizure type, neonatal convulsions were observed in 7 cases, West syndrome in 3 cases, and generalized tonic clonic (GTC) seizures in 9 cases. All cases with neonatal convulsions died in early infancy and 3 of them showed brain anomalies observed by CT scanning. Two cases

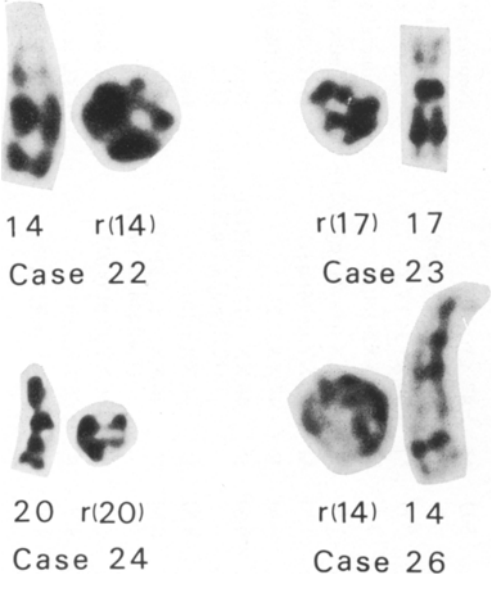

Fig. 1. Partial karyotypes of cases 22, 23, 24, and 26.

Table 2a. Clinical features of patients with chromosome abnormalities having associated seizures in MCA group.

	Age	Sex	Karyotype	Seizure type	Onset of seizures	Prognosis	Cranial CT scan	References
1.	2 D	M	47,XY,+18	Neonatal seizures	4 D	died at 7 D	not available	
2.	3 D	M	47,XY,+18	Neonatal seizures	4 D	died at 14 D	not available	
3.	5 D	M	47,XY,+18	Neonatal seizures	3 D	died at 10 D	cerebellar hypoplasia	
4.	5 D	F	46,XX,del(7)(q32)	Neonatal seizures	3 D	died at 4 M	holoprosencephaly	
5.	7 D	M	47,XY,+18	Neonatal seizures	3 D	died at 1 M	cerebellar hypoplasia	
6.	7 D	F	46,XX,i(18q)	Neonatal seizures	7 D	died at 3 M	normal	(Ieshima *et al.*, 1985)
7.	1 M	F	46,XX,t(14;21)(p11;p11)	Infantile spasms	11 M	good	striatum hypodensity	
8.	1 M	M	46,XY,del(4)(q31)	GTC seizures	10 M	died at 2 Y	normal	
9.	6 M	F	47,XX,+21	Infantile spasms	7 M	good	normal	
10.	6 M	F	46,XX,−12,+der(12), t(12;15)(q24.3;q22.2)mat	Neonatal seizures GTC seizures	20 D	died at 8 M	Dandy-Walker malformation	(Ieshima *et al.*, 1985)
11.	8 M	F	46,XX,r(18)	Infantile spasms	22 M	good	normal	
12.	8 M	F	46,XX,−1,+der(1), t(1;4)(q44;q25)mat	GTC seizures	1 Y	died at 3 Y	normal	
13.	5 Y	M	46,XY,dup(5)(p23)	GTC seizures	6 Y	controlled	normal	
14.	8 Y	F	46,XX,21p+	GTC seizures	6 Y	controlled	normal	
15.	8 Y	F	46,XX,del(1)(q42)	GTC seizures	6 M	controlled	dilation of lateral ventricles	
16.	16 Y	M	46,XY,21p+	GTC seizures	3 Y	controlled	normal	
17.	24 Y	M	46,XY,del(9)(p23)	GTC seizures	3 Y	controlled	dilation of lateral ventricles	
18.	25 Y	F	46,XX,4q+	GTC seizures	7 Y	controlled	dilation of lateral ventricles	

Table 2b. Clinical features of patients with chromosome abnormalities having associated seizures in non-MCA group.

	Age	Sex	Karyotype	Seizure type	Onset of seizures	Prognosis	Cranial CT scan	References
19.	7 M	M	47,XY,+M	Infantile spasms	7 M	intractable	normal	
20.	8 M	M	46,XY,inv(9)(p11q12)	Infantile spasms	6 M	controlled	normal	
21.	9 M	M	46,XY,inv(10)(p11q12)	Lennox syndrome	6 Y	intractable	normal	
22.	6 Y	F	46,XX,r(14)	GTC seizures	17 M	intractable	normal	(Ieshima *et al.*, 1983)
23.	10 Y	F	46,XX,r(17)	GTC seizures Complex partial	11 M	intractable	normal	(Ono *et al.*, 1974)
24.	13 Y	M	46,XY,r(20)/46,XY	Lennox syndrome	6 Y	intractable	normal	
25.	15 Y	M	48,XXXY	GTC seizures	15 Y	controlled	normal	
26.	16 Y	F	46,XX,r(14)	Lennox syndrome	11 M	intractable	normal	(Ieshima *et al.*, 1983)
27.	25 Y	M	47,XY,+22/46,XY	GTC, myoclonic	15 Y	controlled	normal	

D, days; M, months; Y, years.

