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Original article

Multi-institutional study on the correlation between chromosomal abnormalities and epilepsy☆

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Abstract

While there is an abundance of literature describing the association of chromosome aberrations with epilepsy, only a few refer to the detailed features of epilepsy. It is important to investigate the associations between specific chromosome abnormalities and features of epilepsy to identify genes involved in epilepsy and treat them more effectively. We investigated the correlation between specific chromosome aberrations and epilepsy by sending questionnaires to the members of Kyoto Multi-institutional Study Group of Pediatric Neurology. Seventy-six patients were collected from 10 institutions. Chromosome abnormalities included: Down syndrome ($n = 19$); Angelman syndrome ($n = 8$); Prader-Willi syndrome ($n = 4$); 4p- syndrome ($n = 3$); 1q- syndrome ($n = 2$); 5p- syndrome ($n = 2$); Miller–Dieker syndrome ($n = 2$); 18q- syndrome; ($n = 2$); Klinefelter syndrome; ($n = 2$); and 32 other individual chromosomal aberrations. Overall, the severity of mental retardation correlated with the severity of epilepsy. We could abstract characteristic features of epilepsy in some syndromes. In Angelman and Prader-Willi syndromes, febrile seizures occurred frequently, the onset of epilepsy was in early childhood and seizure phenotype was multiple. Paroxysmal discharge of the occipital region and diffuse high voltage slow wave on electroencephalography were characteristic in Angelman syndrome. In Down syndrome, West syndrome and focal epilepsy were common and the prognosis of epilepsy in West syndrome with Down syndrome was good. In 4p- syndrome, febrile seizures were often seen, and unilateral or generalized clonic or tonic-clonic status epilepticus were characteristic. For the other chromosomal aberrations investigated here, the patient numbers were too small to abstract common features of epilepsy.

Keywords: Epilepsy; Chromosome aberrations; Mental retardation; Febrile seizures; Genes responsible for epileptogenesis

1. Introduction

It has been reported that patients with certain chromosome aberrations are likely to have epilepsy. While there is

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an abundance of literature describing the association of chromosome aberrations and epilepsy, only a few reports and textbooks refer to the detailed features of epilepsy [1–5]. It is important to characterize the features of epilepsy which are associated with each chromosome aberration to identify genes involved in epilepsy and better treat seizures. However, most of these chromosome aberrations are rare, therefore it is difficult to collect sufficient patients to identify characteristic features of epilepsy for each syndrome, especially within one institution. To address this problem we examined patients with chromosome aberrations and epilepsy in a multi-institutional collaborative study.

2. Patients and methods

We investigated the correlation between chromosome aberrations and epilepsy by sending questionnaires to members of Kyoto Multi-institutional Study Group of Pediatric Neurology. Through these questionnaires we sought details of chromosomal karyotype, age at onset of epilepsy, clinical seizure semiology, classification of epilepsy, prognosis of epilepsy, EEG findings, cranial MRI findings, and severity of mental retardation, retrospectively. We also investigated the frequency of epilepsy associated with chromosome aberrations in each institution. Patients with a chromosome aberration and epilepsy who had consulted each institution during the previous year (from 2001.8.1 to 2002.7.31) were selected for this study.

Chromosome aberration was defined as abnormality detected by G-banding or fluorescence in situ hybridization (FISH). We classified epilepsy into four groups by seizure semiology and EEG: (1) generalized; (2) focal; (3) undetermined, when the characteristics showed both generalized and focal types; and (4) unclassified, when there was too little information for classification. The prognosis of epilepsy was defined as: good when there was a seizure-free period longer than 1 year with or without medication; poor when seizures occurred during the previous one year; and unknown when there was insufficient information about recent seizure attacks. The severity of mental retardation was classified as severe when the IQ was below 35, and as mild/moderate between 35 and 75.

