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Original article

An analysis of epilepsy with chromosomal abnormalities☆

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Abstract

We retrospectively reviewed the medical records of neonates with chromosomal abnormalities and epilepsy who had been admitted to the neonatal intensive care unit (NICU) and followed up at the outpatient clinic of Dokkyo University School of Medicine. Chromosomal anomalies were diagnosed in 128 of 5789 patients admitted from 1978 through 2001. Seventy-one neonates had trisomy 21, 29 had trisomy 18, 8 had trisomy 13, and 20 had other chromosomal anomalies. Seizures occurred in five patients with trisomy 21 and in one patient each with trisomy 18, 6q−, 13q−, 21q−, and mosaicism trisomy 13. Two patients with 4p- [Wolf–Hirschhorn syndrome] were admitted to the NICU, but were not followed up at our outpatient clinic. The boy with 6q− (46,XY,-6, +der(6)t(6;11)(q25.1;q23.3)mat) had agenesis of the corpus callosum and multiple congenital anomalies as well as intractable epilepsy. The girl with 13q− (46, XX, t(2,4)(q24.2;p14), del (13)(q21.2q31.2)) had infantile spasms at 12 months, which were well controlled with nitrazepam and vitamin B6. The girl with mosaic trisomy 8q; (46, XX, der(8) (qter→q11.2::p23.3→qter)/46, XX), was not born at our hospital, but showed unique clinical features. She had intractable epilepsy characterized by episodes of vomiting and staring with astatic seizures. Computed tomography of the brain revealed bilateral calcification in the globus pallidus, associated with bursts of high-amplitude slow waves on electroencephalography. One of the two patients with del(15)(q12)[Angelman syndrome] had giant-amplitude visual evoked potential, suggesting hyperexcitability of the visual cortex.

Keywords: Epilepsy; Chromosome; Cytogenetics; Trisomy 21; Trisomy 18; Trisomy 13; Monosomy

1. Introduction

Various chromosomal abnormalities have been found in patients with epilepsy and epileptic syndromes. Genetic linkage and karyotype analysis may provide cytogenetic clues leading to the identification of genes linked to specific types of epilepsy. The Human Genome Project has identified most human genes, including many with unclear functions. The compilation of clinical data on the association between epilepsy and chromosomal abnormalities is likely to improve our understanding of the functions and mechanisms of genes related to epilepsy. To date, little attention has been paid to cytogenetic studies examining clinical features of epilepsy and epileptic syndromes. In this report, we review the clinical features and course of children with epilepsy associated with chromosomal anomalies who were admitted to our neonatal intensive care unit (NICU) over the past 24 years. Many of the patients were subsequently followed up as outpatients.

2. Patients and Methods

From 1978 through 2001, a total of 13,716 babies were born at our hospital. Among them, 3120 premature or critically ill neonates were admitted to our NICU. In addition, 2669 babies were transferred to our NICU from other hospitals. The total number of admitted neonates during the study period was 5789.We searched the hospital NICU and cytogenetic laboratory databases to identify newborns with chromosomal anomalies. A total of 128 patients

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Table 1
Patients with chromosomal abnormality found in NICU

Chromosomal abnormality	Number of patients	Number of patients with epilepsy
Trisomy 21	71	5
Trisomy 18	29	1
Trisomy 13	8	1
Trisomy 22	1	0
Trisomy 10, mosaic	1	0
Trisomy 8, mosaic	1	0
del (22)(q11.2)	3	0
del(4)(p16.3)	2	na
del(13)(q21.2q31.2) t(2;4)(q24.2;p14)	1	1
del(9)(q22.3q32)	1	0
del(8)(q13.1q21.2)	1	0
21q−	1	1
r (12)(p13;q24)	1	0
46, XY, -6, +der(6)t(6;11) (q25.1;q23.3)	1	1
46, XY/46, XY, t(2:13)(q31;q21.2)	1	0
ins(14;16)(p12;p13.3)	1	0
47 XX, +der 15 t(3:15)(q23:q11.2) mat	2	0
Add(7)(p22)	1	0
Add (6)(q25.3)	1	0
Total	128	10

na: data not available due to a lack of follow up study.

had such anomalies, including 71 (55%) with trisomy 21, 29 (23%) with trisomy 18, 8 (6%) with trisomy 13, and 20 (16%) with other anomalies. A review of medical records from the outpatient clinic showed that 10 of these patients had epilepsy. Five patients had trisomy 21, and one each had trisomy 18, mosaic trisomy 13, 6q− (46, XY, -6, +der(6)t(6;11)(q25.1;q23.3)mat), 13q− (46, XX, t(2,4)(q24.2;p14), del (13)(q21.2q31.2)), and 21q− (Table 1).

