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Psychomotor development and seizure features in idiopathic myoclonic epilepsy in infancy

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Abstract

Myoclonic epilepsy in infancy (MEI) is a rare syndrome characterized by generalized myoclonic seizures (MS) that occur within the first 3 years of life. In the present study, the form of onset, and clinical and electroencephalogram (EEG) features were analyzed. A retrospective chart review was conducted for 16 MEI patients between March 2009 and July 2022 in Peking Union Medical College. The clinical and video EEG (VEEG) characteristics, treatment strategy, and follow-up information were analyzed. Four cases presented with afebrile generalized tonic-clonic seizures (GTCS) at the onset of MEI (GTCS at onset or atypical MEI), while 12 cases presented with MS at onset (MS at onset or typical MEI). The 24-hour VEEG revealed a generalized discharge of polyspike (or spike)-and-wave complexes that lasted for 1–3 seconds in the ictal phase. All patients were treated with valproic acid monotherapy, and none of the patients experienced seizure recurrence. Furthermore, all patients had normal psychomotor development at the end of the follow up period. Typical MEI (MS at onset) and atypical MEI (GTCS at onset) were described in the present study. These 2 groups differed in form of onset, but there were no significant differences in clinical or EEG features.

Abbreviations: EEG = electroencephalographic, GTCS = generalized tonic–clonic seizures, IGE = idiopathic generalized epilepsies, ILAE = International League Against Epilepsy, MEI = Myoclonic epilepsy in infancy, MRI = magnetic resonance imaging, MS = myoclonic seizures, MS = myoclonic seizures, VEEG = video EEG, VPA = valproate, WISC-R = Wechsler Intelligence Scale for Children-Revised

Keywords: generalized tonic-clonic seizure, idiopathic epilepsy, myoclonic epilepsy in infancy, myoclonic seizure, type of onset

1. Introduction

Benign myoclonic epilepsy in infancy (MEI), also named as MEI, according to the recommendations of the International League Against Epilepsy (ILAE) in 2022,[1,2] is a rare variety of idiopathic generalized epilepsies (IGEs) that was first described by Dravet and Bureau in 1981.[3] Brief generalized myoclonic seizures (MS) associated with generalized spike-wave or polyspike-wave paroxysms that occur within the first 3 years of life in otherwise developmentally normal infants are the pathological hallmarks of MEI.[4,5] MEI accounts for 1–2% of early childhood-onset epilepsy (<3 years), and boys outnumber girls on its occurrence.[3,6,7] The etiopathogenesis of MEI remains unknown, but most scholars consider that age-related genetic defects might be the reason for the manifestation of MEI.[8,9] Indeed, this hypothesis is supported by the fact that MEI therapy with antiepileptic drugs (AEDs, such as valproic acid [VPA]) usually lead to good results and prognoses, indicating that there may be a specific age-dependent genetic hyperexcitability of the motor cortex.[7,10] However, some children with MEI may present with delay in learning, particularly delayed language development and behavioral problems, which cause certain economic burden and social problems.

In 2006, MEI was categorized as an epilepsy syndrome with age-related onset in infancy in the revised ILAE classification.[11,12] The newly modified seizure classification was based on 3 key features: the origin of the seizure in the brain, the level of awareness during the seizure, and the unique seizure features.[13] From 1981 to 2012, nearly 200 MEI cases have been reported worldwide.[14] In the present study, the clinical and electroencephalogram (EEG) features of 16 MEI patients were retrospectively examined. The present study aimed to gain insight on the potential diagnostic markers for MEI based on the features presented by MEI patients, which could help improve our knowledge on MEI with preceding afebrile generalized tonic-clonic seizures, and lead to the better identification of the syndrome, positively impacting the prognosis of patients.

2. Materials and Methods

The study protocol was approved by the Ethics Committee of Peking Union Medical College Hospital, China. Informed written consents were obtained from the parents of the enrolled patients. The investigators confirm that they have read the Journal's position on issues involved in ethical publication, and affirm that the present report is consistent with those guidelines.