3. Results

We analyzed 76 patients from 10 institutions. There were 34 males and 42 females and the patients' ages at the time of investigation ranged from 4 months to 34 years. Epilepsy classifications were as follows: 22 generalized, 30 focal, 13 undetermined, and 11 unclassified. The prognosis was good for 40 patients, poor for 31 patients, and unknown for the remaining five patients. Regarding the severity of mental retardation, 55 were severely retarded, 20 patients were mildly/moderately retarded, and one with a ring chromosome 20 was not retarded. While 24 of the 55 patients (43.6%) with severe mental retardation showed a poor prognosis, only two of 20 patients (10%) with mild/moderate mental retardation showed a poor prognosis of epilepsy ($P < 0.005$). This tendency was seen in Down syndrome, but not in Angelman syndrome (AS). All eight patients with the latter were severely mentally retarded but five of them showed good seizure prognosis. The number of the other chromosome aberrations is too small to make it possible to assess any such tendency. Fifty-six patients were examined by MRI. Twenty-two were normal and 34 were abnormal. Most of the abnormal MRI findings represented diffuse cerebral atrophy, however other findings included agenesis of the corpus callosum in 1q- syndrome, Dandy-Walker cyst in a case of mosaic trisomy 9, lissencephaly in Miller–Dieker syndrome, and cerebral white matter dysmyelination in 18q- syndrome. These abnormalities are typical features of these syndromes. No correlation could be established between abnormalities on MRI and prognosis of epilepsy.

We investigated the frequency of epilepsy associated with chromosome aberrations in five institutions. In a hospital for children, 17.6% (29/165) of patients with chromosome abnormalities had epilepsy and in two rehabilitation centers 8.6% (8/93) and 25.8% (8/31) of patients were affected. The remaining two institutions were a general hospital, in which 33.3% (1/3) of patients with chromosome abnormalities were affected, and an epilepsy center in which 81.8% (18/22) of patients were affected.

Detailed data of those patients are shown in Tables 1–3c. Table 1 describes eight patients with AS and four patients with Prader-Willi syndrome (PWS). In all patients with AS and PWS, epilepsy started within the first three years of life. Febrile seizures occurred with higher frequency in patients with these two syndromes than in patients with any of the other chromosome aberrations investigated. Of the 12 patients with either AS or PWS, 10 had febrile seizures, while only 18 of the remaining 64 patients had febrile seizures ($P < 0.005$). In AS, five patients had remained seizure-free for more than 1 year. The classification of epilepsy was undetermined in five patients. All patients had multiple seizure semiology such as myoclonic, tonic, atonic, complex partial, and generalized tonic–clonic seizure. Spikes or spike-wave complexes of the occipital region on EEG were often seen (6/8 patients), and diffuse high voltage slow waves were sometimes seen (3/8 patients). All of these patients had severe mental retardation. In PWS, the prognosis of epilepsy was good in three patients and the seizure semiology was varied and multiple.

Table 2 shows 19 patients with Down syndrome, which were divided into two groups. One group included 10 patients with West syndrome, while the other group included nine patients with epilepsy other than West syndrome. Of 12 patients with Down syndrome who showed onset of epilepsy in infancy, 10 patients (83%) had infantile spasms. In seven of 10 patients with Down

Table 1
Epileptological features in patients with Angelman and Prader-Willi syndromes in our series

Age/Sex	Chromosomal karyotype	Synd.	Age of onset	EEG	Epilepsy classification	Seizure semiology	FS	Seizure prognosis	MRI	MR
12yF	46,XX,del(15)(q11.1q12)	AS	2y6m	Bil.O, P sp Diffuse sp-w	Undetermined	GTC, tonic, atonic	○	Good	Demyelination	Severe
10yF	46,XX,inv(9)(q22.32q34.11) del(15)(q11.1q12)	AS	2y5m	Bil.O sp-w diffuse sp-w	Undetermined	CPS, GTC, myoclonic	○	Poor	WNL	Severe
13yM	46,XY,del(15)(q11.1q12)	AS	2y9m	Rt.O sp diffuse sp-w	Undetermined	CPS	○	Good	Cerebral atrophy demyelination	Severe
3yM	46,XY,del(15)(q11q13)	AS	1y2m	aT, C, diffuse HVS	Undetermined	Tonic, myoclonic	○	Good	WNL	Severe
8yM	46,XY,del(15)(q11.2q13)	AS	3y0m	Bil.O sp-w diffuse sp-w	Undetermined	CPS, GTC, atonic, myoclonic	○	Poor	WNL	Severe
7yM	46,XY,del(15)(q11.2q11.2)	AS	2y5m	Bil.O sp-w, bil, Fp, sharp Diffuse HVS	Focal	CPS, GTC, atonic, myoclonic	○	Poor	WNL	Severe
8yM	FISH (detalias unknown)	AS	2y10m	O sp	Focal	CPS, myoclonic	○	Poor	ND	Severe
3yF	FISH (details unknown)	AS	2y	Diffuse HVS	Generalized	CPS, myoclonic	○	Good	WNL	Mild/moderate
12yM	46,XY,del (15)(q11.1q12)	PWS	3y1m	Normal	Generalized	GTC	○	Good	Cerbral atrophy	Sever
5yM	46,XY,del (15)(q11.2q11.2)	PWS	1y11m	Multifocal sp Diffuse HVS, sp-w	Undetermined	CPS, GTC, tonic myoclonic	○	Poor	ND	Mild/moderate
7yF	46,XX,del (15)(q11.2q11.2)	PWS	3y11m	Lt.P sp	Focal	CPS, hermiclonic	○	Good	WNL	Mild/moderate
3yF	46,XX,del (15)(q11.2q13)	PWS	1y2m	Rt.C sp	Focal	GTC, CPS, myoclonic	○	Good	WNL	Mild/moderate