(case 7, 9) with Down syndrome and case 11 with ring chromosome 18 had West syndrome, which were not controlled by anticonvulsants but spontaneously stopped at late infancy. Chromosome abnormalities in non-MCA group consisted of trisomy or partial trisomy in 3 cases, ring chromosome in 4 cases, and pericentric inversions in 2 cases. It is noted that intractable seizures were frequently observed in 6 out of 9 cases, especially in all those with ring chromosomes (Fig. 1). It is not known whether pericentric inversion in case 20 and 21 caused the seizures or not. Cranial CT scannings in the non-MCA group revealed no abnormal findings.

As shown in Table 3, the chromosome abnormalities in MCA group were frequently detected in cases of neonatal convulsions, West syndrome and GTC. Those in the non-MCA group were frequently found in the cases of Lennox syndrome,

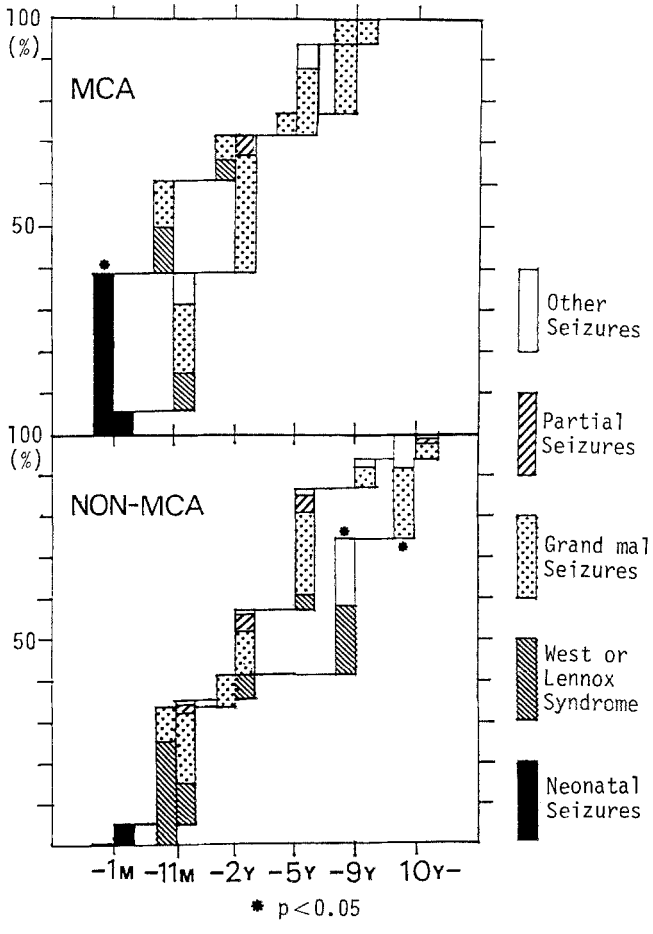

Fig. 2. Cumulative frequency distribution of seizure onset and seizure type comparing patients with chromosome abnormalities (left column) and those with normal karyotype (right column).

West syndrome, GTC seizures and intractable seizures. Chromosome abnormalities were not detected in the partial seizures and absence seizures.

The age at onset of seizures and the type of seizures was compared between the two groups with chromosome abnormalities and the normal karyotype (Fig. 2). Neonatal seizures in MCA group and seizures more than 6 years of age in non-MCA were associated significantly in the patients with chromosome abnormalities.

DISCUSSION

Not much attention has been paid to chromosome abnormalities in patients with epileptic seizures. In our study, it was found that seizures in the mentally retarded are one of the indicators of chromosome abnormalities. Chromosome abnormalities were found in 50% of patients associated with both multiple congenital anomalies and seizures. When patients with multiple dysmorphic features were excluded, the incidence of chromosome abnormalities was 6.6% (9/136). Such 9 cases with chromosome abnormalities showed no dysmorphic features, 6 of them had intractable seizures and 4 of them showed ring chromosomes.

