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ORIGINAL ARTICLE

Clinical characteristics of two cohorts of infantile spasms: response to pyridoxine or topiramate monotherapy

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Abstract

Background Infantile spasms (IS) was an epileptic disease with varied treatment widely among clinicians. Here, we aimed to compare and analyze the clinical characteristics of IS response to pyridoxine or topiramate monotherapy (TPM control IS).

Methods The clinical manifestations, treatment processes and outcomes were analyzed in 11 pyridoxine responsive IS and 17 TPM-control IS.

Results Of the 11 patients with pyridoxine responsive IS, nine were cryptogenic/idiopathic. Age of seizure onset was 5.36 ± 1.48 months. Spasms were controlled within a week in most of the patients. At the last follow-up, EEG returned to normal in 8. Psychomotor development was normal in 6, mild delay in 3, severe delay in 2. Of the 17 patients with TPM-control IS, 10 were cryptogenic/idiopathic. The age of seizure onset was 5.58 ± 2.09 months. All patients were controlled within a month. At the last follow-up, EEG was normal in 10. Psychomotor development was normal in 8, mild delay in 5, severe delay in 4. Genetic analysis did not show any meaningful results.

Conclusions The clinical characteristics and disease courses of pyridoxine responsive IS and TPM-control IS were similar, which possibly clued for a same pathogenic mechanism. Pyridoxine should be tried first in all IS patients, even in symptomatic cases. If patients were not responsive to pyridoxine, TPM could be tried.

Keywords Infantile spasms · Pyridoxine · Topiramate

Introduction

Infantile spasms (IS), characterized by brief, symmetric axial muscle contraction (neck, trunk and/or extremities), was first described by West in 1841 [1]. IS most often occurred during the first year of life with an incidence of approximately 1 per 2000–4000 live births [2]. The treatment of IS varied widely among clinicians. Adrenocorticotrophic hormone (ACTH) and vigabatrin (VGB) were suggested as the first-line treatments. Other antiepileptic drugs (AEDs) as well as ketogenic diet might also be useful [3]. Besides, high-dose pyridoxine had been recognized as a treatment choice since first attempted by Ohtahara [4], and widely used as the initial therapeutic agent of IS in Japan [5]. After excluding other pyridoxine-related diseases such as pyridoxine deficient seizures and pyridoxine dependent epilepsy (PDE) [6–8], those IS controlled by pyridoxine was termed as pyridoxine responsive IS, the most common type of pyridoxine responsive epilepsy (PRE) [5]. Up to now, the studies on pyridoxine responsive IS were limited. In recent years, high-dose pyridoxine has been used for the IS patients as the initial or add-on therapy in our hospital. Herein, we analyzed the clinical characteristics of a cohort of patients with pyridoxine responsive IS.

Pyridoxine responsive IS having easier controlled seizures and better outcomes reminded us that there might have rare but noteworthy IS patients, whose spasms could be controlled by AEDs rapidly, such as topiramate (TPM), valproate, levetiracetam [9–11]. Of them, TPM was a popular second-line treatment of IS and was often used as first trial in China under the condition of hard access to ACTH and VGB [12]. Most studies focused on the efficacy and tolerance of TPM, but few on detailed characteristics of IS controlled by TPM monotherapy. Therefore, we analyzed such a cohort of patients controlled by TPM monotherapy rapidly (TPM-control IS) here. At the same time, we compared

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the similarities and differences of clinical features between TPM-control IS and pyridoxine responsive IS, hoping to find some clues to clarify their potential pathogenic mechanisms.

Methods

Ethics statement

This study was approved by the Ethical Committee of Peking University First Hospital. The individuals' parents had given written informed consent to publish these cases details. All data were analyzed anonymously.

Patients

Eleven patients were diagnosed as pyridoxine responsive IS in our hospital between January 2012 and May 2015. The following criteria were established: [5, 13] 1) onset of seizures with IS; 2) demonstration of hypsarrhythmia on the interictal electroencephalogram (EEG) before treatment. Hypsarrhythmia was defined as a chaotic mixture of giant abnormal, arrhythmic and asynchronous biological brain electrical activity of slow and sharp waves, multifocal spikes and polyspikes, which was evaluated by a qualified neurophysiologist; 3) seizures were controlled by pyridoxine monotherapy or combination with previously ineffective AEDs for more than 1 month; 4) *ALDH7A1* analysis showed wildtype.

