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Brain & Development 27 (2005) 95–100

BRAIN & DEVELOPMENT
Official Journal of the Japanese Society of Child Neurology

www.elsevier.com/locate/braindev

Original article

Relationship between severity of epilepsy and developmental outcome in Angelman syndrome☆

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Received 14 July 2003; received in revised form 1 September 2003; accepted 3 September 2003

Abstract

To clarify the relationship between the degree of developmental disturbance and the severity of epilepsy in Angelman syndrome, we investigated 11 patients and measured both clinical outcomes and EEG parameters. Seven patients were followed up until after 8 years of age. Eight patients were found to have 15q11–q13 deletions.

All patients experienced epileptic seizures and all but one displayed nonconvulsive status epilepticus (NCSE) during the period of observation. Epileptic seizures, including NCSE, disappeared by around 8 years of age. In addition, specific epileptic discharges, as measured by EEG, tended to subside with age. Although development seemed almost normal or only slightly delayed during the first 6 months of life, all patients eventually developed severe retardation. Two patients displayed very severe retardation and were unable to comprehend language or walk independently at the last follow-up. Only one patient was able to speak a few meaningful words. In one of the most severely affected patients, who showed the earliest onset of seizures and NCSE, it is possible that the repetitive bouts of NCSE might be responsible for the severe developmental outcome. However, the other patient with particularly severe retardation did not experience NCSE, while the patient with the most favorable outcome had repetitive episodes of NCSE.

Therefore, we conclude that the severity of developmental disturbance in Angelman syndrome is not necessarily related to the degree of epilepsy. However, intensive therapy for NCSE might still be justified because there are some patients in whom NCSE results in a transient and sometimes permanent decline in mental and motor functioning.

Keywords: Angelman syndrome; Development; Epilepsy; Nonconvulsive status epilepticus; EEG

1. Introduction

Although patients with Angelman syndrome (AS) eventually develop severe mental retardation, in most cases early development may seem almost normal [1,2]. During their clinical course, they begin to have epileptic seizures, especially nonconvulsive status epilepticus (NCSE), and display severe EEG abnormalities. In other forms of childhood epilepsy, such as Lennox-Gastaut syndrome, patients who experience repetitive bouts of NCSE usually develop mental retardation [3]. Therefore, we hypothesized a relationship between the severity of developmental disturbance in AS and the presence of NCSE associated with severe EEG abnormalities. This study was designed to explore this relationship.

2. Subjects and methods

We studied 11 patients with AS, both in terms of clinical outcomes and EEG profiles (Table 1). Eight of these patients have a deletion in chromosome 15. Cases 8 and 9 are identical twins who display typical clinical and EEG findings, but show no evidence of deletion, paternal disomy, or imprinting center mutations. We are currently investigating whether these patients have a mutation in the UBE3A gene. Seven patients (cases 1–7) were more than 8 years old at the last follow-up. All patients, except case 11, were admitted to our hospital at least once. During hospitalization, all patients except case 2 experienced

☆ The paper is based on the lecture given at the 6th annual meeting of the Infantile Seizure Society, Tokyo, March 15–16, 2003.

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doi:10.1016/j.braindev.2003.09.015

