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Original article

Benign myoclonic epilepsy in infancy with preceding afebrile generalized tonic–clonic seizures in Japan

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Abstract

Benign myoclonic epilepsy in infancy (BMEI) is the youngest form of idiopathic generalized epilepsy, characterized by myoclonic seizures (MS) in the first three years of life in otherwise normal infants, and the lack of other seizure types except for rare simple febrile seizures. Although afebrile generalized tonic–clonic seizures (GTCS) have been described to develop later in the clinical course of BMEI, mostly during adolescence, an association with GTCS in the early stage of BMEI has never been recognized. We herein report seven children who satisfied the criteria of BMEI except for the recurrence of GTCS before the onset of MS. The age of onset and ictal video-polygraphic features of MS, as well as the long-term seizure and developmental outcome in these children were similar to those of children with typical BMEI. Furthermore, these GTCS mostly disappeared within several months and were replaced by MS. Our study indicates that these children may constitute a BMEI subgroup, expanding the spectrum of BMEI.

Keywords: BMEI; GTCS; Video-polygraph; Genetic contribution; Classification; Nosology

1. Introduction

Benign myoclonic epilepsy in infancy (BMEI) is a rare epileptic syndrome, first reported by Dravet and Bureau in 1981 [1], and has been recognized as the youngest form of idiopathic generalized epilepsy in the International Classification of Epilepsies and Epileptic Syndromes [2]. This epileptic syndrome is characterized by myoclonic seizures (MS) in the first three years of life in otherwise normal infants, and the lack of other seizure types except for rare simple febrile seizures (FS). Dravet and Bureau recently reviewed the literature including 127 cases of BMEI, and again stressed the criterion that patients with BMEI should not have other seizure types except for rare simple FS before the development of MS, or other seizures long after the remission of MS. In contrast, an association of afebrile generalized tonic–clonic seizures (GTCS) before the onset of MS and in the early stage of BMEI has never been recognized [3–10]. In this study, we report seven children showing GTCS recurrence before the onset of MS, but who were otherwise consistent with the clinical features of BMEI.

2. Methods

We retrospectively reviewed consecutive Japanese children meeting the criteria of BMEI [3] except for the recurrence of afebrile GTCS before the onset of MS, visiting Tokyo Women's Medical University between 1983 and 2006. For the differentiation of GTCS from clusters of MS, which may resemble and be mis-

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diagnosed as GTCS, the occurrences of GTCS were confirmed by careful history-taking from their caregivers and at least two occurrences with a loss of consciousness and subsequent post-ictal sleep. In all subjects, interictal electroencephalographies (EEGs) as well as ictal video-polygraphs, brain magnetic resonance imaging and/or computed tomography, and neuropsychological assessment including Wechsler Intelligence Scale-Revised (WISC-R) and modified Binet scale for Japanese were performed. In addition, the demographic data as well as the clinical and EEG manifestations were compared between children with preceding GTCS (BMEI+ group) and with typical BMEI without preceding GTCS (BMEI− group). Genetic testing including *SCN1A* mutation analysis was not performed in these children because their clinical course and prognosis were different to those of Dravet syndrome. Significance was evaluated by Mann–Whitney *U*-test, and a *p*-value below 0.05 was considered significant.

3. Results

Thirteen children were included the analysis and seven were categorized in the BMEI+ group and six in the BMEI− group (Table 1).

3.1. Personal and family histories

Pre-, peri-, and postnatal histories as well as psychomotor development before the onset of seizures were unremarkable in both groups. Simple FS developed in two out of the seven cases with BMEI+ and three of the six cases with BMEI− before the onset of MS. Neuroimaging was normal in all cases. Family histories of FS within third degree relatives were shown in five cases with BMEI+ and three cases with BMEI−.

3.2. Clinical and EEG manifestations

In the BMEI+ group, afebrile GTCS occurred infrequently (median: 11, range: 4–14) before the onset of MS (median: 2 month, range: 0–16 months). All GTCS had disappeared before or shortly after the onset of MS (median: 1 month, range: −1–6 months). The onset age (BMEI+: median: 2 y 9 m, range: 0 y 6 m–5 y 2 m; BMEI−: median: 2 y 6 m, range: 1 y 10 m–3 y 6 m; $p = 0.73$) and the clinical and EEG manifestations of MS analyzed from the ictal video-polygraphs showed no differences between the two groups. Myoclonic seizures occurred several to hundreds of times a day during wakefulness and sleep, and involved mainly the neck and proximal upper limbs, and occasionally the trunk and lower limbs. Two cases with BMEI+ showed brief vocalization during MS. Three cases with BMEI+ and one case with BMEI− sometimes experienced MS provoked by sudden noise or contact. There was no patient who dropped to the floor due to MS. The ictal EEGs showed generalized polyspike-wave complexes (PSW) ranging in frequency from 1.5 to 3 Hz, corresponding to MS in both groups (Fig. 1). The interictal EEGs showed generalized spike-wave complexes and PSW faster than 2.5 Hz, without a significant disturbance of the background activity. During the follow-up period, photoparoxysmal discharges were observed in each one case with BMEI+ or BMEI−, and focal spikes were transiently observed in three cases with BMEI−.

3.3. Treatment

In two out of the seven cases of BMEI+, MS were controlled with VPA monotherapy, and MS in the remaining five cases required additional antiepileptic drugs (AEDs), including ethosuximide (ESM) in three cases, clonazepam (CZP) in one case, and ketogenic diet (KD) therapy in one case (Table 1). In contrast, four out of the six cases with BMEI− were successfully treated by VPA monotherapy, and the remaining two cases successfully underwent adrenocorticotropic hormone (ACTH) or KD therapy, following a failure to respond to VPA. These cases undergoing ACTH or KD therapy had been treated before the concept of BMEI was established. At that time, we aggressively treated patients with myoclonic epilepsies in infancy because they were believed to be an early form of Lennox-Gastaut syndrome.

3.4. Outcome and prognosis

The median follow-up period was 108 months (range: 49–249 months) in BMEI+ group and 121 months (range: 31–201 months) in BMEI− group. The duration of the active seizure period was not significantly different between the groups (BMEI+: median 7 months, range: 4–19 months; BMEI−: median 11.5 months, range: 3–22 months; $p = 0.94$). The AEDs were successfully discontinued in six out of the seven cases with BMEI+ (median 69.5 months, range: 34–136 months) and in all six cases with BMEI− (median 74 months, range: 28–172 months; $p = 1.00$). One case with BMEI+, MS recurred at 18 y of age after a 14 y seizure-free period, and was immediately controlled by VPA. Neuropsychological outcomes were generally favorable in both groups, although one case in BMEI+ and two cases in BMEI− had mild mental retardation, estimated by WISC-R (BMEI+: median 89, range: 61–115; BMEI−: median 94.5, range: 61–112; $p = 1.00$).

4. Discussion

We reported seven children who satisfied the criteria of BMEI except for the recurrence of afebrile GTCS