A total of 744 patients were diagnosed as IS in our hospital from January 2009 to May 2015. Seventeen patients were included in the group of TPM-control IS for meeting the following criteria (Fig. 1): 1) & 2) were identical with the first two criteria of pyridoxine responsive IS, and 3) seizures were controlled by TPM monotherapy within 1 month, lasting for at least 1 month.

The clinical manifestations, treatment processes and outcomes were collected from 11 patients with pyridoxine responsive IS and 17 with TPM-control IS. EEG, magnetic resonance imaging (MRI), biochemical studies, plasma amino acids and urine organic acids were performed in all. A complete absence of generalized slowing, focal slowing and epileptiform discharges in EEG was thought as normal. Genetic analysis of gene panel, including 470 genes associated with epilepsy, was performed in all pyridoxine responsive IS patients and most TPM-control IS patients using targeted next-generation sequencing [14]. Follow-up was primarily conducted through telephone or return visit for a mean period of 40 months (range: 2–80 months). Etiology of IS was divided into two groups, symptomatic and cryptogenic/idiopathic, according to the criteria reported previously [12]. Cognitive assessment was performed according to clinical judgment and/or intelligence test (Gesell Development Scale).

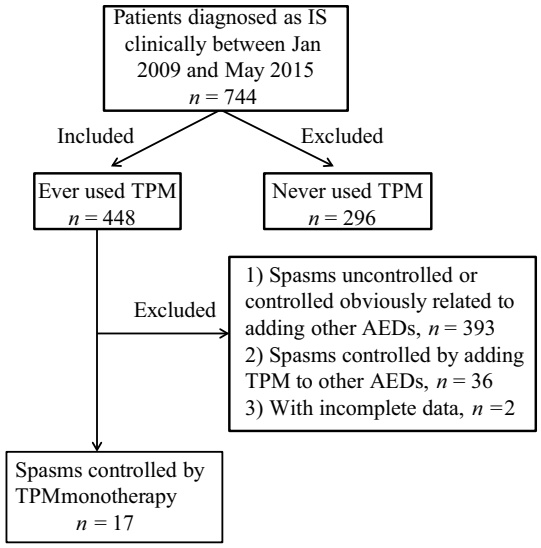

Fig. 1 The screening diagram of 17 pyridoxine or topiramate monotherapy (TPM)-control infantile spasms (IS) patients included in the study

Statistical analysis

All statistical analyses were completed using SPSS 20.0. The Shapiro–Wilk test was used to test whether variables were normally distributed. Continuous variables with normal distribution were expressed as mean ± standard deviation (SD), and those with no normal distribution were expressed as median (range). Categorical variables were presented using percentages. The Student's *t* test or Mann–Whitney *U* test was used for comparison between cohorts of continuous variables. Categorical variables were compared using Pearson Chi-square test or Fisher exact test as appropriate. The significance level was set at 0.05 and all tests to assess *P* values were two-sided.

Results

Pyridoxine responsive IS

Of the 11 patients, six were male, and five were female. Two of them had intracranial hemorrhage or anoxia at birth, and the others were normal. The age of seizure onset was from 3.5 to 8.0 months and the mean age was 5.36 months (Table 1). Biochemical studies, plasma amino acids and urine organic acids were normal in all. MRI showed abnormal in two patients, including subarachnoid hemorrhage (patient 7) and multiple encephalomalacia foci (patient 2),

Table 1 The clinical characteristics of patients with pyridoxine responsive infantile spasms