Table 1
Epileptic seizures and gene abnormalities in the subjects

Case(Sex)	Last follow-up	15q11–q13 deletion	Seizure onset	Last seizure	Atypical absence	GT/GTC	CPS	NCSE	Therapy for NCSE
1(F)	15y 4m	(+)	11 m	2y 5m		(+)	(+)	(+)	iv DZP, high-dose DZP, VPA
2(M)	15y 2m	(+)	2y 10m	4y 2m		(+)			
3(M)	13y 10m	(+)	2y 10m	6y 11m			(+)	(+)	iv DZP, CZP, CLB, VPA
4(M)	13y 2m	(+)	3y	3y 5m	(+)			(+)	iv DZP, VPA
5(F)	12y 1m	(+)	1y 6m	8y 1m	(+)	(+)	(+)	(+)	iv DZP, VPA, ESM, ACTH
6(M)	8y 6m	(+)	6m	7y 6m	(+)	(+)	(+)	(+)	iv DZP, CZP, VPA ESM, ACTH
7(F)	8y 1m	(+)	1y 6m	3y 10m	(+)		(+)	(+)	iv DZP, CZP, VPA
8(M)	4y 5m	(−)	2y 9m	3y 4m	(+)			(+)	VPA
9(M)	4y 5m	(−)	3y 1m	3y 3m	(+)			(+)	VPA
10(F)	3y 4m (died*)	?	2y 3m	2y 6m				(+)	iv DZP, VPA
11(F)	2y 11m	(+)	2y 7m	2y 11m	(+)			(+)	CZP, VPA

*, she died of burn; ?, only G band analysis was performed; GT, generalized tonic seizure; GTC, generalized tonic–clonic seizure; CPS, complex partial seizure; NCSE, nonconvulsive status epilepticus.

NCSE, and simultaneous video-EEG–EMG recordings were performed during such episodes. Follow-up periods ranged from 1 year and 3 months to 14 years and 4 months and for six of the patients the follow-up was greater than 7 years. During the follow-up periods, we personally examined all patients, paying special attention to epileptic seizures, as well as mental and motor development. EEGs were performed at least yearly. If our observations, or those of the parents of patients, detected reduced alertness, mental or motor deterioration, or paroxysmal phenomena such as myoclonias, brief atonias and epileptic seizures, we made every effort to evaluate them by means of simultaneous video-EEG–EMG recordings in addition to interictal EEGs.

To investigate the temporal relationship between EEG findings and the severity of epilepsy, as well as the relationship between developmental disturbance and epilepsy, we focused on 7 patients who were followed up until after the age of 8 years.

3. Results

3.1. Epileptic seizures

All patients experienced epileptic seizures; atypical absences were seen in 7 cases, generalized convulsions (generalized tonic–clonic or generalized tonic seizures) in 4 cases, complex partial seizures in 5 cases and NCSE in 10 cases (Table 1) Age at onset ranged from 6 months to 3 years and 1 month. Four patients had a febrile seizure as their first presentation. All epileptic seizures disappeared by around 8 years of age (Table 1).

Except for case 2, all patients experienced NCSE, which was the most prominent seizure type among the cases we studied. Clinical signs of NCSE included reduced alertness, as well as mental and motor deterioration. NCSE was often associated with brief atonias and erratic myoclonias, mainly in the distal regions of the limbs. In the 7 patients who were followed up until after the age of 8, NCSE was observed between the ages of 8 months and 8 years and 1 month (Table 2).

3.2. Interictal EEG findings

AS characteristically demonstrates two types of epileptic discharges on EEGs: bursts of high-voltage frontal dominant activity (2–3 Hz) associated with spikes and sharp waves, and bursts of occipital dominant high-voltage activity (3–4 Hz) associated with spikes [4,5] (Fig. 1). These somewhat diffuse epileptic discharges were observed in the patients we studied between the ages of 6 months and 12 years and 1 month (Table 2). Among the 7 patients who were followed up until after the age of 8, these discharges had disappeared in 5 of the patients by 7 years of age. However, they persisted until the age of 11 years and 8 months in case 4 (last follow-up: 13 years and 2 months). In case 5, they continued until the age of 8 years and 1 month, and reappeared on the last follow-up EEG at

Table 2
Nonconvulsive status epilepticus and diffuse epileptic discharges in 7 long-term follow-up cases