3. Results

3.1. Trisomy 21 (Down syndrome)

Five patients with trisomy 21 had a diagnosis of epilepsy. In 3 patients, seizures were caused by hypoxic-ischemic encephalopathy due to respiratory failure, cardiac failure, or both in neonatal period or early infancy. Another patient had hemiconvulsions associated with infarction due to moya-moya disease, a vascular abnormality commonly occurring in children with Down syndrome. The other patient had cryptogenic infantile spasms. He was initially treated with a combination of nitrazepam and valproic acid, and the spasms resolved. Subsequently, atypical absence and tonic seizures developed, and Lennox–Gastaut syndrome was diagnosed. He received zonisamide, ethosuximide, nitrazepam and valproic acid. He is now 15 years old and has been seizure free for more than 3 years (Table 2).

3.2. Trisomy 18 (Edwards syndrome)

Only 1 of the 29 patients with trisomy 18 had epilepsy. Her karyotype was 47, XX, +18. Clinical features included severe mental retardation, thinness, and short stature. She had a large ventricular septal defect and a patent ductus arteriosus. Other anomalies included low-set ears, short sternum, overlapping fingers, and 'rocker-bottom' feet. The patient had a history of generalized convulsions since the age of 4 years. She had brief tonic seizures lasting 10 seconds, commonly occurring during sleep, at a frequency of about once per week. Electroencephalography (EEG) showed multifocal spikes in the right parietal and left temporal areas. Magnetic resonance imaging (MRI) showed cerebellar hypogenesis, a thin corpus callosum, and a dysplastic hippocampus (Fig. 1). She was treated with phenobarbital, but seizures were poorly controlled. She died of pneumonia at the age of 6 years.

3.3. Trisomy 13 (Patau syndrome)

Only one of the eight patients with trisomy 13 was followed up at our outpatient clinic. The other seven patients died neonatally. The surviving patient was a boy born after 38 weeks' gestation and weighing 3366 g at birth. He was admitted for meconium aspiration syndrome. Gastrointestinal malrotation was noted and surgically corrected in the neonatal period. He had a small ventricular septal defect, which later spontaneously closed. Minor anomalies included a capillary hemangioma on the forehead, frontal alopecia, a narrow palate, cryptorchidism, and penis palmatus. Fluorescence in situ hybridization (FISH) analysis showed that 73% of cultured cells had a karyotype of 47, XY, +13. The remainder had a normal karyotype, suggesting a mosaic form of trisomy 13. Seizures developed neonatally. Most seizures were multifocal clonic type, and the EEG showed multifocal spikes in the right temporal and left parietal areas, independently. Seizures initially occurred several times a day, but were well controlled by treatment with clonazepam. He died of pneumonia at the age of 7 years. Autopsy showed olfactory aplasia and fenestration of the septum pellucidum as well as an atrophic brain with a thin corpus callosum.

3.4. 6q−/11q+ syndrome

This neonate was born at 38 weeks' gestation as the first child of non-consanguineous parents. Body weight at birth was 2300 g. Multiple congenital anomalies were noted at birth, including hypertelorism, epicanthic folds, low-set ears, micrognathia, cleft palate, overlying fingers, and posterior prominence of the heels. His karyotype was 46, XY, -6, +der(6)t(6;11)(q25.1;q23.3)mat. EEG showed multiple spikes in the occipital, central, and frontal areas,

Table 2
Summary of clinical features of patients with chromosomal abberations and epilepsies

