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Early and Late-Onset Epilepsy in Autism: High Rate of Secondarily Generalized Seizures

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Abstract

Background: The purpose of this study was to better characterize the features of early and late-onset epilepsy in individuals with autism.

Methods: We reviewed the charts of all patients with autism referred to Shiga University Hospital between 2002 and 2012. Patients who were identified as having epilepsy were examined, and they were divided into two groups according to the age of seizure onset (younger or older than three years).

Results: Of the 274 patients with autism, 40 individuals with epilepsy were identified. We detected two peaks of seizure onset in the patients with epilepsy, one in early childhood and one in adolescence, with a high incidence of West syndrome (p=0.005) in the early-onset group and a high level of secondarily generalized seizures (p=0.01) in the late-onset group.

Conclusion: The present results are closely consistent with those published previously; however, the high rate of secondarily generalized seizures in the late-onset epilepsy group of autism is herein reported for the first time.

Keywords: Autism; Epilepsy; Intellectual disability; Secondarily generalized seizure

Introduction

Autism is a complex neurodevelopmental disorder with a highly variable phenotype that may occur secondary to a variety of different genetic and nongenetic etiologies. Defined by impairments in social, communicative and behavioral functioning, individuals with autism also display associated features, such as intellectual disability and co-occurring/comorbid medical conditions [1]. A common co-occurring medical condition affecting a significant portion of individuals with autism is epilepsy [2,3]. The prevalence of epilepsy in patients with autism ranges from 5% to 46% and is increased in those with greater intellectual disability, symptomatic versus idiopathic autism, an older age and a history of cognitive/developmental regression [4]. On the other hand, in a large community-based cohort of patients with childhood onset epilepsy, 5% of children with epilepsy had a diagnosis of autism [5]. It has been suggested that the prevalence of autism is highest among children whose seizures begin around two years of age or earlier [6], indicating that the occurrence of seizures in the early developmental period is a risk factor for autism. It has been also reported that there are two peaks of seizure onset in autism patients-one in early childhood and the other in adolescence [7]; however, the epilepsy patients with the second peak in seizure onset is not well understood. In the present study, we retrospectively studied all patients with autism referred to Shiga University Hospital and examined the characteristics of epilepsy in autism patients. The purpose of this study was to better characterize the features of early and late-onset epilepsy in individuals with autism.

Patients and Methods

Study of autism and epilepsy patients

We reviewed the charts of all patients with autism referred to the Pediatric Neurology Clinics in the Department of Pediatrics at Shiga University Hospital between 2002 and 2012. Autism was diagnosed using the DSM-IV criteria (299.00 Autistic Disorder) [8]. The Pervasive Developmental Disorder-Autism Society Japan Rating Scale (PARS) was used to evaluate autism [9]. Among the autistic individuals, epilepsy patients were selected and divided into two groups according to the age of seizure onset, that is, younger or older than three years of age; because the delays or abnormal functioning associated with autism occur with an onset before age three. The seizures were classified according to the International League Against Epilepsy (ILAE, 1993) criteria [10].

When data were available, the following information was recorded: age at first visit, gender, history and type of seizures, age at seizure onset, type of epilepsy (as defined by the ILAE), seizure frequency, treatment response to antiepileptic drugs, neuroimaging findings on brain computed tomography (CT) or magnetic resonance imaging (MRI) and electroencephalography (EEG) recordings. Associated underlying disorders, such as perinatal or genetic abnormalities, were also recorded. Full-scale IQ and developmental quotients (DQs) were assessed using the WISC-III or WAIS-III in late childhood and adolescence, and the Kyoto scale of Psychological Development 2001 in patients under the age of five, and divided into five categories: average (IQ/DQ>85), low average (IQ/DQ=85~70), and mild (IQ/DQ=69~50), moderate (IQ/DQ=49~35) and severe (IQ/DQ<35) intellectual disabilities. The seizure-controlled patients were defined as those who demonstrated freedom from all seizures, including aura, for more than 12 months. The diagnosis of epilepsy was made based on the evaluations of the age at seizure onset, type of seizures, interictal and ictal EEG findings and the results of neuroimaging studies, including brain MRI, CT and single photon emission computed tomography

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(SPECT) by three epilepsy specialists in our department according to the ILAE criteria.