Case(Sex)	Nonconvulsive status epilepticus		Diffuse epileptic discharge		Mental retardation
	Onset	End	Onset	End	
1(F)	1y 7m	2y 5m	2y 1m	5y	Moderate
2(M)	(−)	(−)	11m	5y	Severe
3(M)	2y 10m	6y 11m	2y 1m	6y 11m	Moderate
4(M)	3y 2m	3y 5m	3y 4m	11y 8m	Moderate
5(F)	?	8y 1m	?	12y 1m	Mild
6(M)	8m	6y	6m	6y 4m	Severe
7(F)	2y 11m	3y	2y 4m	3y	Moderate

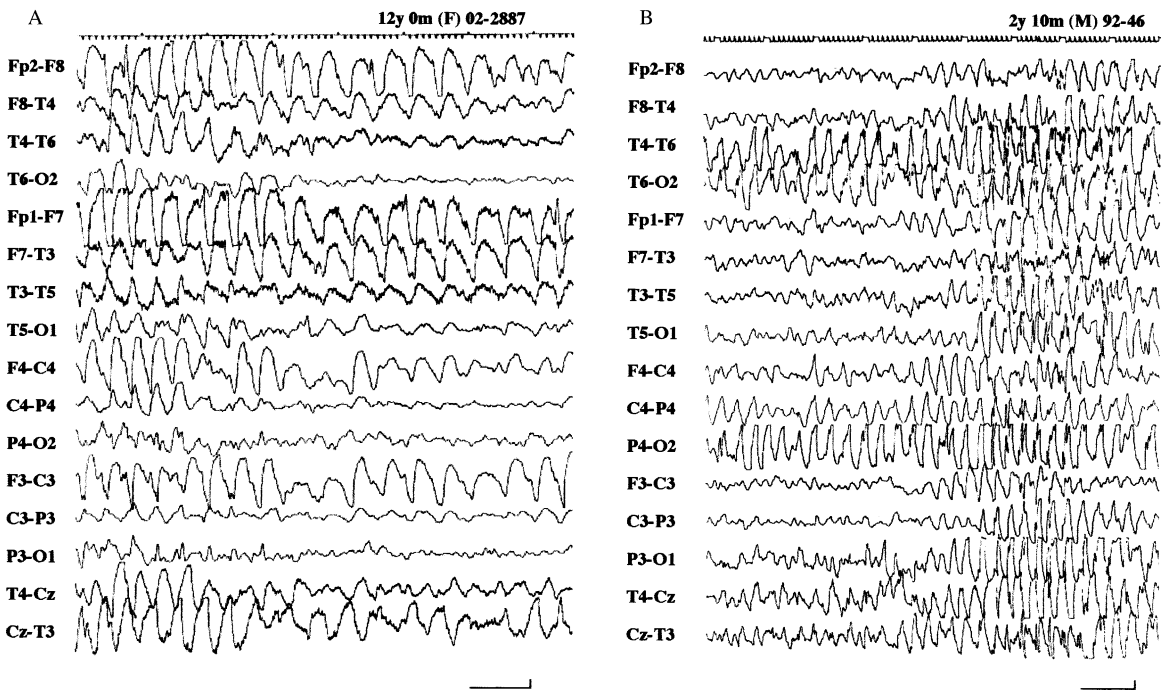

Fig. 1. Specific epileptic discharges in Angelman syndrome. (A) Bursts of bilateral frontal dominant 2–3 Hz activity associated with spikes and sharp waves observed in case 5 at 12 years of age. (B) Bursts of bilateral occipital dominant 3–4 Hz activity associated with spikes observed in case 2 at 2 years and 10 months of age. Calibration: 50 μV, 1 s.

the age of 12 years and 1 month (Table 2). EEGs of 6 out of the 7 patients (cases 1–6) began to display occipital alpha activity by the time the patients had reached 4 or 5 years of age. Prior to that the EEGs of most patients showed 4–6 Hz diffuse theta activity, as described by Boyd et al. [4].