Patient	Chromosomal abnormalities	Onset	Gender	Main types of seizure	Etiology of seizure/structural abnormality	Treatment	Outcome
1	Trisomy 21	1y	Male	Infantile spasms followed by Lennox–Gastaut syndrome	Mild cerebral atrophy	NZP, VPA, ZNS, ESM	Well controlled
2	Trisomy 21	1y	Female	Hemiconvulsion	Moyamoya diesease	PB	Well controlled
3	Trisomy 21	3y	Male	Generalized convulsion	Hypoxic ischemic encephalopathy	PB	Well controlled
4	Trisomy 21	11m	Male	Generalized tonic convulsion	Hypoxic ischemic encephalopathy	PB, VPA, PHT	Poorly controlled
5	Trisomy 21	5m	Male	Generalized convulsion	Hypoxic ischemic encephalopathy	PB	Well controlled
6	Trisomy 18	4y	Male	Brief tonic convulsion	Cerebellar hypogenesis, dysplasitic hippocampus (Fig.1)	PB	Poorly controlled
7	Trisomy 13, mosaic	0m	Male	Neonatal convulsion	Olfactory aplasia, dysplasia of septum pellucidum, cerebral atrophy	CZP	Well controlled
8	6q−/11q+	2y	Male	Generalized convulsion	Callosal agenesis, colpocephaly, small cerebellum (Fig. 3)	VPA, CZP	Well controlled
9	13q−	1m	Female	Infantile spasms	Mild cerebral atrophy	VPA, CBZ, CZP	Well controlled
10	21q−	3y	Male	Prolonged febrile convulsion	Normal brain	PB	Well controlled
11	Trisomy 8q, mosaic	3y	Female	Complex partial seizure, astatic seizure	Calcification in the globus pallidus, mild cerebral atrophy (Fig. 5)	CZP, VPA, ZNS	Poorly controlled
12	Angelman syndrome	2y	Female	Astatic seizure, myoclonic seizure	Mild cerebral atrophy	VPA, CZP	Well controlled
13	Angelman syndrome	1y	Female	Myoclonic seizure	Mild cerebral atrophy	VPA	Well controlled

The judgement of 'well controlled' is made when the patient has no seizure for over 2 years. Frequency of seizures in patient 3 was 2–3 times or more a day. See the text for more detailed information of seizures. Patients 11, 12 and 13 were not born nor admitted in our hospital in neonatal period. NZP: nitrazepam, VPA: valproic acid, ZNS: zonisamide, ESM: ethosuximide, PB: phenobarbital, PHT: phenytoin, CZP: clonazepam.

with secondary generalized spike-wave discharges (Fig. 2). Generalized convulsions initially occurred at 2 years of age, and three times of episodes of status convulsivus lasting for more than 1–h appeared at 6 years. He is now 15 years old, and his seizures are relatively well controlled by valproic acid and clonazepam. MRI at 3 years showed callosal agenesis associated with colpocephaly, a disproportionately small cerebellum, and a flattened pons (Fig. 3).

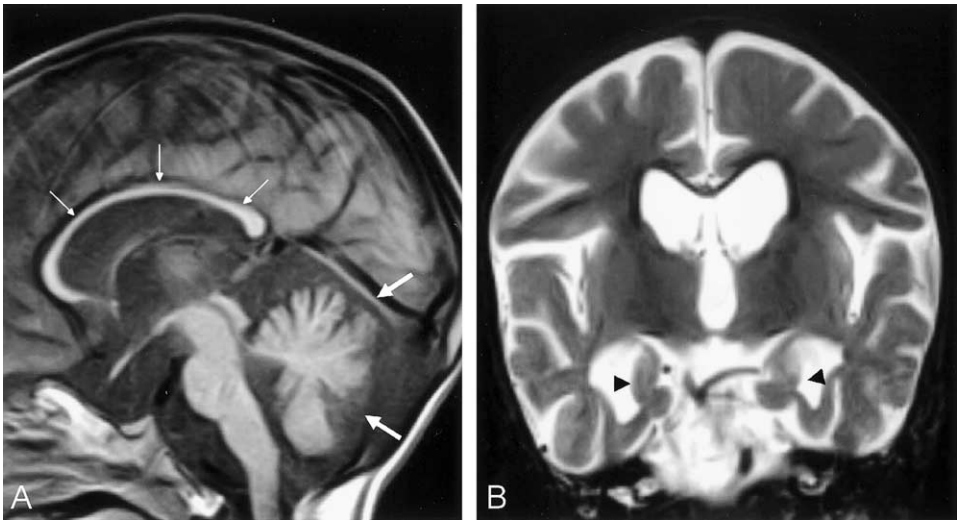

Fig. 1. Magnetic resonance image in a 4-year-old girl with trisomy 18, showing cerebellar hypogenesis (arrow in A), a thin corpus callosum (small arrow in A), and a dysplastic hippocampus (arrowhead in B).