The datasets generated and analyzed during the present study are available from the corresponding author on reasonable request.

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The present retrospective study was conducted in the Department of Neurology, Peking Union Medical College, China, between March 2009 and July 2022. Inclusion criteria: (1) MS without other seizure types, except for rare simple febrile seizures in normal children, and the psychomotor development remained normal; (2) no other diagnosed or possible etiologies (neurodegenerative, metabolic, inflammation, autoimmune, etc), except for genetics; (3) the onset of seizures was between 6 months and 3 years of life; (4) the presence of generalized paroxysms of polyspike or spike-and-wave complexes. Patients with structural or metabolic etiologies were excluded. Finally, a total of 16 patients (11 boys and 5 girls), with a mean age of 34 months, were enrolled for the present study. All patients were followed up for 1–11 years. The flowchart is presented in Figure 1.

All family members were instructed to complete a questionnaire, which included the personal and familial history at the time of initial diagnosis. In addition, the neurologic function and psychomotor development at onset and during the follow up visits were analyzed. All included patients were contacted for neuropsychological or electrophysiologic studies, or both. Neuropsychological assessments, including the Wechsler Intelligence Scale for Children-Revised (WISC-R), was performed by the parents or guardians of the patients during the follow-up period. Photoparoxysmal response was performed for all patients. The features of the epileptic seizures, including age at onset, clinical description, and BMEI with or without preceding generalized tonic-clonic seizure (GTCS), as well as the use of AEDs, were examined. In addition, the ictal and interictal video EEG (VEEG) findings during wakefulness and sleep, and the magnetic resonance imaging (MRI) results were investigated. The long-term outcomes were evaluated for each patient, in terms of the seizure recurrence, VEEG findings and neuropsychological tests. The researcher did not perform a cognitive test, because the detailed examination of cognitive function was beyond the scope of the present study.

3. Statistical analysis

Statistical analysis was performed using the Statistical Package of Social Sciences (SPSS, version 21.0). Student *t*-test and Mann-Whitney test were used to compare the characteristics and EEG results between patient groups. A *P*-value of < 0.05 was considered statistically significant.

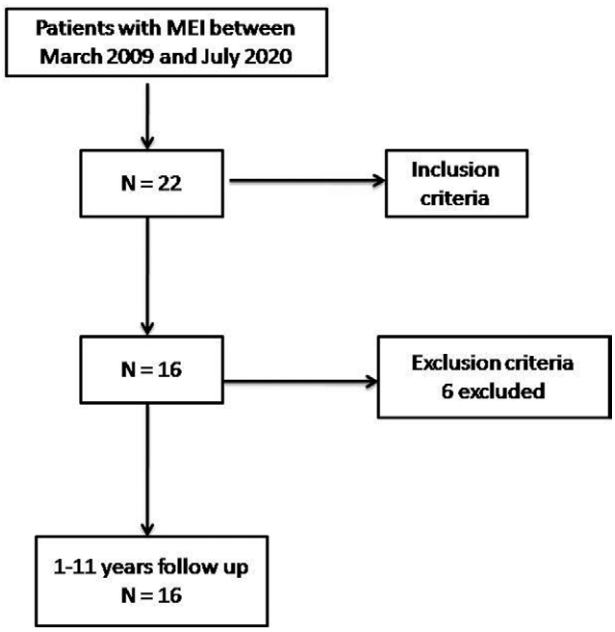

Figure 1. Flowchart for the patient enrollment.