FS, febrile seizures; Synd, syndrome; MR, mental retardation; AS, Angelman syndrome; PWS, Prader-Willi syndrome; sp, spikes; sp-w, spike and wave; aT, anterior temporal; Fp, front polar; F, frontal; C, central; P, parietal; O, occipital; bil., bilateral; tonic, tonic seizures; atonic, atonic seizures; HVS, sharp, sharp wave; high voltage slow wave; WNL, within normal limit; ND, not described.

syndrome accompanied by West syndrome, seizures stopped and the prognosis of epilepsy was good.

In Down syndrome with epilepsy other than West syndrome, epilepsy started during early childhood in three patients, in the teens in three patients, and in the twenties in two patients. The seizure semiology was variable, including tonic seizure (five patients), generalized tonic–clonic seizure (GTC, three patients), secondary GTC, atonic, and clonic-myoclonic seizure (one patient each). In total, only one of 19 patients with Down syndrome had febrile seizures.

Tables 3a–c show other chromosomal aberrations, in which three patients with 4p- syndrome, two patients each with 1q- syndrome, 5p- syndrome, Miller–Dieker syndrome, 18q- syndrome and Klinefelter syndrome, and one patient each with several other chromosome aberrations are included.

All three patients with 4p- syndrome showed status epilepticus and had hemi-clonic convulsions, and two had both generalized tonic–clonic seizure and febrile seizures. Two cases had febrile seizures.

Both patients with 1q- syndrome had deletion of 1q42. Common characteristics were that the onset of epilepsy was before 3 years of age, the classification of epilepsy was localized, and the seizure semiology was hemi-clonic convulsion.

No characteristic features were seen in 5p-, Miller–Dieker, 18q-, or Klinefelter syndromes (two patients each).

4. Discussion

In general, patients with severe mental retardation showed a poor seizure prognosis in this study ($P < 0.005$). This tendency was seen in Down syndrome, but not in AS, which showed a relatively good prognosis of epilepsy in spite of severe mental retardation.

It has been reported that patients with chromosome aberrations have a higher risk of seizures than the general population [4,5]. Our results support this finding, however there were differences in epilepsy frequency among the institutions investigated. In the epilepsy center, not surprisingly, the frequency of epilepsy was higher than that in the other four institutions: a general hospital, two rehabilitation centers and a hospital for children. Ieshima et al. reported that chromosome aberrations were observed in 27 of 172 patients (15.7%) with mental retardation and epilepsy [6]. These findings suggest that epilepsy frequently occurs in patients with chromosome aberrations, and that patients with mental retardation and epilepsy should be investigated for chromosome abnormalities.