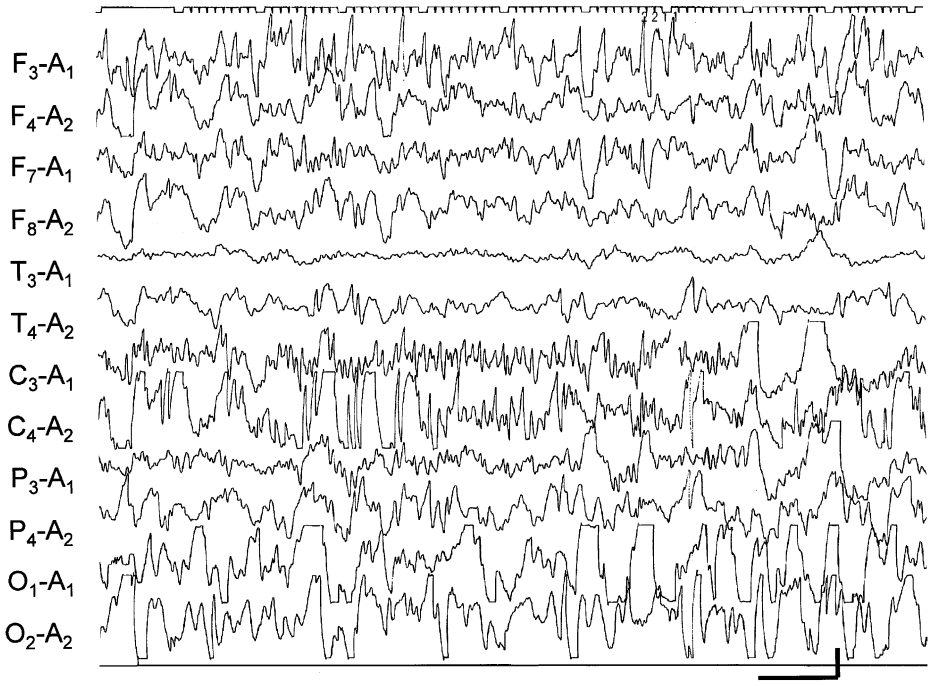

Fig. 2. Electroencephalography in a 3-year-old boy with 6q−/11q+ syndromes, showing multiple spikes in the occipital, central, and frontal areas, with secondary generalized spike-wave discharges. Calibration 50 μV, 1 s.

3.5. 13q− syndrome

This patient had a deletion between q21.2 and q31.2 of chromosome 13 as well as a translocation between chromosomes 2 and 4; 46, XX, t(2,4)(q24.2;p14), del (13)(q21.2q31.2). She was born at 39 weeks' gestation, delivered spontaneously, and weighed 2500 g. She underwent surgery in the neonatal period for intestinal malrotation. Tonic spasms started at the age of 1 month. An EEG showed hypsarrythmia, leading to the diagnosis of infantile spasms. Computed tomography showed mild atrophy of the brain. Spasms were controlled by nitrazepam and vitamin B6. She had dysmorphic facies with large auricles and a flexed right ring finger. The range of motion of the extremities was restricted with moderate joint contractures. Neurological examination showed brisk deep tendon reflexes. An EEG at 5 years of age showed spikes in the right occipital area.

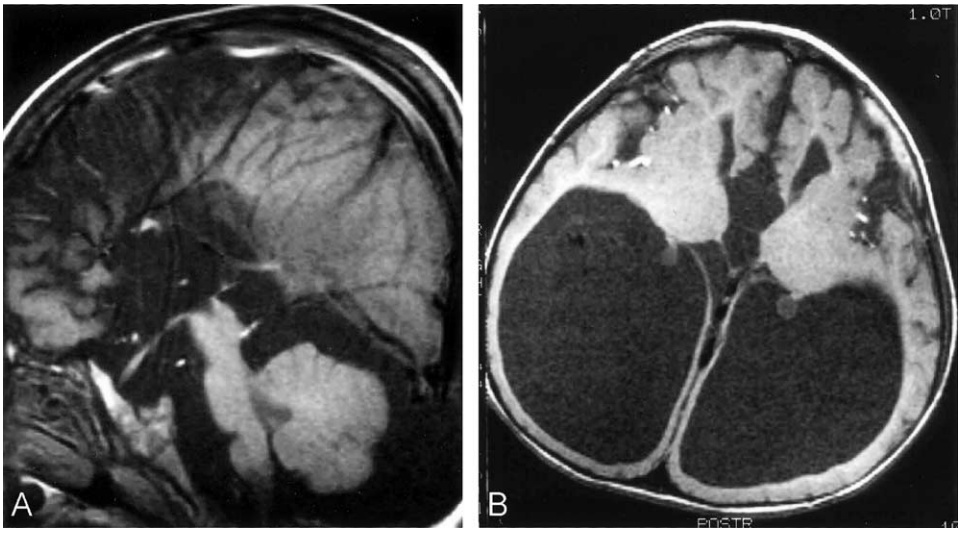

Fig. 3. Magnetic resonance image in a 3-year-old boy with 6q−/11q+ syndrome, showing callosal agenesis associated with colpocephaly, a disproportionately small cerebellum, and a flattened pons.

