Brain & Development 36 (2014) 613–619

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

www.elsevier.com/locate/braindev

Original article

Early onset and focal spike discharges as indicators of poor prognosis for myoclonic-astatic epilepsy

Takahito Inoue [a], Yukiko Ihara [a], Yuko Tomonoh [a], Noriko Nakamura [a], Shinya Ninomiya [a], Takako Fujita [a], Hiroshi Ideguchi [a], Sawa Yasumoto [a], Bo Zhang [b], Shinichi Hirose [a,*]

[a] *Department of Pediatrics, School of Medicine, Fukuoka University, Fukuoka, Japan*
[b] *Department of Biochemistry, School of Medicine, Fukuoka University, Fukuoka, Japan*

Received 23 April 2013; received in revised form 19 July 2013; accepted 14 August 2013

Abstract

Background: Myoclonic-astatic epilepsy (MAE) is an epileptic syndrome characterized by unique myoclonus, myoclonic-astatic, or astatic seizures in childhood. MAE prognosis vary from spontaneous remission to intractable seizures with profound mental retardation. *Aim:* Identifying early risk factors may optimize the treatment of children with MAE. Our hypothesis is early onset age and focal spike discharges on EEG indicate a poor MAE prognosis. *Methods:* Using the medical records of 9 children with MAE, we analyzed their clinical histories, EEG findings, and seizure symptoms. All patients were given follow-up observations/treatments by our department for at least 2 years after MAE onset. *Results:* Five of the patients were given favorable prognoses because their seizures disappeared within 2 years of onset; the other 4 received poor prognoses because their seizures continued more than 2 years. MAE onset in patient with refractory seizures was earlier than that in those with a favorable prognosis (7–24 months vs. 23–38 months). All the patients with refractory seizures showed moderate or severe mental retardation. Among the 5 patients with good prognosis, EEGs showed two with focal spike discharges and three with only generalized spike discharges. In contrast, all cases with a poor prognosis had focal spike discharges. *Conclusions:* MAE onset in patients with refractory seizures occurs earlier than in those with favorable prognosis. Prognosis was excellent when EEG findings show no focal spike discharges. Both early seizure onset and the focal spike discharges associated with MAE are indicators of poor prognosis.

Keywords: Myoclonic-astatic epilepsy; Doose syndrome; Prognosis; Early onset; Focal spike discharges

1. Introduction

First described in 1970, myoclonic-astatic epilepsy (MAE) is an idiopathic generalized epilepsy syndrome characterized by unique myoclonic, myoclonic-astatic, or astatic seizures, by early childhood onset, and by generalized spike discharges [1]. In 1989, the International League Against Epilepsy (ILAE) recognized generalized cryptogenic or symptomatic epilepsy with myoclonic-astatic seizures in its revised classification of epilepsies and epileptic syndromes [2]. This decision, however, was subsequently revised by the ILAE in 2001 and the condition was reclassified as idiopathic generalized epilepsy [3]. MAE is a very rare disease; its incidence is about 1:10,000 [4]. In 94% of cases, onset occurs within the first 5 years of life, and in 24% within the first year [5]. While its EEG indicates background activity can be normal at seizure onset, a characteristic 4–7 Hz

* Corresponding author. Address: Department of Pediatrics, School of Medicine, Fukuoka University, 45-1, 7-Chome, Nanakuma, Jonan-ku, Fukuoka 814-0180, Japan. Tel.: +81 92 801 1011; fax: +81 92 863 1970.
E-mail address: hirose@fukuoka-u.ac.jp (S. Hirose).

0387-7604/$ - see front matter © 2013 The Japanese Society of Child Neurology. Published by Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.braindev.2013.08.009

monomorphic theta activity with diffuse distribution – but prominent on centro-parietal areas – is often observed [6]. As the disease progresses, EEG findings show brief bursts of 2–5 Hz spikes, polyspikes, and wave complexes [7]; asymmetrical paroxysmal events are possible, but focal activity is very unusual [8]. MAE prognosis vary from spontaneous remission with normal developmental outcome to intractable seizures with profound mental retardation. Favorable outcomes are reported in half to two-thirds of cases [9–11]; the reasons for unfavorable outcomes, however, remain unclear, although failure to identify early risk factors and provide prompt treatment may be responsible. In the present study, we propose the hypothesis that early onset age and EEG evidence of focal spike discharges during the course of the disease indicate poor MAE prognosis.