3.3. Ictal EEGs of NCSE

EEGs performed during episodes of NCSE showed almost continuous diffuse spike-wave discharges (Type A) or diffuse high-voltage slow waves mixed with spike-waves

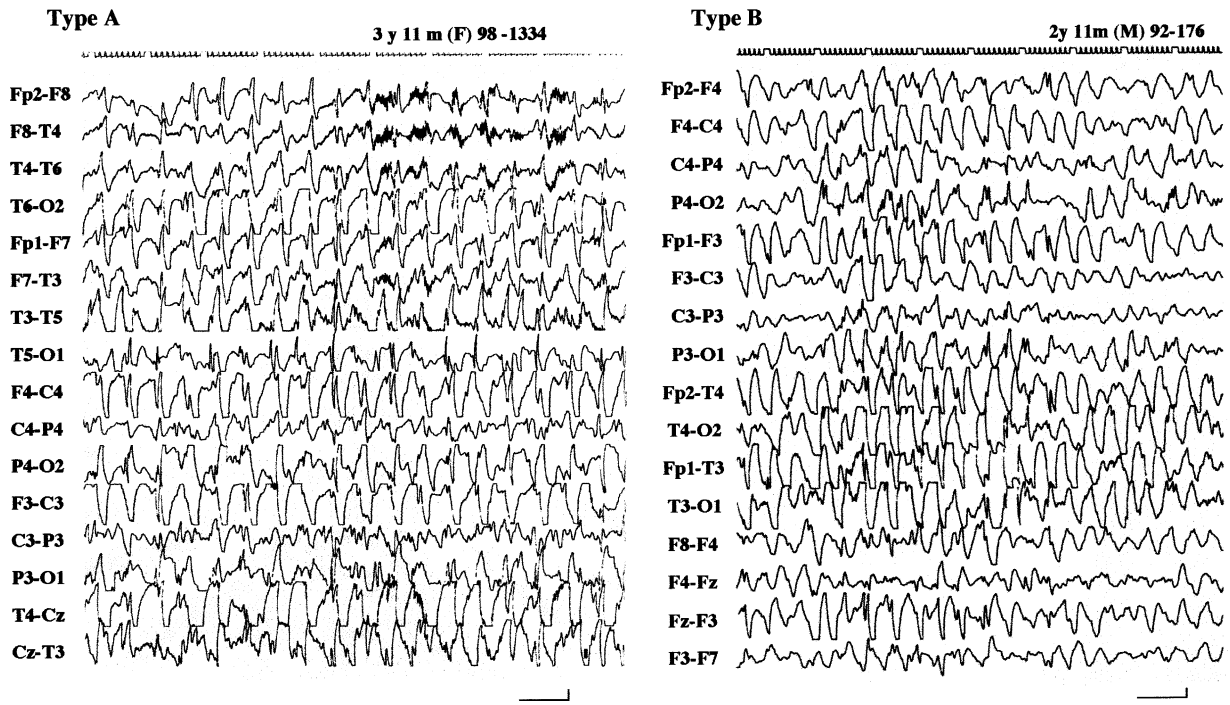

Fig. 2. EEG during nonconvulsive status epilepticus in Angelman syndrome. Type A, Continuous 2 Hz diffuse spike-wave bursts. Type B, Diffuse 2–3 Hz irregular high-voltage slow waves intermixed with spikes. Calibration: 50 μV, 1 s.