In AS and PWS, some common characteristics were seen. Firstly, febrile seizures occurred more frequently in these syndromes than in patients with other chromosome aberrations ($P < 0.005$). This finding will be discussed further below. Secondly, the onset of epilepsy occurred in early childhood (under 3 or 4 years of age), and thirdly,

Table 2
Epileptological features in patients with Down syndrome in our series

Age	Sex	Age of onset	EEG	Epilepsy classification	Seizure semiology	FS	Seizure prognosis	MRI	MR
1y3m	M	0y9m	Hyps → multifocal sp-w	Generlized	Spasm		Unknown	Cerebral atrophy	Severe
3y	M	0y6m	Hyps → diffuse sp-w	Generlized	Spasm		Poor	Cerebral atrophy	Severe
3y	F	0y4m	Hyps → It.O sp-w	Generlized	Spasm		Good	ND	Mild/moderate
8y	M	0y5m	Hyps → normal	Generlized	Spasm		Good	Cerebral atrophy	Mild/moderate
11y	F	0y5m	Hyps → bil.F sp-w	Generlized	Spasm → atonic, GTC		Poor	Cerebral atrophy	Severe
8y	M	0y7m	Hyps	Generlized	Spasm		Good	Cerebral atrophy	Mild/moderate
9y	M	0y10m	Hyps → bil.F sp	Generlized	Spasm		Good	ND	Severse
7y	M	0y10m	Hyps → normal	Generlized	Spasm		Good	ND	Severe
2y	F	0y7m	Hyps	Generlized	Spasm		Good	WNL	Severe
6y	M	0y11m	Hyps → diffuse	Generlized	Spasm		Good	Cerebral atrophy	Severe
23y	F	16y	Rt.O sp	Focal	Tonic		Good	WNL	Mild/moderate
14y	F	7y5m	Multifocal sp-w, sp	Focal	Tonic	○	Poor	WNL	Severe
8y	F	0y10m	Rt.C sp-w	Focal	Tonic		Good	ND	Mild/moderate
28y	M	16y	Rt.Fp, At sp-w	Focal	Secondary GTC		Good	ND	Mild/moderate
20y	F	20y	Normal	Unclassified	GTC		Good	Hipocampus abnormality	Mild/moderate
15y	M	1y6m	Diffuse → bil.C, P sp-w	Generalized	Tonic, clonic, myoclonic		Poor	Cerebral atrophy	Severe
16y	M	14y	Diffuse sp-w	Generalized	Tonic, atonic		Poor	Hipocampus atrophy	Severe
32y	M	27y	Lt.aT sp	Focal	GTC		Unknown	WNL	Mild/moderate
22y	M	0y4m	Bil.F	Uhclassified	GTC		Good	Slightly poor development	Mild/moderate

M, male; F, female; FS, febrile seizures; MR, mental retardation; hyps, hypsarrythmia; sp, spikes; sp-w, spike and wave; bil., bilateral; lt., left; rt., right; Fp, front polar; F, frontal; C, central; P, parietal; O, occipital; aT, anterior temporal; GTC, generalized tonic and clonic seizures; tonic, tonic seizures; atonic, atonic seizures; clonic, clonic seizures; myoclonic, myoclonic seizures; WNL, within normal limit; ND, not described.

seizure semiology was multiple. Though these findings have previously been recognized for AS [1], the association of these characteristics of epilepsy with PWS has been rarely reported. Recently, Wang et al. showed the detailed profile of eight patients with epilepsy in PWS, in which seven had GTC, one had atypical absence, and febrile seizures occurred in only one patient [7]. This result differed from ours in the frequency of febrile seizures and variable seizure semiology. In PWS, larger amount of profiles of patients with epilepsy should be collected for the purpose of clarifying the characteristics of epilepsy.

Spikes or spike-wave complexes of occipital region and diffuse high voltage slow waves on EEG findings were common features in AS. Previous reports described diffuse bifrontally dominant high amplitude 1–3 Hz notched or triphasic or polyphasic slow waves, or slow and sharp waves. Persistent rhythmic 4–6 Hz high-amplitude activities, often more prominent anteriorly and sometimes with discharges have also been reported [8–10]. In addition, spikes mixed with 3–4 Hz high-amplitude components, which are mainly posteriorly facilitated by, or only seen with, eye closure have been described [8,11]. In this study, the anterior dominancy of high amplitude slow waves was not seen. However, discharge in the occipital region may be one of the common features in AS, although we could not investigate whether patients' eyes were closed or open during EEG monitoring.