4. Results

4.1. Demographic characteristics and clinical features

The demographic characteristics and clinical findings are detailed in Table 1. A total of 16 patients (11 boys and 5 girls) with MEI visited our department between 2009 and 2020. Among these patients, 4 patients presented with GTCS at onset (GTCS at onset or atypical MEI), while the remaining 12 patients presented with MS at onset (MS at onset or typical MEI). The mean age at seizure onset was 26 months old (range: 8–44 months old, median age: 34 months old). Fifteen patients had their first seizure during their third year of life, while 1 patient had recurrence of febrile seizures. In addition, 1 patient (1/16, 0.06%) had a positive family history of epilepsy. Due to the retrospective nature of the present study, it was difficult to identify the exact type of febrile seizure and epileptic syndrome observed in the patient's family members. In addition, all patients had uneventful prenatal, perinatal and postnatal histories, and their neuroimaging results (3.0 T multimodal brain MRI) returned to normal. The neuropsychological assessments of the patients were normal.

4.2. Seizure manifestations

The onset date of the clinical manifestations was retrospectively reconstructed, since these were initially dismissed by the parents, and caused no special concern. In the present study, the GTCS type of onset (n = 4) and MS type of onset (n = 12) were observed (Table 1). In the GTCS type of onset group (atypical MEI), 4 patients developed 1 episode of afebrile GTCS several months before the onset of MS, and they satisfied all the clinical features of MEI. These 4 cases both had brief loss of consciousness during the MS episode. In all patients, MS occurred for numerous times a day during wakefulness and/or sleep (Table 1). Seizures occurred in some of the patients in the present study when they were awake or during the first 1 hour of sleep, based on the medical history and 24-hour VEEG. The MS mainly involved the neck and proximal upper limbs, and occasionally, the trunk and lower limbs. However, there were no drop attacks observed in any of these patients.

4.3. VEEG features

The background VEEG revealed normal activity during wakefulness and sleep in all patients. The ictal VEEG revealed brief bursts of generalized spike-and-wave and polyspike-and-wave, which lasted for approximately 1–2 seconds (Fig. 2). Furthermore, the interictal VEEG disclosed a generalized spike-and-wave in 4 patients and a polyspike-and-wave in 11 patients in the form of brief and spontaneous manifestations, which lasted for approximately 300–800 ms. One patient exhibited normal interictal VEEG (Case 8) (Fig. 3). There were no observed differences between the typical and atypical MEI, in terms of the overall ictal and interictal VEEG recordings ($P > .05$).

4.4. Treatment strategy

The treatment data of these patients are summarized in Table 2. All patients were treated with VPA monotherapy, and their seizures were well-controlled. The treatment onset ranged within 3–4 years, while the treatment duration ranged within 2–5 years (mean: 3.5 years).[11] There was no significant difference in mean treatment period between typical and atypical MEI patients ($P > .05$). For the 2 patients with atypical MEI (GTCS at onset), the seizures were controlled after a mean period of 60 months.

Table 1

Clinical and EEG manifestation data of the 16 MEI patients.

		GTCS		Myoclonic seizure			Circadian rhythm	EEG features		
Patient.	Gender	Onset Age	Duration	Onset Age	Duration (month/sleep)	Frequency (per day)		Capture seizure	Ictal	Interictal
1	Male	3Y	1min	3Y6M	1	<10/d	S	Sudden double upper extremity twitch	PSW	Normal
2	Male	3Y	2min	3Y9M	2	10–20/d	AW/S	Sudden nod, double upper limb jitter	PSW	PSW
3	Male	2Y	1min	2Y6M	1	<10/d	AW/S	Sudden nod, double upper limb jitter	PSW	PSW
4	Male	3Y	1min	3Y2M	1	<10/d	AW/S	Sudden double upper limb jitter	PSW	PSW
5	Male	None		3Y	2	<10/d	AW	Sudden double upper limb jitter	PSW	PSW
6	Male	None		11M	1–2	<10/d	AW	Sudden nod with trunk forward bend and double arm lift	PSW	PSW
7	Female	None		2Y1M	2–4	10–20/d	AW	Sudden nod, eyes look up	PSW	PSW
8	Male	None		8M	1–2	<10/d	AW	Sudden nod, double upper extremity twitch	PSW	SW
9	Female	None		3Y8M	1–2	10–20/d	AW/S	Suddennod, double arm up	PSW	SW
10	Male	None		2Y4M	1–2	<30/d	AW/S	Sudden double upper limb jitter	PSW	PSW
11	Male	None		2Y8M	1–2	<10/d	S	Sudden nod with trunk forward bends	PSW	PSW
12	Male	None		2Y10M	1–2	10–20/d	S	Sudden nod, double upper limb jitter	PSW	PSW
13	Female	None		1Y9M	1–2	10–20/d	AW/S	Bilateral myoclonic jerks in upper limb	PSW	PSW
14	Female	None		2Y1M		10–20/d	AW	Sudden nod, double arm up	PSW	SW
15	Female	None		3Y10M		<10/d	S	Sudden nod with trunk forward bends	PSW	PSW
16	Male	None		1Y9M		<10/d	S	Sudden nod with trunk forward bends	PSW	SW