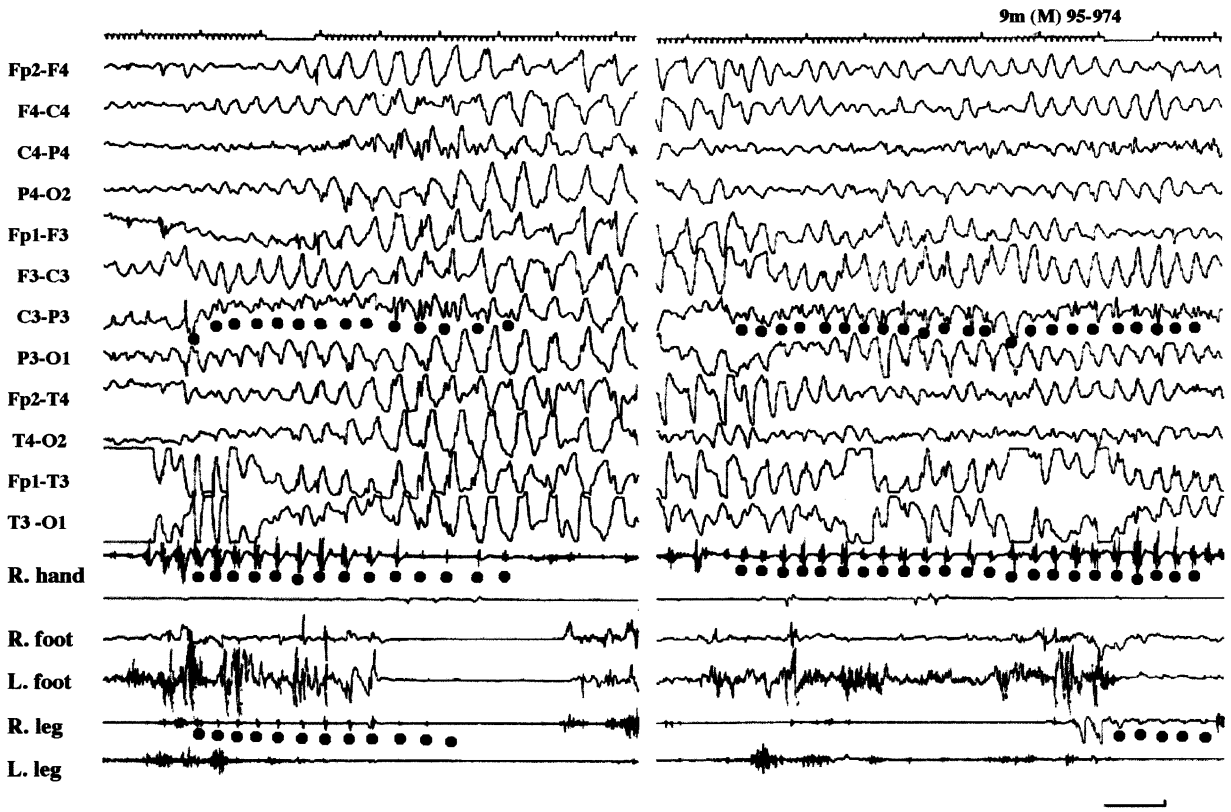

Fig. 3. Polygraphic recording during NCSE in case 6 at 9 months of age. Dots indicate myoclonias involving right hand and leg, and left central-parietal spikes. Calibration: 50 μV, 1 s.

(Type B) (Fig. 2). Type A patterns are typically associated with a more clinically distinct reduction in alertness, compared with Type B patterns. Four patients displayed Type A patterns, while 5 displayed Type B. The remaining case (case 6) displayed Type A patterns during one episode of NCSE (3 years and 11 months of age) and Type B during another (8 months of age). Myoclonias and brief atonias experienced during episodes of NCSE were not usually associated with specific epileptic discharges on EEG, but myoclonias were sometimes associated with spikes in case 6 (Fig. 3).

3.4. Developmental disturbances

Table 3 shows developmental milestones for our patients Early development, such as head control, was normal or

Table 3
Developmental milestones in the subjects

Case(Sex)	Last follow-up	Head control	Sitting up	Crawling	Independent walking	Comprehension of words	Speaking meaningful words
1(F)	15y 4m	4m	1y 1m	?	5y 6m	(+)	(−)
2(M)	15y 2m	3m	1y 6m	1y 4m	(−)	(−)	(−)
3(M)	13y 10m	3m	11m	1y 8m	3y 9m	(+)	(−)
4(M)	13y 2m	4m	1y 5m	2y 6m	6y 7m	(+)	(−)
5(F)	12y 1m	5m	1y 1m	?	4y 5m	(+)	(+)
6(M)	8y 6m	5m	4y 1m*	(−)	(−)	(−)	(−)
7(F)	8y 1m	5m	10m	2y 1m	5y 10m	(+)	(−)
8(M)	4y 5m	4m	13m	(−)	3y 5m	(+)	
9(M)	4y 5m	3m	10m	(−)	3y 5m	(+)	
10(F)	3y 4m (died)	4m	1y 2m	1y 2m			
11(F)	2y 11m	4m	1y	1y 8m			