As to seizure type, chromosome abnormalities were frequently observed in neonatal seizures, West syndrome, Lennox syndrome and GTC seizures. Two groups of seizures of chromosome abnormalities can be characterized. The first group is patients with multiple dysmorphic features and neonatal convulsions. These patients had a poor prognosis as to survival. Such neonatal convulsions in these cases may be caused by brain anomalies or hypoxic brain damage during the terminal stage. The second group is made up of patients with intractable seizures, no dysmorphic features, and few characteristics different from outpatients with epilepsy. It is noted that 4 out of 6 patients in the latter group had ring chromosomes.

The incidences of epileptic seizures in chromosome abnormalities reported in the literatures and in our own cases are shown in Table 4. As to common chromosome abnormalities such as Down syndrome, trisomy 18 and Klinefelter syndrome,

Table 3. Incidence of chromosome abnormalities in each seizure type.

	Total	MCA group	Non-MCA group
Neonatal seizures	36.8% (7/19)	58.3% (7/12)	0 % (0/7)
West syndrome	19.2% (5/26)	37.5% (3/8)	11.1% (2/18)
Lennox syndrome	13.6% (3/22)	0 % (0/0)	13.6% (3/22)
GTC seizures	13.4% (13/97)	40.9% (9/22)	5.3% (4/75)
Myoclonic seizures	20 % (1/5)	0 % (0/0)	20 % (1/5)
Complex partial seizures	25 % (1/4)	0 % (0/0)	25 % (1/4)
Partial seizures	0 % (0/14)	0 % (0/0)	0 % (0/14)
Intractable seizures	14.3% (6/42)	0 % (0/3)	15.4% (6/39)
Total	15.7% (27/172)	50 % (18/36)	6.6% (9/136)

Table 4. Frequencies of seizures in chromosome abnormalities——reported cases and our own cases.

	Reported cases	Our cases	References
1. Constantly associated			
* r(14)	100% (16/16)	2/2	(Ieshima *et al.*, 1983)
* r(20)	100% (8/8)	1/1	(Stewart *et al.*, 1979; Jalbert, 1977; Herva *et al.*, 1977)
2. Frequently associated (30–70%)			
trisomy 3q	66.7% (4/6)	—	(Salazar *et al.*, 1979)
* trisomy 5p	66.7% (10/15)	1/1	(Kunze, 1980)
trisomy 18	62.5% (5/8)	4/11	(Hodes *et al.*, 1978)
* r(21)	62.5% (10/16)	—	(Kunze, 1980)
trisomy 16p	62.5% (5/8)	—	(McMorrow *et al.*, 1984; Cohen *et al.*, 1983; Roberts and Duckett, 1978; Leschot *et al.*, 1979)
monosomy 6q	60.0% (3/5)	—	(Liberfarb *et al.*, 1978)
distal 13q trisomy	60.0% (6/10)	—	(Schutten *et al.*, 1978)
* distal 1q monosomy	60.0% (6/10)	1/1	(Speevak *et al.*, 1985)
* r(17)	57.1% (3/3)	1/1	(Carpenter *et al.*, 1981; Stratton *et al.*, 1984)
proximal 14q trisomy	54.5% (6/11)	—	(Miller *et al.*, 1979)
monosomy 20p	50.0% (2/4)	—	(Garcia-Cruz *et al.*, 1985)
* monosomy 4p	46.6% (27/58)	—	(Johnson *et al.*, 1976; Stengel-Rutkowski *et al.*, 1984)
distal 15q trisomy	46.2% (6/13)	1/1	(Ieshima *et al.*, 1985)
* r(18)	33.3% (5/15)	1/1	(Kunze, 1980)
monosomy 10p	33.3% (5/15)	—	(Koenig *et al.*, 1985)
* monosomy 18p	common	0/2	(de Grouchy and Turleau, 1984)
* XYY	33.3% (2/6)	—	(Baughman and Mann, 1972)

Table 4. Frequencies of seizures in chromosome abnormalities——reported cases and our own cases (continued).