GTCS = generalized tonic-clonic seizure, PSW = polyspikes-wave, SW = spikes-and-waves, AW = awake, S = sleep.
Patient 1 and 2 presented with GTCS at onset, while the remaining 9 patients had MS at onset.

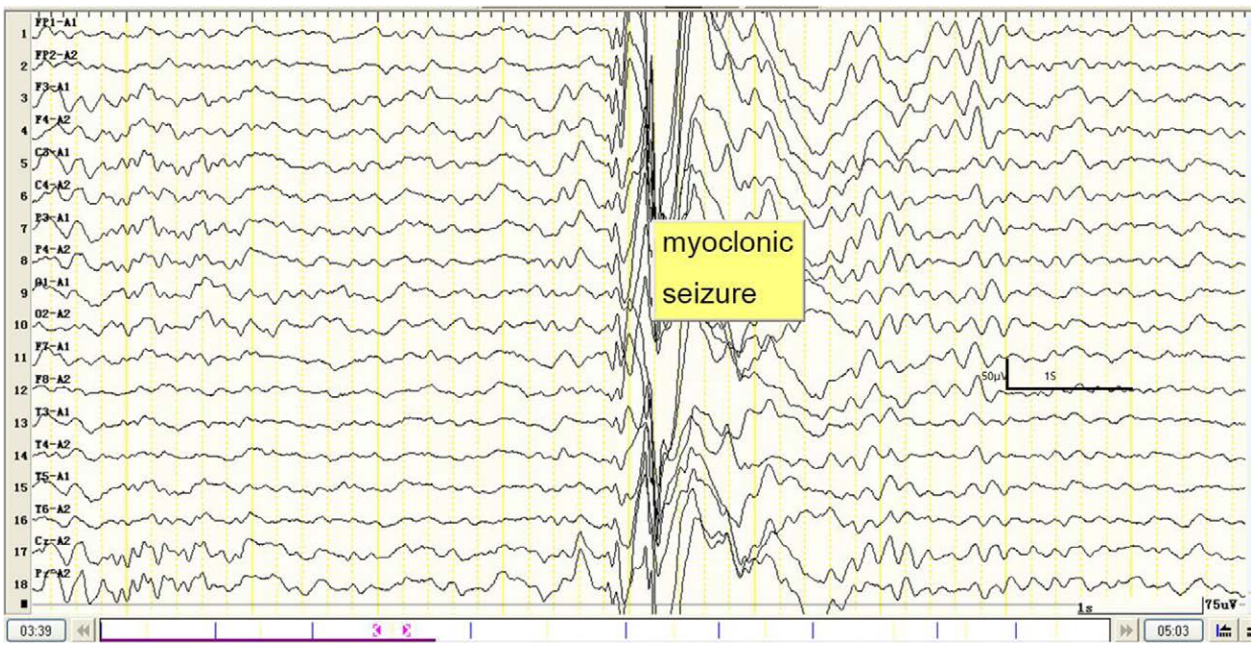

Figure 2. Ictal EEGs demonstrating the 2-3 Hz generalized high-amplitude polyspike-wave complex (PSW) discharges, which were synchronous with the sudden nod and double upper limb jitters that lasted for approximately 2 seconds, in a representative typical MEI case of a 15-month-old boy (Case #8), who presented with a double upper extremity twitch.