*, he soon lost the ability to sit up.

slightly delayed in all patients. Although sitting was delayed by around one year in the patients we studied, all of them eventually gained the ability to sit up. Seven out of the 9 patients who were followed up until after the age of 4 years achieved independent walking; ages ranged from 3 years and 5 months to 6 years and 7 months. Case 5 is a female patient who demonstrated the most favorable outcome for mental development. Although unable to walk independently until the age of 4 years and 5 months, she began to speak some meaningful words at around 5 years of age. In addition, her level of comprehension was the highest amongst all the patients studied. Cases 2 and 6 represent the patients with the most severe developmental disturbances. Case 2 is a male who gained head control at 3 months and sat alone at 1 year and 6 months of age, however, he could neither walk independently nor understand any words at his last follow-up. Case 6 is a male who gained head control at 5 months and was able to sit alone at 4 years and 1 month. However, he was unable to sit, walk, or understand any words at the last follow-up.

3.5. The relationship between epilepsy and developmental disturbances

Our series included 2 patients who had very severe developmental disturbances (Tables 2 and 3). In case 6, epileptic seizures began at 6 months of age, with episodes of NCSE at 8 months of age. This was the earliest presentation of seizures and NCSE in our series. In addition, this patient experienced refractory bouts of NCSE until 6 years of age. In terms of development, he began to sit up at 4 years and 1 month of age, but soon lost this ability. Around 4 years of age, he was hospitalized several times due to repeated episodes of NCSE and was unable to regain the ability to sit up after suppression of NCSE. In contrast, in case 2, the onset of seizures was later and their frequency was less. In addition, this patient did not experience NCSE. This patient has been intensively followed up and has received rehabilitation therapy since the age of 10 months because of developmental disturbances. Therefore, in this case, it appears that the developmental disturbances were not significantly influenced by epilepsy or by other environmental problems.

Case 5 is a female patient who demonstrated the most favorable outcome for mental development (Tables 2 and 3). She was admitted to our hospital at 8 years of age because of NCSE. According to medical records from another hospital, she had frequent atypical absences with some fluctuation from the age of 1 year and 6 months, up until the age of 5 years and 11 months. During this period, her EEGs showed a hypsarrhythmia-like pattern. Therefore, it is likely that she suffered repetitive bouts of NCSE during this period. Finally, at 5 years and 11 months of age, she was treated with synthetic ACTH to suppress NCSE, and she remained seizure-free until 8 years of age, when she was admitted to our hospital and was diagnosed with NCSE secondary to AS.

In the other patients, who showed moderate developmental retardation, the EEG abnormalities and the severity of epilepsy varied from case to case (Table 2).