The EEG recordings used the 10-20 International System of electrode placement with referential and bipolar montage. Activation procedures with photic stimulation and hyperventilation were routinely performed if the patient was able to cooperate. The following EEG studies were reviewed: (1) routine: outpatient monitoring for 60 minutes, including the light sleep stage; (2) video-EEG monitoring: inpatient prolonged EEG monitoring with video recording lasting at least 24 hours.

MRI studies were performed using a 1.5-T Signa scanner (General Electric Medical Systems, Milwaukee, WI). Axial scans were obtained parallel to the orbitomeatal line with a slice thickness of 5 mm. All images were obtained using spin-echo pulse sequence (TR: 600 ms, TE: 35 ms, T1 weighted; TR: 2000 ms, TE: 100 ms, T2 weighted). Fluid attenuated inversion recovery images were also analyzed (TI: 2200 ms, TR: 10,002 ms, TE: 142 ms), to detect more subtle brain lesions.

The statistical analyses were performed using the Chi-square test. p values of less than 0.05 were considered to be statistically significant.

Results

Autism patients

A total of 274 patients with autism (213 males, 61 females) were identified (Table 1). These cases included the children, who were referred due to suspected autism and thus were diagnosed at Shiga University Hospital as new patients, and also children who were referred from other hospitals in Shiga prefecture after a diagnosis had already been made, but they could not be sufficiently managed by their local physician. The mean age at the initial visit was 7.4 years (S.D.=7.8). A frequency histogram of age at the first visit is shown in Figure 1, revealing an almost normal distribution from one to 17 years of age. Of the autism individuals, 40 (14.6%) were found to have epilepsy. The percentage of males was significantly higher, at 80.3% in the cases with autism without epilepsy, compared with that in patients with both autism and epilepsy (62.5%) (p=0.01). In the evaluation of the intelligence level, approximately half of the autistic patients without epilepsy (49.1%) had average intelligence; however, none of the autistic individuals with epilepsy exhibited an average intelligence level (p<0.0001).

Epilepsy patients

A total of 40 patients with epilepsy (25 males, 15 females) were identified (Table 2). The mean age of seizure onset was 49.0 ± 54.0 months (range: three months to 16 years and five months). A frequency histogram of age at the onset of seizures is shown in Figure 2. The histogram revealed that 13 patients (32.5%) with epilepsy developed seizures in the first year of life, and 27 patients (67.5%) developed

Table 1: Gender and intelligence level of autism patients with and without epilepsy.

	All cases (n=274)	Autism without epilepsy (n=234; 85.4%)	Autism with epilepsy (n=40; 14.6%)	*P* value
Gender				
Male	213 (77.7%)	188 (80.3%)	25 (62.5%)	0.01*
Female	61 (22.3%)	46 (19.7%)	15 (37.5%)	
Intelligence level				
Average	115 (41.9%)	115 (49.1%)	0 (0.0%)	<0.0001*
Low average	51 (18.6%)	47 (20.1%)	4 (10.0%)	
Mild	67 (24.5%)	46 (19.7%)	21 (52.5%)	
Moderate	24 (8.8%)	19 (8.1%)	5 (12.5%)	
Severe	17 (6.2%)	7 (3.0%)	10 (25.0%)	<0.0001*

*Statistically significant.

Figure 1: Frequency histogram of age at the first visit.