3.6. 21q− syndrome

This boy was born after 40 weeks' gestation, delivered vaginally, and weighed 2340 g. Multiple congenital anomalies were noted neonatally, including a narrow nasal root, downward slanted palpebral fissures, and cryptorchidism. Early motor milestones were normal: he obtained head control at 4 months, sat without support at 8 months, and stood alone at 11 months. Language development was delayed; he could not speak words at 4 years of age. He had an episode of status convulsivus associated with fever at 3 years. EEG showed no spike discharges. No further seizures occurred during the next 6 years of observation at our outpatient clinic. A detailed karyotype was not available for this patient.

3.7. Wolf–Hirschhorn syndrome

Two patients were given a diagnosis of 4p− [Wolf–Hirschhorn syndrome] in the neonatal period, but were not followed up at our outpatient clinic. The patients' clinical course therefore could not be evaluated.

3.8. Trisomy 8q

This child was born and admitted to the NICU at a local hospital, and later followed up at our outpatient clinic for delayed psychomotor development and epilepsy. She was born at 39 weeks' gestation and had a birth weight of 3285 g. The neonatal period was uneventful. Developmental milestones were delayed: she could sit without support at 9 months, stood alone at 2 years, and walked at 2 years 9 months of age. She was not able to speak even single words at 5 years. She had a round face and thick lips. No visceral organ anomaly was noted. She was given a diagnosis of trisomy 8q; 46, XX, der(8)(qter→q11.2::p23.3→qter)/46, XX. Mosaicism was found in 53% of cultured cells, as confirmed by FISH analysis. She had an episode of generalized convulsions at 3 years of age. Three months later, she started to have episodes of sudden unconsciousness with staring and frequent vomiting, lasting from 30 min to 1 h. Astatic episodes also sometimes occurred. Interictal EEG showed polyspike or spike-wave complexes in the right frontal and anterior temporal areas as well as bursts of paroxysmal high voltage slow waves (Fig. 4). Laboratory studies, including an assessment of parathyroid function, showed no relevant findings. Computed tomography of the brain showed bilateral high-density areas in the globus pallidus (Fig. 5). MRI revealed non-specific cerebral atrophy. The astatic episodes and generalized convulsions disappeared after she started to receive zonisamide, but episodes of staring and vomiting persisted despite treatment with several anticonvulsant drugs, including zonisamide, clonazepam, and carbamazepine.

3.9. Angelman syndrome

Two patients with Angelman syndrome, diagnosed on the basis of FISH analysis showing 46, XX, ish del (15)(q11.2q11.2)(SNRPN-), were followed up at our outpatient clinic. They were not admitted to our hospital in the neonatal period, but were observed for psychomotor retardation associated with hypotonia. Generalized clonic convulsions and myoclonic seizures appeared at 2 to 3 years