Patients	Sex	Age of spasm onset (mon)	Duration to spasms-control (d)[a]	Duration to EEG return to normal (mon)[a]	AEDs used prior/after B6 onset	Seizure recurred	Age at last follow-up	Pyridoxine dose at last follow-up	AEDs at last follow-up	EEG at last follow-up	Cognitive development
1	M	5.0	5	4.5	TPM[b]/none	−	1 y 5 mon	5 mg/kg/d	None	Normal	Normal
2	M	6.0	3	/	TPM[b]/none	+	3 y 9 mon	2 mg/kg/d	None	Abnormal	Severe delay
3	F	5.0	4	2	TPM[b]/TPM	−	1 y 6 mon	8 mg/kg/d	TPM	Normal	Normal
4	M	8.0	45	2	None/TPM	−	2 y 10 mon	4 mg/kg/d	TPM	Normal	Mild delay
5	M	8.0	7	/	VPA/VPA	+	2 y 3 mon	0.4 mg/kg/d	VPA	Abnormal	Normal
6	F	5.0	3	3	TPM, VPA/none	−	1 y 7 mon	8 mg/kg/d	None	Normal	Mild delay
7	M	5.0	5	2.5	TPM, VPA/none	−	1 y 4 mon	3.5 mg/kg/d	None	Normal	Normal
8	F	4.0	1	1.5	None/none	−	6 mon	10 mg/kg/d	None	Normal	Normal
9	F	3.5	3	2.5	TPM, VPA, LEV, ACTH/none	−	2 y 10 mon	3.5 mg/kg/d	None	Normal	Severe delay
10	F	4.0	1	10	VPA/none	−	4 y 1 mon	Withdrawal	None	Abnormal	Mild delay
11	M	5.5	3	10	None/VPA	−	3 y 9 mon	Withdrawal	VPA	Normal	Normal

EEG electroencephalograph, *AEDs* antiepileptic drugs, *TPM* topiramate, *VPA* valproate, *LEV* levetiracetam, *ACTH* adrenocorticotropic hormone, *F* female, *M* male, / the EEG was still abnormal until the last follow-up, − there was no seizure recurrence during the course, + there was seizure recurrence during the course. [a] From initial using pyridoxine, [b] TPM was added with pyridoxine simultaneously

who were classified as symptomatic. Nine patients were classified as cryptogenic/idiopathic. Genetic analysis of 470 epilepsy-related genes, including *ALDH7A1*, showed negative results in all patients.

The initial dose of pyridoxine was 10.0 mg/kg/day in all patients. Patient 8 had received no AEDs before or after pyridoxine (Table 1). Three patients (patient 1–3) were treated with pyridoxine and TPM simultaneously. Because the dosage of TPM was much lower than the minimum effective maintenance, we do not think it had strong enough effects to control the seizures in these patients. Five patients (patient 5–7, 9, 10) were treated with multiple drugs without effect (TPM, valproate, levetiracetam, ACTH) before pyridoxine. Two patients (patient 4, 11) did not receive AEDs before pyridoxine and added TPM or valproate after spasms being controlled for two months, possibly because of existing a lot of interictal epileptic discharges.

Seizures disappeared completely within a week after using pyridoxine in 10 patients and at 1.5 months in patient 4. The hypsarrhythmia of EEG disappeared rapidly in all patients. During the follow-up, nine patients were seizure-free. Among them, eight patients' EEG returned to normal within 1.5–10.0 months and remained normal; and one patient (patient 10) once returned to normal, but showed epileptic discharges once again after pyridoxine withdrawn. While for the other two patients (patient 2, 5), seizures recurred due to pyridoxine withdrawn at the age of 16 months (seizures controlled for 8 months) and 9.5 months (seizures controlled for 1 month) respectively, and the EEG presented focal or multifocal discharges after hypsarrhythmia disappearing. When pyridoxine was restarted, spasms were remitted again in patient 5, but uncontrolled in patient 2, which were resolved by combination with TPM eventually. The EEGs of patient 5 before and after using pyridoxine are shown in Fig. 2. At the last follow-up, the age of patients was 28.2 ± 14.2 months, seizures were controlled in all patients. Pyridoxine was withdrawn in two patients (patient 10, 11). Patient 11 remained a tiny amount of valproate. In the other 9 patients, pyridoxine was used at a dose of 0.4–10.0 mg/kg/day, monotherapy in 6 and co-administration with low dose of one AED in 3 (patient 3–5). In all 11 patients, the psychomotor development was normal in 6 (1 symptomatic), mild delay in 3 (all cryptogenic/idiopathic), and severe delay in 2 (1 symptomatic).

