

## Evaluation of Behavior and Cognitive Function in Children with Myoclonic Astatic Epilepsy

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### Abstract

**Background:** Myoclonic astatic epilepsy (MAE) is an idiopathic and generalized childhood epileptic syndrome. Although several studies have reported on cognitive function and intellectual outcome in MAE, little is known about the behavioral problems associated with this disease. The aim of this study was to clarify behavior and cognitive function in children with MAE.

**Methods:** Four children who were diagnosed as having MAE using the proposed criteria of the International Classification of Epilepsies were retrospectively analyzed using patient records with regard to clinical and neuropsychological findings such as age of seizure onset, semiology and severity of seizures, treatment course, behavioral problems, EEG findings, and WISC-III and Pervasive Developmental Disorders Autism Society Japan Rating Scale (PARS) scores that indicate the tendency of autistic behaviors.

**Results:** Disease onset in our cohort ranged from 9 to 35 months of age. Seizures were controlled within 3-8 months over a follow-up period of 4-12 years. All patients had borderline normal intelligence (mean IQ: 75.8 at 5-7 years of age) and exhibited impaired coordination, clumsiness, hyperactivity or impulsivity, and impaired social interaction after improvement of seizures. Though these autistic social problems manifested gradually, the children were able to adapt to school life with appropriate support. Interestingly, the behaviors of impaired social interaction and hyperactivity or impulsivity had already been observed before the onset of MAE in most patients, whose PARS scores were all higher than reference values (<9) during infancy.

**Conclusion:** Our results showed that children with MAE tend to have autistic behavioral problems and mild intellectual impairment along with wide ranges in WISC-III subtest scores. These behavioral and cognitive features appear to exist before the onset of epilepsy.

**Keywords:** Myoclonic astatic epilepsy; Doose syndrome; Cognitive function; Behavior; Autism spectrum disorders

### Introduction

Myoclonic astatic epilepsy (MAE) is an idiopathic, generalized form of childhood epilepsy. As initially described by Doose in 1970, this disease is characterized by different seizure types, generalized spike and wave discharges, and slow waves or slowing down of background activity in electroencephalogram (EEG) [1]. MAE occurs in children with previously normal psychomotor development. With regard to cognitive function and intelligence outcome, 26-80% of MAE patients were reported to be intellectually normal, with others having mildly to moderately impaired intelligence [1-4]. However, little is known about the behavioral problems in MAE and the relationships between the symptoms of epilepsy, cognitive function, and behavior. The aim of this study was to clarify these features in children with MAE.

### Methods

We enrolled 4 children with MAE who had been referred to the pediatric department of Shinshu University Hospital between 2003 and 2008, and who satisfied the following criteria; 1) normal development before the onset of epilepsy and the absence of organic cerebral abnormalities, 2) onset of myoclonic, myoclonic-astatic, or astatic seizures between 7 months and 6 years of age, 3) presence of generalized spike- or polyspike-wave EEG discharges at 2-3 c/s without focal spike discharges, 4) follow-up for more than 3 years, 5) exclusion of severe and benign myoclonic epilepsy in infants and cryptogenic Lennox-Gastaut syndrome based on International League Against Epilepsy (ILAE) definitions [5]. We retrospectively analyzed

patient records with regard to clinical and neuropsychological findings that included age of seizure onset, semiology and severity of seizures, treatment course, behavioral problems, EEG findings, and Wechsler Intelligence Scale for Children-third edition (WISC-III) and Pervasive Developmental Disorders Autism Society Japan Rating Scale (PARS) scores that indicated the tendency of autistic behaviors. Informed consent was obtained from all parents.

### Results

#### Patient

Representative patient 1 is the second child of twins of healthy non-consanguineous parents. The boy was delivered at 35 weeks of gestation by Caesarian section (Table 1). His birth weight was 1111 grams. He experienced transient neonatal pulmonary hypertension and cardiac failure that was treated without any obvious ensuing neurological impairments. There was a family history of epilepsy. His growth and