In Down syndrome with epilepsy, about half of the patients had West syndrome, especially when the onset of seizure occurred in infancy. One previous literature reported that 1.4% (13/844) of children with Down syndrome under 15 years of age had epilepsy, and infantile spasms occurred in 30.8% (4/13) of them [12]. Another report showed that 8.1% (33/405) of children with trisomy 21 had seizures, while in 40% (10/25) of patients (eight patients were excluded due to insufficient data) seizure occurred before one year of age, and 60% (6/10) of patients had infantile spasms [13]. In this study, the prognosis of epilepsy in West syndrome with Down syndrome is good compared with that of symptomatic West syndrome in the general population. Previous reports support this finding [14,15]. We found that 70% (7/10) of patients with West syndrome became seizure-free, while 56% (5/9) of patients with other types of epilepsy became seizure-free. In the literature, the onset of seizure showed two peaks of age: in infancy (10/25 patients); and in the third decade (10/25 patients). The types of epilepsy other than West syndrome consisted of tonic–clonic, myoclonic, partial simple, and partial complex seizure [13].

In epilepsy other than West syndrome with Down syndrome, the onset of seizure, the classification of epilepsy, and seizure semiology were also varied in our study. West syndrome and reflex epilepsy are described as common seizure types in Down syndrome [1,16], however, we had no reflex epilepsy in this study. Febrile seizures rarely occurred in the patients with epilepsy and Down syndrome in our study, and were noted in only 2 of 231 patients (0.9%) with Down syndrome with or without

Table 3a
Epileptological features in patients with other chromosome aberration syndromes in our series

Age/ sex	Chromosomal karyotype	Synd.	Age of onset	EEG	Epilepsy classification	Seizure semiology	FS	Seizure prognosis	MRI	MR
8y M	46,XY,t(1;1)(p11;q21)		1y0m	Rt.T, lt.O sp	Focal	CPS	○	Poor	Frontal cerebral atrophy	Severe
7y M	46,XY,del(1)(q42)	1q-	1y3m	Rt.O sp	Focal	CPS, hemi-clonic		Poor	Frontal cerebral atrophy	Severe
4y F	46,XX,del(1)(q42.3)	1q-	2y7m	Normal	Focal	hemi-clonic		Good	Agenesis of corpus callosum	Severe
6y F	46,XX,inv(2)(p21p22)		0y11m	Normal	Undetermined	GTC, CPS, hemi-clonic-status	○	Poor	ND	Severe
6y F	46,XX,del(2)(q24.2q31.1)		1y	Rt.P, O sp	Unclassified	Tonic, GTC-status		Poor	Cerebral atrophy	Severe
0y6m F	46,XX,add(3)(p24)		0y0m	Rt.Fp sp	Focal	CPS(apena)		Unknown	ND	Mild/ moderate
9y F	46,XX,3p-		1y8m	Unknown	Focal	CPS	○	Good	ND	Severe
17y F	46,XX,-4, + der(4) t(4:14)(q34:q24.3)		Unknown	Lt.aT sp	Focal	Myoclonic		Good	PVL, HIE	Severe
5y F	46,XX,del(4)(p16.3)	4p-	0y6m	Unknown	Undetermined	GTC-status	○	Good	Cerebral atrophy, agenesis of corpuscallosum	Severe
15y F	Details unknown	4p-	Unknown	Bil.O sp	Focal	Hemi-clonic-status, FC-status	○	Good	ND	Severe
7y F	46,XX,del(4)(p15.1)	4p-	1y8m	Unknown	Focal	Hemi-clonic-status, Tonic, clonic		Poor	ND	Severe
3y F	46,XX,-5, + der(5) t(5;13)(p14.2;q31.1)	5p-	0y8m	Bil.O sp-w Diffuse sp-w	Focal	CPS(apena), myoclonic		Poor	Cerebral atrophy	Severe
13y F	46,XX,5p-	5p-	2y2m	Multifocal sp	Focal	CPS	○	Good	ND	Severe
4y F	46,XX,t(5;13)(q23.2;q21.3)		0y1m	Normal	Focal	CPS, tonic		Poor	WNL	Mild/ moderate
7y M	46,XY,ring(6)		2y8m	Unknown	Unclassified	Tonic, hemi-clonic		Poor	Hydrocephalus/ agenesis of corpus callosum	Severe

M, male; F, female; Synd, syndrome; FS, febrile seizures; MR, mental retardation; bil., bilateral; lt., left; rt., right; Fp, front polar; P, parietal; O, occipital; aT, anterior temporal; sp, spikes; sp-w, spike and wave; GTC, generalized tonic and clonic seizures; CPS, complex partial seizures; tonic, tonic seizures; clonic, clonic seizures; myoclonic, myoclonic seizures; WNL, within normal limit; ND, not described.

epilepsy in a previous report [17]. Our study confirms that patients with Down syndrome rarely demonstrate febrile seizures.