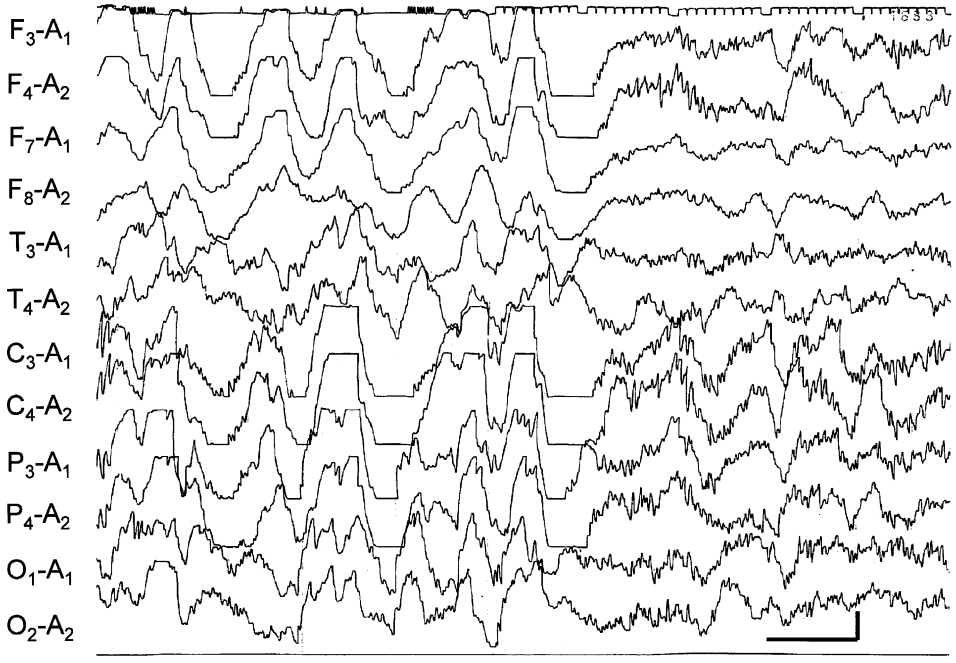

Fig. 4. Electroencephalography in a patient with trisomy 8q, showing paroxysmal high voltage slow wave bursts. Calibration 50 μV, 1 s.

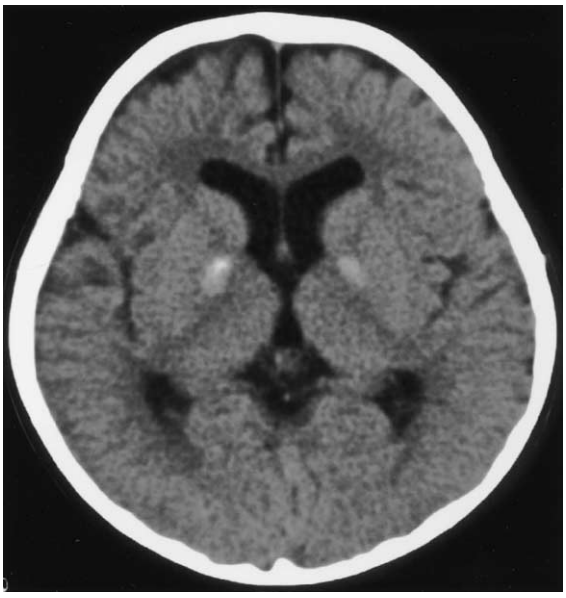

Fig. 5. Computed tomogram of the brain in a patient with trisomy 8q, showing bilateral high-density areas in the globus pallidus as well as cerebral atrophy.

of age and were controlled by treatment with valproic acid and clonazepam. Visual evoked potential testing was done in one patient and showed markedly increased interpeak amplitude between waves III and IV as well as IV and V, suggesting hyperexcitability of the visual cortex to photic stimulation (Fig. 6).

4. Discussion

4.1. Down syndrome

In our study, the overall prevalence of epilepsy associated with Down syndrome was 7%. Previous studies have reported a prevalence of 6% [1] to 16% [2]. These differences probably arise from the ages of the study groups. In four of our five patients with Down syndrome, epilepsy

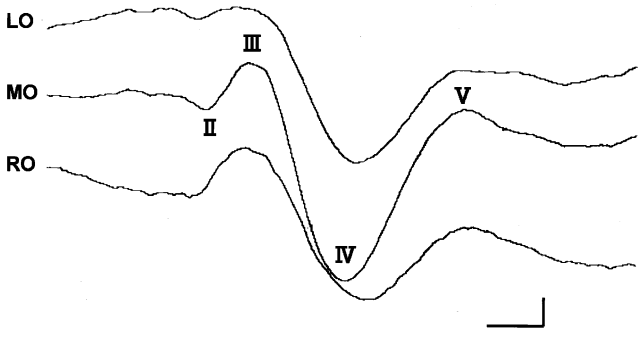

Fig. 6. Visual evoked potentials in a 2-year-old girl with Angelman syndrome. Note giant amplitudes of waves III–IV (58 μV) and IV–V (45 μV). Calibration 10 μV, 30 msec. LO: left occipital point, MO: middle oocipital point, RO: right occipital point. The reference electrode was palced on the midfrontal point.

was attributed primarily to impaired cerebral perfusion, associated with hypoxic-ischemic encephalopathy or moya-moya disease. Epilepsy was directly ascribed to Down syndrome in only one patient with infantile spasms; thus the primary prevalence of epilepsy directly due to Down syndrome was estimated to be 1.5% in our study. Any type of epilepsy can be associated with Down syndrome, but West syndrome/infantile spasms are most common [3,4].

4.2. Trisomy 18 (Edwards syndrome)

Trisomy 18 is the second most common chromosomal disorder occurring in neonates. Postnatal survival is very poor because of critical visceral anomalies. Survival for longer than several months is rare. Few patients with this syndrome have been reported to have epilepsy, because most die of severe complications shortly after birth. The precise incidence of epilepsy associated with trisomy 18 is unclear. Most reported cases have been associated with a mosaic form or partial trisomy [5–7], with relatively mild clinical features.