TPM-control IS

Of the 17 patients, 12 were male, and 5 were female. Eleven of them had abnormal history of pregnancy or delivery. The age of seizure onset was 5.58 ± 2.09 months. Biochemical studies, plasma amino acids and urine organic acids were normal in all. MRI results were abnormal in 10 patients, including delayed myelination of posterior horn of lateral ventricle and/or corpus callosum hypoplasia in 3, white matter dysplasia in 2, brain dysplasia in 1, epidural hematoma in 1, encephalomalacia in 1, enlarged ventricles in 1, periventricular leukomalacia and ventricle multiple calcification in 1. These 10 patients were classified as symptomatic, and the other 7 patients were classified as cryptogenic/idiopathic. Genetic analysis of 470 epilepsy-related genes was

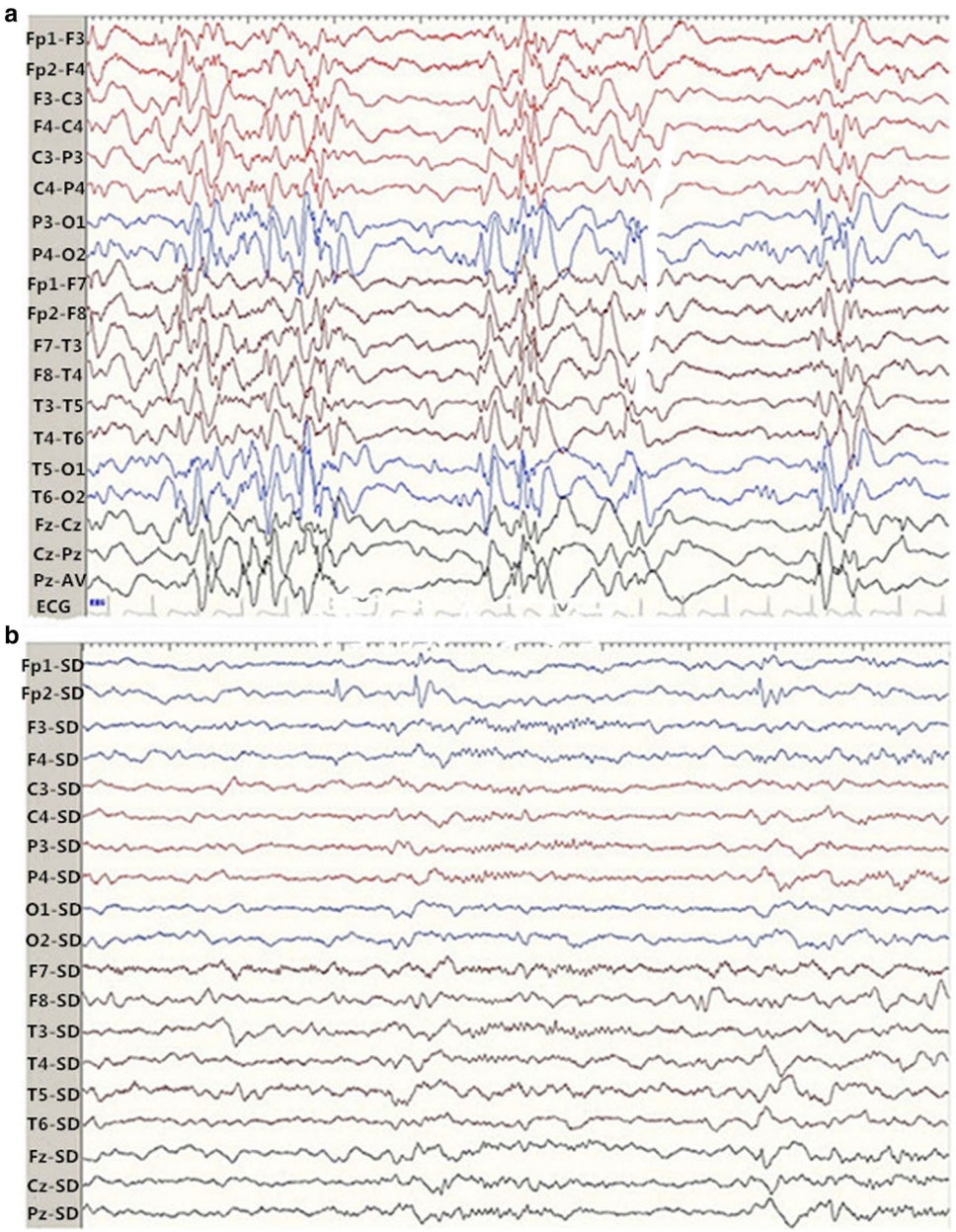

Fig. 2 EEGs of one patient (patient 5) with pyridoxine responsive infantile spasms. **a** Hypsarrhythmia at the age of 8 mon, before pyridoxine used. **b** Focal discharges in right frontal and pre-temporal areas at the age of 9 mon, after spasms controlled by pyridoxine for 2 wks