For other chromosome aberrations, we had too few cases to abstract common characteristics of epilepsy. However, in some chromosome aberrations, such as 4p-, Miller–Dieker, 15q inv dup, ring chromosome 20, 1q-, and Klinefelter syndrome, epilepsy sometimes or often occurred and there are some previous reports about the characteristics of epilepsy, which are discussed below.

In 4p- syndrome, unilateral or generalized clonic or tonic–clonic status epilepticus was likely to occur. This seizure phenotype is typical of this syndrome [18]. Atypical absence, which is the other typical semiology, was not seen in the three patients with 4p- syndrome in our study. Reported EEG abnormalities include high-voltage slow waves with sharp waves or spikes dominantly centro-parietal or parieto-occipital, elicited by eye closure, sometimes generalized [19]. These abnormalities were not seen in our patients.

The common features in our two patients with Miller–Dieker syndrome were the onset of seizure in early infancy and severe mental retardation. In one patient, the seizure semiology was infantile spasms and the EEG pattern was hypsarrythmia. In the other patient, the seizure semiology was GTC and myoclonic seizures, and the EEG abnormality included diffuse alpha waves (not described in Table 3b). In a previous report which describes 15 patients with lissencephaly including one patient with Miller–Dieker syndrome, diffuse high amplitude theta activity alternating with high or low amplitude alpha or beta activity, resembling hypsarrythmia on EEG was common (13 of 15 patients). Infantile spasms were seen in seven of 15 patients, the onset of seizure was variable and occurred in infancy in nine patients, at less than 2 years of age in four patients, and at greater than 3 years of age in two patients [20]. Mental retardation was severe in all seven patients described in detail. In our study, more detailed research in a larger series is necessary to assess the common features of epilepsy in this syndrome.

In 15q inv dup syndrome and ring chromosome 20 syndrome, both of which were associated with epilepsy in high frequency [1,2], the characteristics of epilepsy in each syndrome were typical of previously reported cases. In 15q inv dup syndrome, the onset of seizure was early childhood and various seizure semiology, including tonic,

Table 3b
Epileptological features in patients with other chromosome aberration syndromes in our series

Age/ sex	Chromosomal karyotype	Synd.	Age of onset	EEG	Epilepsy classification	Seizure semiology	FS	Seizure prognosis	MRI	MR
15y F	46,XX,fra(8q22)		8y	Normal	Unclassified	Tonic		Good	WNL	Mild/ moderate
10y F	46,XX/47,XX, + 9	9 trisomy mosaic	0y5m	Lt.T sp	Undetermined	GTC, tonic, CPS		Poor	Dandy-Walker cyst	Severe
11yF	46,XX,9p-		9y	F sp-w	Undetermined	Myoclonic		Good	WNL	Severe
18y F	46,XX,ins(10;14)(q22;q21q22)		0y	F, C, O sp	Undetermined	CPS, spasm, myoclonic		Poor	ND	Severe
11y F	47,XX, + der(22), t(11;22)(q23;q11.2)mat		10y	Normal	Unclassified	GTC, clonic	○	Poor	Cingulate gyrus hypoplasisa	Severe
15y F	46,XX, + 11q		3y2m	Lt.f sp, sharp	Focal	Myoclonic	○	Good	ND	Severe
3y M	46,XY, + der(11), add(11)(p15)add(11)(q13)		0y1m	Bil.aT sharp	Focal	Secondary-GTC-status		Good	ND	Severe
5y F	47,XX, + 13	13 trisomy	0y0m	Unknown	Unclassified	CPS(apnea), myoclonic		Poor	ND	Severe
13y F	46,XX,inv(14)(q21q31)		1y6m	Rt > lt. Csp-w	Generalized	Tonic		Good	Cerebral atrophy	Severe
23y F	47,XX, +dic (15)(q12 or q13)	15q inv dup	12y	Diffuse poly sp-w	Undetermined	CPS-status, GTC, tonic, atonic, myoclonic		Poor	Cerebral atrophy	Severe
21y F	47,XX, + proximal 15		18y6m	Lt.mT sp	Focal	CPS, tonic	○	Good	Cerebral atrophy, agenesis of corpus callosum	Mild/ moderate
23y F	46,XY,del(17)(p11.2p11.2)	Smith–Magenis	19y	Lt.C sp	Generalized	GTC		Poor	WNL	Severe
0y4m F	46,XX,qh + ,22ps + , del (17)(p13.3p13.3)	Miller–Dieker	0y3m	Diffuse HVα	Generalized	Spasm	○	Unknown	Lissencephaly	Severe
10y F	46,XX,del(D17S379-)	Miller–Dieker	0y1m	Diffuse sp-w	Generalized	GTC, myoclonic		Poor	Lissencephaly	Severe
33y M	46,XY/46,XY,add(17)(q25)		15y	Unknown	Unclassified	CPS, tonic		Poor	WNL	Severe