2. Subjects

The nine patients with MAE in our study are children diagnosed at Fukuoka University Hospital using criteria proposed by the International League Against Epilepsy (ILAE) in [2]. Before onset each case showed normal development with no neurological deficits and no organic cerebral abnormalities. Seizure onset occurred between 7 months and 3 years 2 months of age; EEG findings showed generalized spike- or polyspike-wave discharges at 2–5 Hz.

3. Methods

We analyzed the medical records of 9 children with MAE, evaluating their clinical histories, EEG findings, and seizure symptoms. More specifically, we investigated the following: age of onset, family history, type of seizure at onset, EEG findings (location of focal spike discharges and age of onset), treatment, seizure outcome, and intelligence quotient (IQ) test results. Video-EEG monitoring may improve MAE diagnosis in young infancy and childhood, but it was not performed in the present study. Instead, an EEG-polygraph monitored by several pediatric neurologists was used in cases 7 (Fig. 1(a)), 8 (Fig. 1(b)), and 9 (Fig. 1(c)). These polygraphs demonstrated that whole body or upper limbs myoclonic jerks are time-locked to generalized spike and wave complexes and suggests that children presenting myoclonic jerks can be diagnosed with MAE. All patients were followed-up at observations/treatments by our department for anywhere from 4 to 17 years after MAE onset. All patients were divided two groups: an A group (5 patients) with no seizures for 2 years; and a B group (4 patients) with continuing seizures.

For most of the children, mental development was evaluated using the Tanaka-Binet IQ test, and they were placed in 4 groups: normal (IQ over 80); mild intellectual disability (IQ 60–79); moderate intellectual disability (IQ 30–59); and severe intellectual disability (IQ under 30). For children who were unable to take the Tanaka-Binet IQ test and for whom psychometric data was unable, developmental outcome was defined as normal if the child was in a mainstream educational setting and was found normal on a neurological examination. Children with mildly delayed development were in regular classrooms and were having special educational needs. Moderately delayed development required special needs education, and children with significant abnormalities were given neurological examination. A severely delayed development was defined as a developmental quotient (DQ) test score of under 50. Statistical data analyses were performed using the SAS (Statistical Analysis System) Software Package (Ver. 9.2, SAS Institute Inc., Cary, NC, USA) at Fukuoka University (Fukuoka, Japan). Significant differences in ages between groups A and B patients were examined by an analysis of variance (ANOVA) using the general linear model and by the Wilcoxon rank sum test [12]. Data are presented as the mean ± standard deviation (SD), and the significance level was considered to be less than 0.05 unless indicated otherwise.

4. Results

The clinical characteristics of 9 MAE patients (five boys and four girls) are summarized in Table 1. All patients were divided in two groups: the A group (5 patients, cases 1–5) with no seizures for 2 years after treatment; and the B group (4 patients, cases 6–9) whose seizures continued after treatment. The most significant differences between the two were seizure onset age and EEG evidence of focal spike discharges. MAE onset in patients with refractory seizures was earlier than in those with favorable prognosis (A group: 23–38 months with a mean of 32 months; B group: 7–24 months with a mean of 14 months). Fig. 2 shows the ages of MAE onset in groups A and B patients. The ages of MAE onset were significantly different between groups A and B patients, as assessed by an ANOVA ($p = 0.005$) and Wilcoxon rank sum test ($p = 0.037$).

At seizure onset, all patients presented generalized spike- or polyspike-wave discharges. In group A, 3 cases presented only generalized spike discharges, while 2 showed focal spike discharges. In contrast, all 4 group B cases showed focal spike discharges. In both groups, focal spike discharges appeared at similar age: from 1 year and 6 months to 5 years and 6 months; there was no difference in the brain area in which the spikes appeared. Case 6's family history included a great grandmother's half grandson with a history of one unspecified epilepsy, unfortunately, the boy was dead and his family did not want to speak about his illness. The 8 other subjects had no histories that would suggest