conducted in 10 patients, without any positive results. In all patients, duration from initial treatment with TPM to seizure-control was less than one month, including 8 patients whose seizures disappeared within a week. The dose of TPM for seizure-control was 3.54 ± 1.80 mg/kg/day. Pyridoxine before TPM administration in two of 11 patients had no effects on controlling seizure. EEG returned to normal in 14 patients during the course (range: 0.5–60 months from initial taking TPM), but 4 showed multifocal spike, spike-wave and polyspike-wave again and the abnormal results persisted. No patients had recurrence during the follow-up. At the last follow-up, the age of patients was 56.7 ± 21.3 months. All patients were seizure free and 9 had withdrawn TPM. In 17 patients, the psychomotor development was normal in 8 (4 symptomatic), mild delay in 5 (2 symptomatic), and severe delay in 4 (all symptomatic).

The statistic analysis results are summarized in Table 2. There were no significant differences ($t = 0.292$, $P = 0.772$) in the age of spasms onset between the patients with pyridoxine responsive IS and those with TPM-control IS using Student's t test. Using Mann–Whitney U test, the duration from initial treatment with drug to spasms-control, or to EEG returning to normal between the two groups was not different significantly, respectively ($Z = -1.268$, $P = 0.205$ and $Z = -1.362$, $P = 0.173$). Compared using Fisher exact test, no significant differences were found in sex composition ($P = 0.444$), history of pregnancy and delivery ($P = 0.419$), etiologies classification ($P = 0.054$), EEG returned to normality ($P = 1.00$),

Table 2 A summary of the clinical data of pyridoxine responsive infantile spasms (IS) and topiramate (TPM)-control IS

Variables	Pyridoxine	TPM	*P* value
Sex, *n* (%)			0.444
Male	6 (54.5)	12 (70.6)	
Female	5 (45.5)	5 (29.4)	
History of pregnancy and delivery, *n* (%)			0.419
Normal	9 (81.8)	11 (64.7)	
Abnormal	2 (18.2)	6 (35.3)	
Spasms			
Age at onset (mon), mean±SD	5.36 ± 1.48	5.58 ± 2.09	0.772
Duration from initial treatment with pyridoxine or TPM (d), median (range)	3.00 (1–45)	14.00 (0–30)	0.205
Medications			
Monotherapy, *n* (%)	1 (9.1)	17 (100)	
Combination or ever used other AEDs, *n* (%)	10 (90.9)	0	
Pyridoxine or TPM dosage for seizure-control (mg/kg/d)	10	3.54 ± 1.80	
EEG			
Normality once in the course of the disease, *n* (%)	9 (81.8)	14 (82.4)	1.000
Duration from initial using pyridoxine or TPM to normal (mon), median (range) labels	2.5 (1.5–10)	5.0 (0.5–60)	0.173
Normal at last follow-up, *n* (%)	8 (72.7)	10 (58.9)	0.689
MRI, *n* (%)			
Normal	9 (81.8)	7 (41.2)	
Last follow-up			
Age (mon), mean±SD	28.2 ± 14.2	56.7 ± 21.3	
Development, *n* (%)			0.916
Normal	6 (54.5)	8 (47.1)	
Mild delay	3 (27.3)	5 (29.4)	
Severe delay	2 (18.2)	4 (23.5)	
Non-medication, *n* (%)	1 (9.1)	9 (52.9)	
Etiology, *n* (%)			0.054
Cryptogenic/idiopathic	9 (81.8)	7 (41.2)	
Symptomatic	2 (18.2)	10 (58.8)	

EEG electroencephalograph, *MRI* magnetic resonance imaging

and EEG was normal at last follow-up ($P = 0.689$) between the two groups. The classification of development outcomes between two groups had no statistically difference using Chi-square test ($P = 0.916$). And the development outcomes between symptomatic and cryptogenic/idiopathic in each group were not significantly different in both ($P = 0.324$ in pyridoxine responsive group and $P = 0.074$ in TPM-control group).

Discussion

PRE was defined as that seizures were controlled for at least one month while receiving pyridoxine therapy alone or by its addition to the previously poorly-effective AEDs [13, 15]. PRE was mainly IS [5], in which approximately 15% patients were reported to respond well to high-dose pyridoxine [13]. TPM was effective and well tolerated in patients with IS [16]. In this study, we report 11 patients with pyridoxine responsive IS and 17 with TPM-control IS, and compare the clinical characteristics between them.