M, male; F, female; Synd, syndrome; FS, febrile seizures; MR, mental retardation; bil., bilateral; lt., left; rt., right; F, frontal; C, central; O, occipital; aT, anterior temporal; mT, mid temporal; sp, spikes; sp-w, spike and wave; sharp, sharp wave; HVα, high voltage α wave; GTC, generalized tonic and clonic seizures; CPS, complex partial seizures; tonic, tonic seizures; atonic, atonic seizures; clonic, clonic seizures; myoclonic, myoclonic seizures; WNL, within normal limit; ND, not described.

atonic, atypical absence, myoclonic, complex partial and tonic–clonic seizures, were seen. Similar to previous cases, seizures in our patient with severe mental retardation were resistant to various antiepileptic agents [21]. In ring chromosome 20 syndrome, the nonconvulsive status epilepticus and resistance to antiepileptic medication in our patient were also typical features according to a previous report [22,23].

In our two patients with a 1q42 deletions (1q- syndrome), the onset of epilepsy in early childhood, the focal semiology, the absence of febrile seizures, and the seizure semiology (hemi-clonic convulsion) were common features. In previous reports, seizure was often seen (14 of 29 patients), seizure occurred in late infancy in most of these patients (11 of 13 patients), and the seizure semiology was variable, although hemi-clonic seizure was not demonstrated and febrile seizures were rare (4 of 29 patients) [24]. These findings are somewhat similar to our results.

The prevalence of seizures in Klinefelter syndrome ranged from 2 to 10% in a major series, and the seizure semiology was predominantly partial epilepsy, which was well controlled [4,5]. The two patients with Klinefelter syndrome in this study demonstrated similar features: good prognosis of epilepsy and focal epilepsy.

For some of the chromosome aberrations of which we had few cases, there is little information about epilepsy in the literature.

A report in 1978 described nine patients with 5p- syndrome and seizures, however there was no information about seizure features [25]. In Smith–Magenis syndrome, seizures including febrile seizures are sometimes seen (five of 10 patients), but there is little detail about the features of epilepsy [26].

Several reports suggest the association of epilepsy and 18q- syndrome, but only a few include detailed descriptions of features of epilepsy. In our investigation, a patient with

Table 3c
Epileptological features in patients with other chromosome aberration syndromes in our series