For typical MEI patients (MS at onset), the MS was controlled within 3–22 months after treatment (n = 12). It is noteworthy that 1 typical MEI patient is presently completing a treatment course without the recurrence of MS. All 16 patients received treatment for a mean period of 34 months (range: 4–60 months) after seizure onset.

4.5. Follow-up and treatment outcome

The psychomotor development of the patients remained normal in the cohort. Typical MEI patients were followed up for 68 months (range: 4–104 months), while for atypical MEI patients, the median follow-up period was 72 months (range: 70–73 months). As of July 2020, 15 patients (93.2%) were medication-free during the follow-up period. The active seizure duration was not significantly different between typical and atypical MEI (median of 11 months [3–22 months] and 12 months [10–15 months], respectively; $P > .05$). VPA was successfully discontinued after a median of 28 months (range: 4–36 months) for typical MEI patients (n = 12), and within a median of 60 months for atypical MEI patients (n = 4). The final typical onset MEI patient continued to undergo the treatment course, and the symptoms of this patient significantly improved. Reflex

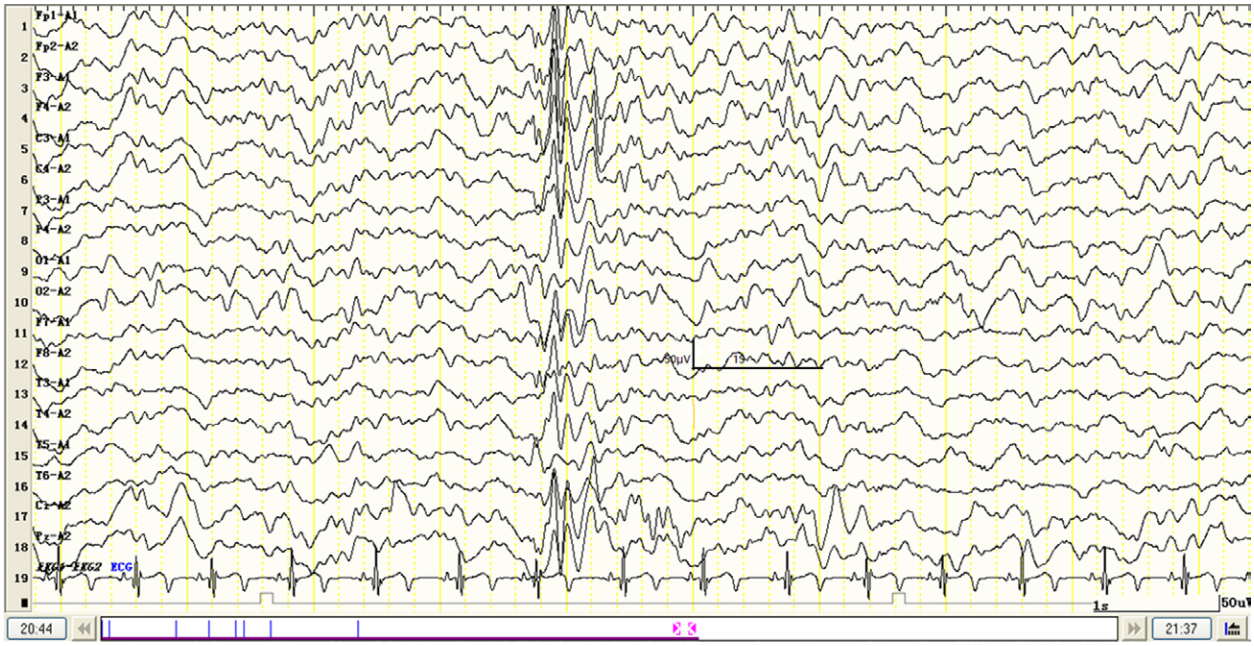

Figure 3. Interictal EEGs that demonstrated generalized high-amplitude spike-wave complex (SW) discharges, which were synchronous in a representative typical MEI case of a 15-month-old boy (Case #8), who presented with a double upper extremity twitch (mainly in the frontal lobes).