3.6. Therapy

The frequency of generalized seizures and complex partial seizures was not high, and these seizures were relatively easy to control with conventional antiepileptic drugs. On the other hand, NCSE and atypical absences were refractory in most cases. Therefore, we investigated the therapy of NCSE on 10 patients with NCSE in our series (Table 1). Effectiveness was defined as a complete suppression of NCSE. Intravenous diazepam (DZP) was effective in 6 of 8 trials (7 patients) but the effect was only transient, lasting for a few hours or less. In case 1, a short cycle of high-dose DZP (5 mg/day for 7 days) suppressed NCSE without recurrence until the last follow-up. In case 3, clobazam (CLB) suppressed NCSE but it recurred 1 year and 7 months later. Clonazepam (CZP) was effective in 3 of 5 trials (4 patients). Valproate (VPA) was effective in 3 of 10 patients. The effect of CZP and VPA lasted for several months up to years. In case 5, NCSE was not suppressed by ethosuximide (ESM) (700 mg/day, 117 μg/ml), although the EEG profile was slightly improved. In this patient, NCSE was completely suppressed at 8 years and 1 month of age using a combination of 600 mg/day of ESM and 1200 mg/day of VPA (blood level: 95 μg/ml). She remained seizure-free until the last follow-up. Synthetic ACTH was effective in case 5 (5 years and 11 months of age) and case 6 (3 years and 11 months of age). NCSE recurred at 8 years of age in case 5 and at 5 years and 5 months of age in case 6.

4. Discussion

The developmental disturbances of AS are somewhat similar to those of Rett syndrome. Although development during the first 6 months of life is not apparently delayed, patients with AS and Rett syndrome eventually develop severe mental retardation associated with motor disturbances such as those specifically affecting gait. These syndromes are characterized by epileptic seizures and, in most cases, specific epileptic discharges on EEG. Both syndromes are now believed to be models of arrested development [1].

Much attention has been paid to the characteristics of developmental disturbance in AS [6–8]. Regarding mental function, it is thought that patients with AS have a greater deficit with expressive language, compared to receptive. Of the 36 patients described by Robb et al. [9], only 7 were able to utter any recognizable words and the maximum

number of words used was 3. As for motor function, patients display an ataxic gait associated with jerky puppet-like movements [10,11]. Viani et al. [11] claimed that the occurrence of a transient myoclonic status epilepticus may account for these abnormal jerky movements, although ataxia is a constant symptom. Guerrini et al. [12] revealed that myoclonias in AS are cortical myoclonias. In our series, case 6 displayed myoclonias during episodes of NCSE that were associated with spikes in the contralateral cortical region. Therefore, we conclude that they originated in the cortex.

NCSE was the most salient epileptic manifestation in our series. NCSE in AS has been extensively investigated [11,13,14]. During NCSE, patients show decreased alertness and mental and/or motor deterioration associated with myoclonias and brief atonias. In some cases, frequent atypical absences are observed during NCSE. Elia et al. [15] reported that myoclonic absence-like seizures are often seen in syndromes with chromosomal abnormalities such as AS, trisomy 12p, and inv dup (15). They argue that abnormal expression of genes related to K^+ channels and γ-aminobutyric acid-3 subunit receptors could be responsible for these types of seizures.

Developmental disturbances in AS may be attributed to a variety of causes. It is thought that there is some relationship between genotype and phenotype in AS. The 15q11–q13 deletion causes the severest phenotype, while mutation of the UBE3A gene results in the most favorable phenotype in terms of epilepsy and development [16]. All of the patients in our series with diagnosed genetic abnormalities were shown to have deletions. In particular, the 7 patients who were followed up until after the age of 8 years had this abnormality. Therefore, the phenotypic differences in our patients are not attributable to different genetic abnormalities.

This study showed that for most of our cases of AS the appearance of seizures, especially NCSE, roughly coincided with the onset of developmental delay. Therefore, we suspect that there might be some relationship between epileptic seizures associated with severe EEG abnormalities, and the severity of developmental disturbance. If this holds true, early aggressive treatment for epilepsy may be able to halt the development of more severe developmental delay. In case 6, the patient had a very poor developmental outcome that may be related to repetitive episodes of NCSE. In fact, this was the only patient whose deterioration persisted even after suppression of NCSE. On the other hand, it seems unlikely that epilepsy was a critical factor that influenced the severe developmental outcome in case 2. Although the patient in case 5 had severe epilepsy with severe EEG abnormalities that persisted over a long period, it resulted in the mildest form of mental retardation in our series. Interestingly, for most of the patients in this series, characteristic epileptic discharges subsided with age, and alpha activity appeared at around 4 or 5 years of age, regardless of the severity of developmental disturbance.