Nine cryptogenic/idiopathic and two symptomatic IS patients were controlled by pyridoxine, suggesting that pyridoxine was effective not only for cryptogenic/idiopathic patients, but also for symptomatic patients. The high ratio of cryptogenic/idiopathic (81.8%) suggested that the efficacy of pyridoxine was better in cryptogenic/idiopathic IS patients, in accordance with the study previously [4]. Kwon et al. [9] found that TPM was more effective in cryptogenic/idiopathic than symptomatic IS. While in our TPM-control IS patients, 58.8% were symptomatic, indicating that TPM may be more effective for symptomatic patients. However, the fairly small sample cases in this study and that of Kwon et al were insufficient to give a clear recommendation at

present. Compared with the pyridoxine responsive group, a conclusion was quite clear that similar to the pyridoxine, TPM had effects on both cryptogenic/idiopathic and symptomatic IS.

In Japan, high-dose pyridoxine treatment is used as the first-choice drug of IS [17]. Ohtahara et al. [5] suggested that 100–200 mg/day or 20–30 mg/kg/day of pyridoxine should be initiated in patients diagnosed as IS electro-clinically. If efficacy was not apparent in the first week, it was better to increase the dose to 300–400 mg/day or 40–50 mg/kg/day, meanwhile carefully monitoring seizure frequency and tolerability. In our pyridoxine responsive IS patients, spasms were all controlled completely at a dose of 10 mg/kg/day, which was much lower than the dose reported in the UK or Japan [18]. Seizures were suppressed rapidly by pyridoxine in our patients. A study showed that seizures were completely suppressed within 10 days in 80% and 20 days in all responsive patients [5]. And similarly, 90.9% of our patients were controlled within one week. Only one patient's spasms disappeared at 1.5 months, a little later than others, which reminded that for the patients uncontrolled immediately, a diagnosis of PRE should not be excluded. One research showed that 30% of patients with IS had cessation of spasm and disappearance of hypsarrhythmia with TPM monotherapy at doses ranging from 4 to 12 mg/kg/day (the mean dose during stabilization: 9.1 ± 3.1 mg/kg/day) [9]. In our study, the doses of TPM at seizure-control (3.54 ± 1.80 mg/kg/day) were lower than the report. This was the first time to indicate that a lower dose of TPM might be tried for a period of time. IS was usually recognized as a devastating pediatric epileptic disorder. Seizures in IS were frequently intractable to conventional AEDs treatment, and even polypharmacy and/or steroids had only partial effects [19]. However, in our patients with pyridoxine responsive or TPM-control IS, spasms were controlled in a short time, which suggested that a cohort of IS patients may be responsive to specific drugs well and rapidly.

Differing from patients with PDE, who need lifelong medication with pyridoxine, patients with pyridoxine responsive IS may stop the treatment and without seizures recurrence. Relatively early discontinuation of pyridoxine without seizure recurrence was reported by Ohtsuka et al. [13]. However, spasms recurred due to pyridoxine withdrawal were observed in two patients of our series, after being controlled for 8 and 1 months, respectively. This might be due to that epileptic discharges were not completely suppressed at the time of withdrawal in the two patients. There were no seizures reappeared in the EEG-normal patients. This finding suggested that early reduction or discontinuation of pyridoxine might result in spasms recurrence, and the recurrence was observed more often in patients with EEG abnormality even after the disappearance of hypsarrhythmia [13]. Therefore, EEG is effective for monitoring treatment in the patients with pyridoxine responsive IS. Considering most patients' EEG recovered within 1.5–10.0 months in our study, we recommended that EEG should be conducted weekly to assess the efficacy at the initial treatment with pyridoxine. During the course of treatment, EEG should be examined once per 1–3 months to evaluate the treatment efficacy. Ohtsuka et al considered that after 1 year of age, the discontinuation might be possible if the EEG did not exhibit any epileptic discharges [13]. But Ohtahara et al. proposed another point that two or more years being free of spikes on EEG might indicate a successful withdrawal of pyridoxine [5]. Two patients of this series with normal EEG for more than 2 years had successfully withdrawn pyridoxine without recurrence during follow-up. For the other patients whose EEG had returned to normal at the last follow-up, a discontinuation was very possible in the future. For the TPM-control patients, EEG returned to normal in 82.4% (14/17) within 0.5–60 months. At the last follow-up, 58.9% (10/17) patients' EEG remained normal and 52.9% (9/17) discontinued TPM treatment. No patients had recurrence during the course and follow-up. There were no significant differences in the duration from initial treatment to EEG normality and the ratio of normal and abnormal EEG between the patients with pyridoxine responsive IS and TPM-control IS. In a word, after spasms controlled, abnormal EEG during disease course might predict a possibility of seizure recurrence and remind to adjust the dosage of pyridoxine or TPM. Normal EEG persisting for a long time indicates a great possibility of drug withdrawal in the future.