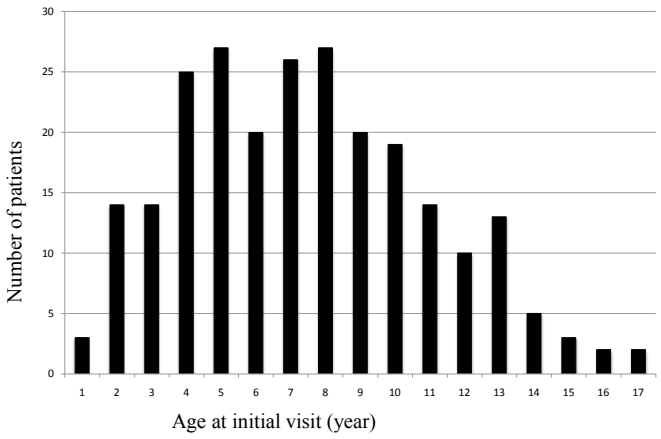
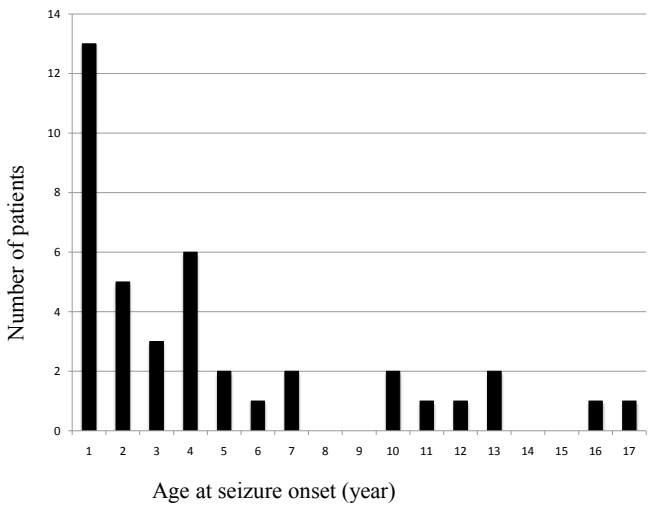


Table 2: Characteristics of epilepsy and intelligence level.

	All cases (n=40)	Early onset (< 3 years old) (n=21)	Late onset (>3 years old) (n=19)	*P* value
Age at seizure onset (month)	49.0 ± 54.0	11.2 ± 8.8	90.6 ± 52.4	
Gender				
Male	25 (62.5%)	16 (76.2%)	9 (47.4%)	0.06
Female	15 (37.5%)	5 (23.8%)	10 (52.6%)	
Type of epilepsy				
TLE	15 (37.5%)	9 (42.9%)	6 (31.6%)	0.46
FLE	9 (22.5%)	3 (14.3%)	6 (31.6%)	0.19
OLE	1 (2.5%)	0 (0.0%)	1 (5.2%)	0.28
West syndrome	7 (17.5%)	7 (33.3%)	0 (0.0%)	0.005*
Other symptomatic generalized epilepsy	8 (20.0%)	2 (9.5%)	6 (31.6%)	0.08
Type of seizure				
SPS	1 (1.7%)	1 (3.8%)	0 (0.0%)	0.24
CPS	32 (53.3%)	15 (57.7%)	17 (50.0%)	0.55
Secondarily generalized seizures	7 (11.7%)	0 (0.0%)	7 (20.6%)	0.01*
Myoclonic seizures	1 (1.7%)	0 (0.0%)	1 (2.9%)	0.37
Tonic spasm	8 (13.3%)	8 (30.8%)	0 (0.0%)	0.0005*
GTCS	9 (15.0%)	2 (7.7%)	7 (20.6%)	0.16
Atonic seizure	2 (3.3%)	0 (0.0%)	2 (5.9%)	0.20
Seizure frequency				
Controlled	24 (60.0%)	13 (61.9%)	11 (57.9%)	0.65
Uncontrolled	16 (40.0%)	8 (38.1%)	8 (42.1%)	
Antiepileptic drugs				
Mono therapy	14 (35.0%)	8 (38.1%)	6 (31.6%)	0.66
Multiple therapy	26 (65.0%)	13 (61.9%)	13 (68.4%)	
Intelligence level				
Low average	4 (10.0%)	1 (4.8%)	3 (15.8%)	0.24
Mild to Severe	36 (90.0%)	20 (95.2%)	16 (84.2%)	

TLE, temporal lobe epilepsy; FLE, frontal lobe epilepsy; OLE, occipital lobe epilepsy; SPS, simple partial seizures; CPS, complex partial seizures; GTCS, generalized tonic-clonic seizures. *Statistically significant.