Taking these findings together, we must conclude that the severity of developmental disturbance in AS is not necessarily related to epileptic seizures such as NCSE, nor is it related to the length of time that a patient might be demonstrating severe epileptic discharges on EEG. We believe that epilepsy is just one manifestation of CNS disorders caused by genetic abnormalities, and that various other factors can influence the developmental outcome in AS. However, we believe that aggressive treatment for NCSE is justified because there are some patients in whom NCSE results in a transient and sometimes permanent decline in mental and motor functioning. Further large-scale studies are necessary to reach a definite conclusion regarding the relationship between developmental outcome and the severity of epilepsy in patients with AS.

References

[1] Philippart M. Rett and Angelman's syndromes: models of arrested development. Pediatr Neurol 2001;25:288–94.
[2] Zori RT, Hendrickson J, Woolven S, Whidden EM, Gray B, Williams CA. Angelman syndrome: clinical profile. J Child Neurol 1992;7:270–80.
[3] Hoffmann-Riem M, Diener W, Benninger C, Rating D, Unnebrink K, Stephani U, et al. Nonconvulsive status epilepticus—a possible cause of mental retardation in patients with Lennox-Gastaut syndrome. Neuropediatrics 2000;31:169–74.
[4] Boyd A, Harden A, Patton MA. The EEG in early diagnosis of the Angelman (happy puppet) syndrome. Eur J Pediatr 1988;147:508–13.
[5] Laan LAEM, Renier WO, Arts WFM, Buntinx IM, V.d. Burget IJAM, Stroink H, et al. Evolution of epilepsy and EEG findings in Angelman syndrome. Epilepsia 1997;38:195–9.
[6] Jolleff N, Ryan MM. Communication development in Angelman's syndrome. Arch Dis Child 1993;69:148–50.
[7] Penner KA, Johnston J, Faircloth BH, Irish P, Williams CA. Communication, cognition, and social interaction in the Angelman syndrome. Am J Med Genet 1993;46:34–9.
[8] Clayton-Smith J. Angelman syndrome: evolution of the phenotype in adolescents and adults. Dev Med Child Neurol 2001;43:476–80.
[9] Robb SA, Pohl KRE, Baraitser M, Wilson J, Brett EM. The 'happy puppet' syndrome of Angelman: review of the clinical features. Arch Dis Child 1989;64:83–6.
[10] Angelman H. 'Puppet' children: a report on three cases. Dev Med Child Neurol 1965;7:681–8.
[11] Viani F, Romeo A, Viri M, Mastrangelo M, Lalatta F, Selicorni A, et al. Seizure and EEG patterns in Angelman's syndrome. J Child Neurol 1995;10:467–71.
[12] Guerrini R, DeLorey TM, Bonanni P, Moncla A, Dravet C, Suisse G, et al. Cortical myoclonus in Angelman syndrome. Ann Neurol 1996;40:39–48.
[13] Sugimoto T, Yasuhara A, Ohta T, Nishida N, Saitoh S, Hamabe J, et al. Angelman syndrome in three siblings: characteristic epileptic seizures and EEG abnormalities. Epilepsia 1992;33:1078–82.
[14] Matsumoto A, Kumagai T, Miura K, Miyazaki S, Hayakawa C, Yamanaka T. Epilepsy in Angelman syndrome associated with chromosome 15q deletion. Epilepsia 1992;33:1083–90.
[15] Elia M, Guerrini R, Musumeci SA, Bonanni P, Gambardella A, Aguglia U. Myoclonic absence-like seizures and chromosome abnormality syndromes. Epilepsia 1998;39:660–3.
[16] Minassian BA, DeLorey TM, Olson RW, Philippart M, Bronstein Y, Zhang Q, et al. Angelman syndrome; correlations between epilepsy phenotypes and genotypes. Ann Neurol 1998;43:485–93.