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	patient 1	patient 2	patient 3	patient 4
age at onset (mo.)	35	21	34	9
seizure type	M, MA, TC, T, A	M, DA, T	M, DA, T, A, CPS	M, DA
seizure frequency	multiple per day	multiple per day	multiple per day	multiple per day
age at remission (mo.)	43	23	42	24
epilepsy duration (mo.)	8	3	8	3
febrile convulsion	-	+	-	-
family history of epilepsy	+	-	-	-
EEG findings	SBA, SW, PSW, MF	SBA, FS, SW	SBA, PSW, SW	SBA, FS, SW
treatment	VPA, ESM, ZNS, CLB, PHT	VPA, CZP, ZNS	CBZ, VPA, ESM, LTG	VPA
effective drug(s)	PHT, ESM, CLB	VPA, CZP	VPA, LTG	VPA
follow-up period (years)	10	12	4	5

A, absence seizure; CBZ, carbamazepine; CLB, clobazam; CPS, complex partial seizure; CZP, clonazepam; DA, drop attack; ESM, ethosuximide; FS, focal spikes; LTG, lamotrigine; M, myoclonic seizure; MA, myoclonic-astatic seizure; MF, multifocal spikes; PHT, phenytoin; PSW, diffuse polyspike and wave complexes; SBA, slowing of background activity consisting mainly of theta rhythm; SW, diffuse spike and wave complexes T, tonic seizure; TC: tonic-clonic seizure; VPA, valproic acid; ZNS, zonisamide

**Table 1:** Clinical characteristics of patients.

developmental course were normal. After an initial tonic seizure that lasted for 1 minute at the age of 2 years and 11 months, several types of seizures, including atonic, myoclonic, and absence seizures, were observed and increased to up to 400 times per day. Interictal EEG showed diffuse spike and wave or polyspike and wave discharges. Ictal records indicated diffuse spike and wave complexes and 2.5 c/s spike and wave bursts corresponding to atonic seizures and absence attacks, respectively. Blood, cerebrospinal fluid, and MRI findings were all normal. MAE was diagnosed and the patient was treated with valproate, zonisamide, phenytoin (PHT), ethosuximide (ESM), and clobazam (CLB) in turn, before establishing a course of combined therapy with PHT, ESM, and CLB for seizure control.

Concerning psychosocial development, the patient had already exhibited mild autistic behaviors, such as a lack of interest in people, restricted interest in play, and resistance to changes, before the onset of MAE (Table 2). His development became stagnant during the approximately 8 months from onset to remission of seizures, but did not regress. After control of his seizures, he resumed psychosocial development and was able to adapt to normal school life. His IQ improved from 79 at 5 years of age to 94 at 12 years of age (Table 3). However, he continued to display poor fine motor skills and autistic behaviors, for example, poor recognition of other people's emotions and appropriate response as well as consuming preoccupations with certain subjects.

### Results of 4 patients

After excluding 1 patient due to a short follow-up period, 4 subjects were enrolled in this study. The clinical characteristics of our cohort are summarized in Table 1. The age of MAE onset was 9-35 months old. All patients achieved complete control of seizures within 3-8 months during an observation period of 4-12 years after seizure onset.

The neuropsychological features of our cohort are presented in Table 2. All patients had normal or slight retardation of motor and language development, and all were noted to have impaired social interaction before the onset of MAE. Hyperactivity or impulsivity was also observed in the group before disease onset except for patient 4, who was too young to evaluate. No patient showed developmental regression despite frequent seizures. After achieving seizure control,

impaired coordination, clumsiness, hyperactivity or impulsivity, and impaired social interaction were witnessed for all children. Patient 2 was noted to have lessened hyperactivity or impulsivity at the age of 11. Restricted interests or inflexibility was seen in 3 out of 4 patients. Though these autistic social problems manifested gradually, the children were able to adapt to normal school life. PARS scores were higher than reference values (<9) in all 4 patients during infancy. Regarding cognitive function, the patients were evaluated by WISC-III at an age of 5-7 years. All had borderline normal intelligence. Although the highest and lowest WISC-III subtest scores for each child varied greatly, no discernible tendencies were evident.

### Discussion

All 4 cases met the diagnostic criteria for autism spectrum disorders (ASD), but not for typical Kanner type autism or Asperger's syndrome. Accordingly, the patients exhibited impaired social interaction and sympathy for other people and had inflexibility and a restricted range of interests. As they rarely asserted themselves strongly or attacked others, all children could adapt to school life with appropriate support. There have been earlier reports of behavioral problems in patients with MAE describing withdrawn, depressed, or aggressive behavior [4], impulsivity and distractibility [6], attention problems [4,7], and hyperkinesia [7]. These studies also indicated that some MAE patients might display behaviors consistent with ASD. We found that all of our patients showed age-dependent autistic behaviors not only after, but also before the onset of MAE through longitudinal observations made using detailed developmental histories.