Figure 2: Frequency histogram of age at the onset of seizures.



seizures within four years of age. The second peak of seizure onset was observed at approximately 10 to 13 years of age.

The epilepsy patients were divided into two groups according to the age of seizure onset, namely early-onset (younger than three years of age) and late-onset (older than three years of age) epilepsy groups (Table 2). There were 21 patients in the early-onset epilepsy group (16 males, 5 females), with a mean age of seizure onset of 11.2 ± 8.8 months (range: three months to two years and 11 months). The late-onset epilepsy group included 19 patients (9 males, 10 females), with a mean age of 90.6 ± 52.4 months (range: three years to 16 years and five months). The most frequent type of epilepsy was temporal lobe epilepsy and West syndrome in the early-onset epilepsy group (42.9% and 33.3%, respectively) and temporal lobe epilepsy, frontal lobe epilepsy and other symptomatic generalized epilepsy in the late-onset epilepsy group (each 31.6%). More than half of the patients developed localization-related epilepsy in both groups, while the incidence of West syndrome was statistically significant in the early-onset epilepsy group ($p<0.005$). An analysis of the seizure type revealed the most frequent type of seizures to be complex partial seizures in both the early-onset (57.7%) and late-onset (50.0%) groups. Due to the high incidence of West syndrome in the early-onset epilepsy group, the rate of tonic spasms was significantly higher in the early-onset group than in the late-onset group ($p=0.0005$). On the other hand, secondarily generalized seizures were significantly more frequent in the late-onset epilepsy group ($p=0.01$). The epileptic seizures were well controlled in 61.9% of the early-onset and 57.9% of the late-onset epilepsy patients. However, most of the patients, including 61.9% of those in the early-onset group and 68.4% of those in the late-onset epilepsy group, required multiple antiepileptic drugs to control their seizures. All 40 patients with epilepsy manifested intellectual disabilities. A total of 36 patients (90.0%) developed mild to severe intellectual disabilities, including 95.2% and 84.2% of the patients in the early-onset and late-onset epilepsy groups, respectively, which was not significantly different.

The interictal EEG recordings obtained at the latest visit revealed generalized epileptic discharges in only one patient in the early-onset group and two patients in the late-onset group (3.6% and 7.0%, respectively) (Table 3). Most patients exhibited focal epileptic discharges that were widely distributed in whole brain areas, although frontal epileptic discharges in the early-onset group (21.5%) and central or occipital discharges in the late-onset group (17.9% each) were relatively frequent. The incidence of no paroxysmal discharges was 35.7% in the early-onset group and 21.4% in the late-onset group, with no statistically significant differences. Positive structural abnormalities were found on neuroimaging in seven patients (33.3%) in the early-onset epilepsy group and two patients (10.5%) in the late-onset epilepsy group. Etiological underlying disorders were observed in nine patients (45%) in the early-onset group, including five cases of perinatal asphyxia, two cases of tuberous sclerosis and one case each of ganglioglioma and polymicrogyria, and five patients (33.3%) in the late-onset group, including one case each of perinatal asphyxia, polymicrogyria, ventricular dilatation, neurofibromatosis type 1 and tuberous sclerosis. Thus, the malformation of cortical development was found in 4 cases (19.0%; tuberous sclerosis, ganglioglioma and polymicrogyria,) and 2 cases (10.5%; polymicrogyria and tuberous sclerosis) in the early-onset and the late-onset group, respectively.

Discussion

In the present study, all 40 autism patients with epilepsy manifested intellectual disabilities. We found two peaks of seizure onset, one in early childhood and one in adolescence, with a high incidence of West syndrome ($p=0.005$) in the early-onset group and a high level of secondarily generalized seizures ($p=0.01$) in the late-onset group. Overall, these results are closely consistent with those published by the other researchers [3]; however, the high rate of secondarily generalized seizures in the late-onset epilepsy group of autism is herein reported for the first time.