Age/ sex	Chromosomal karyotype	Synd.	Age of onset	EEG	Epilepsy classification	Seizure semiology	FS	Seizure prognosis	MRI	MR
0y9m M	46,XY/ 46,XY,del(18)(q12.2q22.3)	18q-	0y3m	Rt.T sp-w → diffuse poly sp-w	Focal	CPS(apnea)		Poor	Cerebral atrophy, dysmyelination	Severe
11y M	Details unknown	18q-	0y11m	Unknown	Unclassified	GTC(FC)	○	Good	Cerebral atrophy	Severe
7y F	46,XX,ins(19;20)(q13;?)		5y5m	Normal	Focal	CPS		Unknown	WNL	Mild/ moderate
22y M	46,XY,r(20)(p13q13)	Ring20	9y	Bil.F HVS	Focal	CPS-status		Poor	Cerebral atrophy	Normal
3y M	46,XY/ 47,XY, + 20		0y3m	Bil.O sp-w	Undetermined	Tonic, hemi-clonic, myoclonic, spasm	○	Poor	Calcification	Severe
15y M	46,XY,-21, + der(21)t(5;21)(p13.1;q22.1)		2y1m	Lt.F, C, rt.C, P sp-w	Focal	Hemi-clonic	○	Good	WNL	Severe
27y F	46,XX,r(21)(p11q22)/ 45,XX,-21		22y	Diffuse sp-w	Focal	CPS		Good	Cerebral atrophy	Mild/ moderate
5y F	46,XX,-21, + mar.ish der(14)t(14;21)(q21;q11.2)		0y8m	Diffuse sp-w	Generalized	Tonic	○	Poor	Agenesis of corpus callosum	Severe
34y M	45,XY, − 22		5y	Unknown	Unclassified	GTC,CPS (apena)		Good	ND	Severe
12y M	46,X, +Xp		5y5m	Rt.F, P sp, sp-w	Generalized	GTC(FC)	○	Good	WNL	Mild/ moderate
1y8m F	46,X,der(X)t(X;1)(p21;q25), der(1),(q25,q13.3),der(19)t(X;19)(?;q13.3)		0y2m	Hyps	Generalized	Spasm		Poor	WNL	Severe
14y M	48,XXYY	Klinefelter	1y4m	Rt.C sp	Focal	Hemi-clonic	○	Good	ND	Mild/ moderate
13y M	47,XXY	Klinefelter	2y4m	aT, mT sp-w	Focal	GTC-status, CPS(status)		Good	WNL	Severe
3y M	46,X,invY(p11.3q11.2)		0y6m	Lt.C sp	Unclassified	Unknown	○	Good	ND	Severe
19y M	47,XY, + mar		10y	Multifocal sp Diffuse sp-w, HVS	Generalized	GTC, tonic		Poor	WNL	Severe

M, male; F, female; Synd, syndrome; FS, febrile seizures; MR, mental retardation; bil., bilateral; lt., left; rt., right; F, frontal; C, central; P, parietal; O, occipital; aT, anterior temporal; mT, mid temporal; sp, spikes; sp-w, spike and wave; HVS, high voltage slow wave; GTC, generalized tonic and clonic seizures; CPS, complex partial seizures; tonic, tonic seizures; myoclonic, myoclonic seizures; WNL, within normal limit; ND, not described.

a deletion of 18q12.3–22.3 had autonomic seizures (apnea) [27]. One report described a patient with an 18q21.3-ter deletion who had autonomic seizures (syncope) [28], and another report showed a patient with autonomic seizures (apnea), in which the detailed data of the deletion site was unknown [29]. These former two patients had a common seizure semiology (autonomic seizure) and a common deletion region of 18q21.3–22.3. It is possible that there may be a new gene responsible for epileptogenesis in this region, however other reports of patients with 18q- syndrome, did not describe autonomic seizures [30–32]. Further accumulation of such patients is needed to clarify the characteristics of epilepsy and to identify a common region responsible for epileptogenesis in this syndrome.

From accumulated data from several previous reports, Singh et al. (2002) speculated that the common locus responsible for epileptogenesis in 2q- syndrome is 2q31 [1]. Our patient had a deletion of 2q24.2–31.1 which includes this common region.

In this study, the incidence of febrile seizures was higher in AS (75.0%, 6/8) and PWS (100%, 4/4) than in other chromosome aberrations (28.1%, 18/64). Previous studies also showed that in AS, 43% (13/30) of patients with epilepsy, and 36% (13/36) of patients with and without epilepsy had febrile seizures [9], and in PWS, 12.9% of patients with or without epilepsy had febrile seizures [33]. The incidence of febrile seizures in both syndromes is higher than the general population incidence of 3–4% [34]. As both syndromes have the same deleted region of 15q11–13, it is possible that an unknown gene responsible for febrile seizures exists at this locus. However, in inv dup 15 syndrome, which has a duplication of the region involved in AS and PWS

(15q11–13), there is little information about the occurrence of febrile seizures. In 4p- syndrome, febrile seizures were often seen, both in the present (66.7%, 2/3) and previous studies [18]. The collection of more information about chromosome aberrations in relation to febrile seizures may allow the detection of a new locus for febrile seizures and epileptogenesis.

This study provides further evidence of the association of specific features of epilepsy with specific chromosome aberrations. Further investigation into these associations may lead to improved treatments and the discovery of new genes involved in epilepsy.

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