4.3. Trisomy 13 (Patau syndrome)

The major structural brain anomaly of trisomy 13 is holoprosencephaly, frequently accompanied by cerebellar dysplasia. Convulsions in the neonatal period or early infancy are relatively common [8]. Our patient had neonatal convulsions with subsequent epilepsy, both of which were relatively easy to control. This mild picture of epilepsy probably correlates with the relatively minor cerebral anomalies, i.e. olfactory aplasia and fenestration of the septum pellucidum.

4.4. 6q−/11q+ syndrome

Our patient had distal monosomy of the long arm of chromosome 6 as well as trisomy of the long arm of chromosome 11, inherited by maternal translocation t(6;11)(q25.1;q23.3). To our knowledge, epilepsy has been reported in 5 out of 20 patients with distal terminal deletion of the long arm of chromosome 6 (Table 3) [9–12]. Most distal deletions associated with epilepsy are located from 6q25 to the terminus. Most patients have ventricular dilatation, microcephaly, and brachycephaly. Seizures are controlled well, although precise types of seizures are poorly documented [9–12]. Our patient had agenesis of the corpus callosum. The etiology of agenesis of the corpus callosum is diverse, and many syndromic forms have been presented. As for chromosome 6, agenesis of the corpus callosum has been associated with a deletion in 6q25 [13].

4.5. 13 q-syndrome

Our series included a patient with partial deletion of the long arm of chromosome 13, del(13)(q21.2q31.2), as well as

Table 3
Literature survey of patients with terminal deletion of the long arm of chromosome 6, associated with epilepsy

Authors	Deletion	Ventriculomegaly	Microcephaly	Brachycephaly	Seizures	Reference
Liberfarb RM, et al.	6q25→qter(?)	na	+	+	Controlled well	[9]
Stevens CA, et al.	6q25→qter	+	+	na	Controlled well	[10]
Oliveira-Duarte, et al. (case 1)	6q25→qter	+	+	+	Controlled well	[11]
Oliveira-Duarte, et al. (case 2)	6q25→qter	+	+	+	Controlled well	[11]
Mcleod DR, et al.	6q26→qter	na	+	na	na	[12]
Our case	6q25.1→qter	+	+	+	Controlled well	

na: data not available.

translocation between chromosome 2 and chromosome 4 with a breakpoint in 2q24.1 and 4p14. Two patients with del(13)(q21–q34) and del(13)(q22–q33) have been reported to have holoprosencephaly as well as Dandy–Walker malformation [14]. A variant form of late infantile neuronal ceroid lipofuscinosis (NCL) is mapped on 13q21.1–q32 [15]. Our patient had no findings suggestive of NCL. She had normal fundi and showed no evidence of progressive myoclonus epilepsy or regression of psychomotor development. Computed tomographic examination showed mild brain atrophy, but no malformation. A search of the Pub Med website of the National Library of Medicine revealed no reported case of West syndrome or related intractable types of epilepsy with onset in infancy associated with this chromosomal aberration.

4.6. Trisomy 8q

Trisomy 8q is a relatively common chromosomal aberration, but its association with epilepsy is poorly defined [16]. Our patient showed unique clinical features: calcification of the globus pallidus, astatic seizures and complex partial seizures with alterations in consciousness, staring and vomiting, and interictal EEG polyspikes or spike-wave complexes in the frontal and anterior temporal areas, as well as paroxysmal high voltage slow wave bursts. Although the clinical and radiological features of trisomy 8q remain uncertain, our findings may be characteristic of this syndrome.

4.7. Angelman syndrome

Angelman syndrome is a neurogenetic disorder resulting from lack of genetic contribution of the maternal chromosome 15q11-13. Patients with this syndrome present with severe mental retardation, poor language skills, inappropriate laughter, and epileptic seizures, including spasms, partial seizures, atypical absences, and myoclonic absences. The 15q11–13 region codes β3 subunit of gamma-aminobutyric acidA/benzodiazepine receptor, suggesting that reduced GABAergic inhibition may cause cortical hyperexcitability. Motor cortex hyperexcitability has been suggested by the results of the burst-locked EEG average method [17]. One of our patients with Angelman syndrome showed giant-amplitude visual evoked potentials. Although this patient had never had photosensitive epilepsy, our findings suggest that patients with Angelman syndrome may have hyperexcitability of the visual cortex.