Autism is likely caused by alterations in the structural organization and/or function of neural systems that process social information, language and sensorimotor integration. Many autism susceptibility genes encode proteins that regulate synapse development and activity-dependent neural responses. The following three additional mechanisms may also contribute to autism: (1) the evolutionarily

Table 3: EEG findings, neuroimaging and associated etiology.

	All cases (n=40)	**Early onset (<3 years old) (n=21)**	**Late onset (≧3 years old) (n=19)**	***P* value**
EEG findings				
Generalized epileptic discharges Focal epileptic discharges	3 (5.4%)	1 (3.6%)	2 (7.0%)	0.55
Fp	3 (5.4%)	2 (7.1%)	1 (3.6%)	0.55
F	10 (17.9%)	6 (21.5%)	4 (14.3%)	0.48
C	8 (14.3%)	3 (10.7%)	5 (17.9%)	0.44
P	5 (8.9%)	1 (3.6%)	4 (14.3%)	0.15
O	7 (12.5%)	2 (7.1%)	5 (17.9%)	0.22
T	4 (7.1%)	3 (10.7%)	1 (3.6%)	0.29
No paroxysmal discharges	16 (28.5%)	10 (35.7%)	6 (21.4%)	0.23
MRI or CT: structural abnormalities				
Positive	9 (22.5%)	7 (33.3%)	2 (10.5%)	0.08
Negative	31 (77.5%)	14 (66.7%)	17 (89.5%)	
Associated etiology				
Positive	10 (25.0%)	7 (33.3%)	3 (15.8%)	0.20
Negative	30 (75.0%)	14 (66.7%)	16 (84.2%)	

Fp, frontopolar; F, frontal; C, central; P, parietal; O, occipital; T, temporal; MRI, magnetic resonance imaging; CT, computed tomography.

driven expansion of the cerebrum and cerebellar size via signaling systems, such as those activated by fibroblast growth factors, (2) an imbalance in the excitatory/inhibitory ratio in local and extended circuits and (3) the hormonal effects of the male genotype [11]. The disruption of the GABAergic circuit function has been implicated in various neurodevelopmental and psychiatric disorders, including schizophrenia, autism, mental retardation and epilepsy [12]. These changes induce abnormal excitability and disrupted synaptic plasticity in the developing brain, resulting in the high level of seizure susceptibility observed in patients with autism.

It has been proposed that autism, epilepsy and intellectual disabilities can be understood as disorders of synaptic plasticity. Recent studies have shown that, in individuals with both of autism and intellectual disabilities, the rate of epilepsy is as high as 20%. In autism patients without intellectual disabilities, the rate of epilepsy is approximately 8% [13]. The causal mechanisms of autism and epilepsy remain controversial; however, it has been suggested that the most common reason for the co-occurrence of autism and epilepsy is that the same brain pathology causes both disorders. It has also been proposed that the coexistence of autism and epilepsy occurs secondarily to an epileptic process in early development that interferes with the development of specific brain networks, thus resulting in the autism phenotype [14]. Therefore, the development of epilepsy and/or spontaneous seizures themselves may result in maladaptive synaptic plasticity that contributes to learning and behavioral difficulties [15].

Generalized tonic-clonic seizures can occur in patients with primary generalized epilepsy or can arise from partial seizures with secondary generalization. In a study of SPECT used to image cerebral blood flow (CBF) changes in patients with secondarily generalized seizures, there were CBF increases in the thalamus, basal ganglia and superior medial cerebellum during generalization, and progressive CBF increases were observed postictally in the cerebellar hemispheres and midbrain [16]. The thalamus and upper brain stem are thought to be critical for synchronizing abnormal cortical-subcortical electrical discharges, generating tonic motor activity and producing impaired consciousness in patients with epilepsy [17]. Thus, the involvement of the upper brain stem and thalamus in patients with secondarily generalized seizures supports the proposed roles of these structures in seizure generalization. The mechanisms underlying the secondary generalized seizures in late-onset epilepsy in autistic subjects are still unclear. Therefore, future research should be performed to better understand the brain network and the mechanisms of subcortical hyper excitability in patients with autism and epilepsy.

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