Several past studies on cognitive function in MAE described incidences of intellectual impairment, with normal level intelligence present in 26% [1], 59% [2], and 80% [3] of subjects. Trivisano et al. suggested that cognitive prognosis was related to genetic factors rather than seizure semiology or time until seizure control in a prospective observation of 18 MAE children [4]. Another report showed poor cognitive prognosis to be associated with tonic or intractable seizures [8]. Although there were no common tendencies among cognitive profiles in our cohort, all children had borderline intellectual impairment and a wide range of WISC-III subtest scores. To our knowledge, there has been no report describing the differences in cognitive profiles among

	patient 1	patient 2	patient 3	patient 4
<b>before onset</b>				
motor retardation	±	±	-	±
language delay	-	±	-	-
hyperactivity or impulsivity	+	+	+	-
restricted interests or inflexibility	+	+	-	-
impaired social interaction	+	+	+	+
<b>after seizure remission</b>				
motor coordination deficits	+	+	+	+
difficulty with verbal communication	-	+	+	+
hyperactivity or impulsivity	+	+	+	+
restricted interests or inflexibility	+	+	-	+
impaired social interaction	+	+	+	+
PARS score	13	11	9	17
<b>WISC-III scores</b>				
age at evaluation	5Y	7Y	6Y	5Y
VIQ	92	80	71	84
PIQ	69	73	78	78
FIQ	79	74	71	79
VCI	88	80	70	86
POI	63	74	80	82
FDI	97	76	68	71
PSI	100	97	72	78
information	11	5	6	12 ⊙
similarities	6	2 ●	4	1 ●
arithmetic	12 ⊙	7	7	6
vocabulary	8	6	4	8
comprehension	7	14 ⊙	6	10
digit span	7	5	2 ●	4
picture completion	5	5	5	4
coding	11	7	6	5
picture arrangement	5	10	9 ⊙	10
block design	4	4	8	7
object assembly	3 ●	5	6	8
symbol search	9	12	4	7
difference between highest and lowest scores	9	12	7	11

VIQ, verbal intelligence quotient; PIQ, performance intelligence quotient; FIQ, full scale intelligence quotient; VCI, verbal comprehension index; POI, perceptual reasoning index; FDI, freedom from distractibility index; PSI, processing speed index  
 ⊙, highest score of subtest; ●, lowest score of subtest

**Table 2:** Neuropsychological features of patients.

age at evaluation	test	FIQ	VCI	POI	FDI	PSI	WMI
5Y	WISC-III	79	88	63	97	100	
10Y	WISC-III	84	91	74	100	90	
12Y	WISC-IV	94	99	82		86	118

WISC-III, Wechsler intelligence scale for children - third edition; WISC-IV, Wechsler intelligence scale for children - fourth edition; VIQ, verbal intelligence quotient; PIQ, performance intelligence quotient; FIQ, full scale intelligence quotient; VCI, verbal comprehension index; POI, perceptual reasoning index; FDI, freedom from distractibility index; PSI, processing speed index; WMI, working memory index

**Table 3:** Intelligence scales for patient 1

individuals with MAE to date. Cognitive profiles do not generally reveal common tendencies in people with ASD, but WISC-III subtest score ranges tend to be large in such individuals, which is consistent with our results. Although we observed autistic behavioral problems before MAE onset, it was impossible to precisely analyze cognitive function before the start of seizures because of our group's age. On the other hand, a recent study showed that patients with juvenile myoclonic epilepsy had cognitive impairment due to frontal lobe dysfunction

that had presented before the onset of epilepsy. These findings suggest that both autistic behavior and impaired cognitive function in MAE patients might exist before seizure onset. Therefore, close observation and evaluation of behavior and cognition in patients with MAE are recommended, even during infancy.

## Conclusions

Patients with MAE tend to have autistic behavioral problems, mild intellectual impairment, and large variability among WISC-III subtest scores. Behavioral, and possibly cognition, features are considered to be present before the onset of epilepsy.

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