	Reported cases	Our cases	References
3. Occasionally associated (10–30%)			
* monosomy 3p	28.6% (2/7)	—	(Merrild *et al.*, 1981; Beneck *et al.*, 1984)
* trisomy 4p	26.1% (12/46)	—	(Reynolds *et al.*, 1983)
trisomy 13	25.0%	0/3	(Taylor, 1970)
	>50%		(Smith, 1976)
monosomy 7q	25.0% (4/16)	1/1	(Kunze, 1980)
distal 14q trisomy	22.2% (2/9)	—	(Atkin and Patil, 1983)
trisomy 2p	20.0% (2/10)	0/1	(Cassidy *et al.*, 1977)
* Klinefelter syndrome	20.0% (5/25)	1/5	(Nielsen and Pedersen, 1969)
* trisomy 20p	20.0% (3/15)	—	(Funderburk *et al.*, 1983)
* trisomy 12p	20.0% (2/10)	—	(Hansteen *et al.*, 1978)
* r(22)	19.0% (4/21)	—	(Hunter *et al.*, 1977)
* trisomy 8	18.9% (7/37)	—	(Riccardi, 1977)
r(4)	13.3% (2/15)	—	(Young and Zalneraitis, 1980)
* trisomy 10p	11.1% (3/27)	—	(Kunze, 1980)
* trisomy 9p	10.0% (6/60)	0/1	(Kunze, 1980)
4. Rarely associated (1–10%)			
* trisomy 8p	7.7% (1/13)	—	(Kunze, 1980)
* XXYY	6.7% (5/75)	0/2	(Kunze, 1980)
monosomy 11q	5.3% (1/19)	—	(Kunze, 1980)
* monosomy 9p	4.8% (1/21)	1/1	(Kunze, 1980)
* trisomy 21	1–10%	2/147	(Smith and Berg, 1976)
	1.4% (13/844)		(Tatsuno *et al.*, 1984)
* monosomy 5p	1.0%	0/6	(Niebuhr, 1978)

* Relatively good prognosis as to life span.

several studies were reported, but most chromosome abnormalities are rarely seen. Therefore, the incidence of epileptic seizures in new chromosome abnormalities was obtained through the accumulation of reported cases. The incidence of seizures in each chromosome abnormality varied with the type of chromosome abnormality, as shown in Table 4. It is important and useful to know the probabilities of association of seizures for the management of patients with chromosome abnormalities. The chromosome abnormalities for which the incidence of seizures was more than 30% and the survival rate was rather good were r(14), r(20), trisomy 5p, r(21), r(17), distal 1q monosomy, monosomy 4p, r(18), monosomy 18p and XYY syndrome, in that order. Brain anomalies including minor morphological changes may cause seizures in some cases, but their frequency of seizures is independent of the survival rate, multiple dysmorphisms and the age at onset. Therefore, the differences in the incidence of seizures may be explained by the differences in the locations of chromosomes. It is noteworthy that 100% of the patients with r(14) and r(20) had the complication of epileptic seizures.

Seizures are specific in these chromosomal anomalies. Although the pathogenesis and etiology of epileptic seizures are unknown, being probably heterogenous, molecular defects produced by some chromosome abnormalities including deletions and duplications may be related to epileptogenesis. The specific chromosome sites involved in seizures, presented in Fig. 3, may include epileptic genes. Further study

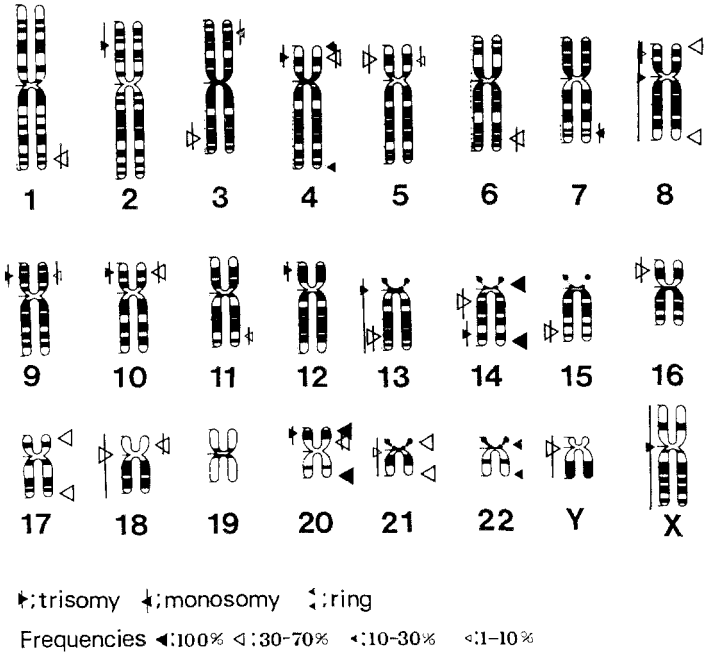

Fig. 3. Chromosome sites concerned with seizures.

is needed to identify the epileptic genes on abnormal chromosomes such as r(14) and r(20) using recently developed recombinant DNA technologies.

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