5. Conclusion

Epileptic syndromes may have unique features related to the specific underlying chromosomal disorder. This report described the clinical characteristics of patients with trisomy 13 and trisomy 18 who survived for relatively prolonged periods (7 years and 6 years at death, respectively). Although both of these trisomy syndromes are commonly encountered, little is known about the features of epilepsy associated with these syndromes. The patient with terminal deletion of 6q had callosal agenesis with colpocephalic ventricular dilatation and had episodes of status convulsivus. The patient with trisomy 8q had complex partial seizures and astatic seizures, as well as a symmetrically calcified globus pallidus on CT scans. Episodes with staring were associated with frequent vomiting. Infantile spasms developed in patients with 13q− and Down syndrome, but were well controlled with anticonvulsants. Further studies are needed to delineate the clinical features of epileptic syndromes and to understand the mechanisms of epilepsy associated with chromosomal abnormalities.

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References

[1] Pueschel SM, Louis S, McKnight P. Seizure disorders in Down syndrome. Arch Neurol 1991;48:318–20.
[2] Van Buggenhout GJ, Trommelen JC, Schoenmaker A, De Bal C, Verbeek JJ, Smeets DF, et al. Down syndrome in a population of elderly mentally retarded patients: genetic-diagnostic survey and implications for medical care. Am J Med Genet 1999;85:376–84.
[3] Ohtahara S, Ohtsuka Y, Yamatogi Y, Oka E, Yoshinaga H, Sato M. Prenatal etiologies of West syndrome. Epilepsia 1993;34:716–22.

[4] Silva ML, Cieuta C, Guerrini R, Plouin P, Livet MO, Dulac O. Early clinical and EEG features of infantile spasms in Down syndrome. Epilepsia 1996;37:977–82.
[5] Novotny Jr EJ, Urich H. The brain in partial trisomy 18: a case report. J Child Neurol 1987;2:194–7.
[6] Greve G, Waaler PE, Rosendahl K. Low frequency mosaicism of normal cells in a 16-year-old girl with trisomy 18. Clin Genet 1993; 43:83–7.
[7] Komine M, Hino M, Shiina M, Kanazawa I, Soma Y, Tamaki K. Linear and whorled naevoid hypermelanosis: a case with systemic involvement and trisomy 18 mosaicism. Br J Dermatol 2002;146: 500–2.
[8] Iannaccone ST, Rosenberg RN. Principles of molecular genetics and neurologic diseases. In: Berg BB, editor. Principles of child neurology. New York: McGraw-Hill; 1995. p. 557–8.
[9] Liberfarb RM, Atkins L, Holmes LB. Chromosome 6q− and associated malformations. Ann Genet 1978;21:223–5.
[10] Stevens CA, Fineman RM, Breg WR, Silken AB. Report of two cases of distal deletion of the long arm of chromosome 6. Am J Med Genet 1988;29:807–14.
[11] Oliveira-Duarte MH, Martelli-Soares LR, Sarquis-Cintra T, Machado ML, Lison MP. Distal monosomy of the long arm of chromosome 6 (6q25→6qter) inherited by maternal translocation t(6q;17q). Ann Genet 1990;33:56–9.
[12] McLeod DR, Fowlow SB, Robertson A, Samcoe D, Burgess I, Hoo JJ. Chromosome 6q deletions: a report of two additional cases and a review of the literature. Am J Med Genet 1990;35:79–84.
[13] Pirola B, Bortotto L, Giglio S, Piovan E, Janes E, Janes A, Guerrini R. Agenesis of the corpus callosum with Probst bundles owing to haploinsufficiency for a gene in an 8 cM region of 6q25. J Med Genet 1998;35:1031–3.
[14] McCormack Jr WM, Shen JJ, Curry SM, Berend SA, Kashork C, Pinar H, et al. Partial deletions of the long arm of chromosome 13 associated with holoprosencephaly and the Dandy–Walker malformation. Am J Med Genet 2002;112:384–9.
[15] Savukoski M, Kestila M, Williams R, Jarvela I, Sharp J, Harris J, et al. Defined chromosomal assignment of CLN5 demonstrates that at least four genetic loci are involved in the pathogenesis of human ceroid lipofuscinosis. Am J Hum Genet 1994;55:695–701.
[16] Bredberg A, Iselius L, Lindgren L, Lundmark KM. Duplication of part of the long arm of chromosome 8 due to a familial 8;13 translocation. Hereditas 1982;96:105–8.
[17] Guerrini R, De Lorey TM, Bonanni P, Moncla A, Dravet C, Suisse G, et al. Cortical myoclonus in Angelman syndrome. Ann Neurol 1996; 40:39–48.