myoclonic episodes, with or without spontaneous MS or other types of seizures or epileptic syndromes, were not observed after the seizure-free period in any of the other patients.

The control EEG recordings were normal in 15 patients (93.2%). The median age at EEG normalization was 3 years old (range: 2–5 years old).[11] The typical MEI patient who had normal interictal VEEG continued to undergo the initial VPA monotherapy (Case 6) (Table 1), and this patient continued to have generalized paroxysms associated with spikes and waves in the frontal regions. At the end of the follow up period (July 2020), all 16 patients had normal neurological and neuropsychological evaluations, including the patient on VPA. There were no significant differences between typical and atypical MEI patients ($P > .05$).

Table 2

Treatment course for the 16 MEI patients.

Patient number	Antiepileptic drug	Treatment onset (year/month)	Treatment duration (year/month)
1	Valproate	3 years and 6 months	5 years
2	Valproate	4 years and 4 months	5 years
3	Valproate	3 years and 8 months	5 years
4	Valproate	4 years and 6 months	5 years
5	Valproate	3 years and 4 months	5 years
6	Valproate	4years and 1 month	3 years
7	Valproate	4 years and 3months	2 years
8	Valproate	3years and 4 months	4 months
9	Valproate	3 years and 9 months	2 years
10	Valproate	3 years and 10 months	3 years
11	Valproate	3 years and 2 months	3 years
12	Valproate	3 years and 2 months	3 years
13	Valproate	2 years	3 years
14	Valproate	2 years and 2 months	3 years
15	Valproate	2 years and 4 months	2 years
16	Valproate	2 years and 6 months	3 years

5. Discussion

In the present study, the clinical features and VEEG data obtained from 16 MEI patients, with and without GTCS precedence (atypical MEI, n = 4; typical MEI, n = 12), were retrospectively analyzed. All patients achieved a favorable outcome after the VPA monotherapy. In the present patient cohort, MEI occurred in accordance with the previously reported MEI features characterized by generalized MS.[4,8,14–16] In addition, childhood focal idiopathic epilepsy with generalized spike-wave or polyspike-wave paroxysms associated with MEI were previously described[8,14,15,17,18]

MEI preferentially affects boys (boys-to-girls ratio = 2:1) (Dravet and Bureau, 2005), and the development of MS in otherwise healthy infants within 4–60 months of age is the major clinical hallmark of MEI.[1] In good agreement, it was observed that the development of MS within 8–44 months old and boys were preferentially affected (boys-to-girls ratio = 2.2:1.0) in the present study. The diagnosis of MEI was established based on the electroclinical features, clinical course, family history, and absence of neurological abnormalities on the brain MRI.[8]

In the present study, 4 male patients presented with 1 episode of afebrile GTCS at several months before the onset of MS (atypical MEI), and these patients attained a favorable outcome after the VPA treatment. Similar observations were previously reported by Ito *et al*,[14] in which 7 cases of male and female patients presented with MEI accompanied by recurrent afebrile GTCS before the onset of MS, and these cases achieved a favorable outcome. The remaining 9 patients presented with typical MEI without the precedence of GTCS. However, Yang *et al* reported a different observation.[15] They divided all 33 patients into 3 groups: 11 patients with typical MEI, 16 patients with MEI experiencing afebrile GTCS before MS onset (atypical MEI), and 6 patients with MEI presenting with afebrile GTCS that occurred concurrently with MS (mixed MEI). They reported that the afebrile GTCS was associated with a stronger cortical hyperexcita, although all 3 groups had similar clinical and EEG features, and outcomes. Furthermore, patients with atypical and mixed MEI, who were treated with 2 or 3 kinds of AEDs, were compared

to patients with typical MEI. Although both types fulfilled the diagnostic criteria for MEI, the underlying etiology needs to be further investigated. To date, the underlying genetic factors associated with MEI remains unknown. Autosomal recessive MEI was previously linked to chromosome 16p13 in an Italian family.[19] Although patients who present with idiopathic myoclonic epilepsy share similar clinical features with MEI patients, former myoclonic jerks may be grouped in long clusters for many hours, which are always associated with GTCS and persists into adulthood.

The first drug of choice should be VPA. For MEI, the outcome is generally benign. The most commonly used AED combination is VPA + Levetiracetam (LEV). VPA is a broad-spectrum and low-cost drug, thereby making this suitable for long term treatment.[20–23] Furthermore, VPA acts on gamma-aminobutyric acid (GABA) levels in the central nervous system, blocks voltage-gated ion channels, and inhibits histone deacetylase.[24] A randomized controlled trial reported that the seizure-free rate for patients who took VPA was 63.33% after the 6-month follow-up and 56.67% after the 12-month follow-up.[25] Furthermore, according to a meta-analysis that compared the relapse rates of different AEDs in seizure-free patients, the epilepsy recurrence rate after treatment with VPA was 42.4%, 41.7% and 41.3% in 3 different studies, respectively.[26] Moreover, a study that followed up 38 patients with MEI reported that most of these patients responded well to VPA, and the investigators concluded that VPA should be the first AED option for treating patients with MEI.[17] VPA with other AEDs, such as LEV, is usually considered. LEV has low drug interactions with VPA.[22] The medication time and effect time of cases with atypical MEI were longer, which may also be correlated to the enrollment of fewer cases. It was speculated that atypical MEI may be associated with a stronger genetically-determined cortical hyperexcitability, when compared to typical MEI, because the former presents with recurrent afebrile GTCS. These present neurophysiologic findings suggest the subcortical origin of the motor manifestations. Studies on neurotransmitters have implicated different neurotransmitters in various types of myoclonus, since these involve different anatomic pathways. However, few is known in humans. Neurotransmitters, such as GABA, glycine, serotonin and glutamate, appear to be involved.[23] For cases with age-dependent benign infantile disorders, it can be speculated that the transient neurotransmitter abnormalities in the immature subcortical structure may explain these abnormal motor manifestations.

There were some limitations in the present study. First, the number of patients with MEI was small, which may have limited the interpretation of the present conclusions. Second, the present study was a single-center retrospective study, which may have introduced an element of selection bias. Third, the follow-up time significantly varied (4–104 months), which may have caused variations in the results of the VEEG findings and neuropsychological tests.

In conclusion, the early diagnosis of MEI positively impacts the treatment outcome and patient prognosis. It has been considered that patients with MEI achieve favorable outcomes. However, recent studies have reported that MEI cases evolved into other types of epilepsies.[15,27,28] The differential diagnoses for the form of onset is equally important, which includes several varieties, such as nonepileptic conditions, including benign neonatal sleep myoclonus and Fejerman syndrome, and epileptic syndromes, such as West syndrome, Dravet syndrome and Lennox-Gastaut syndrome. In the present study, an atypical variant of MEI (MEI proceeded with GTCS) was described. Future prospective studies would be essential to further determine the relationship between these 2 types of MEI onsets, and elucidate the pathogenetic mechanisms of MEI, as well as the common neurobiological and genetic substrates.

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Author contributions

Yongning Jiang designed most of the investigation, data analysis and wrote the manuscript; Yongning Jiang and Xiangqin Zhou contributed to interpretation of the data and analyses. All of the authors have read and approved the manuscript.

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