At the last follow-up, 54.5% patients with pyridoxine responsive IS and 47.1% patients with TPM-control IS were normal in psychomotor development, which was prominently higher than that reported previously (8.8% in all IS patients) [19]. Our study further indicated relatively favorable mental development outcomes in patients with pyridoxine or TPM responsive IS than in those with non-responsive IS. In the present study, two pyridoxine responsive patients had severe developmental delay; one was caused by delayed use of pyridoxine after trying several AEDs ineffectively. Another patient was caused by pyridoxine withdrawal. Development outcome was not significantly different between the two IS groups, as well as between the cryptogenic/idiopathic and symptomatic patients of each group. Therefore, it was considered that a favorable mental outcome of IS might be related to the early suppression of seizures primarily, rather than patients responded to which drugs or belonged to which etiologies.

IS may result from disturbances in key genetic regulatory pathways of brain development: the gene regulatory network of GABAergic forebrain dorsal–ventral development, and abnormalities in the gene expressed at the synapse [20]. Given the fact that most epilepsy associated with structural brain malformations or inborn errors of metabolism

were also genetic; and Paciorkowski et al. [21] proposed a tentatively genetic classification of IS: those with known predisposing genotype and those with unknown predisposing genotype. A lot of IS-related genes have been reported, including *ARX*, *CDKL5*, *FOXG1*, *GRIN1*, *GRIN2A*, *MAGI2*, *MEF2C*, *SLC25A22*, *SPTAN1*, and *STXBP1* [21]. Excepting *MAGI2*, the above genes were included in our 470 genes panel. At present, several PRE caused by gene defect were reported, including phenotypes of pyridox(am)ine-5′-phosphate oxidase deficiency (*PNPO* deficiency), hypophosphatasia (*TNSALP* deficiency), hyperprolinemia type II (*P5CD* deficiency) and Mabry syndrome (*PIGV*, *PIGO,* etc., deficiency) [22]. Of them, *PNPO*, *PIGV* and *PIGO* were included in our genes panel. Because the results of the epilepsy-related genes detection in our patients were all negative, the whole exome sequencing should be conducted in the future to verify it. In our study, there were similar clinical characteristics and disease courses between the pyridoxine responsive IS and the TPM-control IS. In the pyridoxine responsive IS group, high-dose pyridoxine and very low-dose TPM were simultaneously used initially in three patients and continued in one of them, which might clue for that TPM might play roles in these pyridoxine responsive patients. Excepting pyridoxine and TPM, IS can also be controlled by valproate, levetiracetam, sulthiame monotherapy [10, 11, 23]. The evidences above indicated a common pathophysiology related to the IS characteristics itself and shared by some IS patients, such as a possible genetic mechanism, which led them to easily controlled by some certain medications. Further research is needed to clarify the pathophysiological mechanism in the future. This study had several limitations: the retrospective nature limited the acquisition of detailed clinical data, which might induce potential biases; the incidence rate of IS responding to pyridoxine could not be estimated through our research; the cohort was small, multicenter, large-scale studies were needed in the future.

In conclusion, although most IS patients were intractable to AEDs, a minority of patients could be controlled by pyridoxine or TPM dramatically. Considering the following advantages of pyridoxine: [5] 1) far less adverse effects compared with those from ACTH or AEDs; 2) good mental and seizure prognosis in responsive patients; and 3) quick evaluation of efficacy, reducing delay in the reduction of other treatment options in non-responsive patients, pyridoxine should be tried firstly in all IS patients, even in symptomatic cases with severe brain damage. If patients were not responsive to pyridoxine and the first-line drugs such as ACTH was not available immediately, TPM could be used as a treatment choice. Pyridoxine responsive IS and TPM-control IS may share a potential same mechanism because of presenting similar characteristics. If the pathogenesis of these IS patients could be revealed, a targeted precision treatment with pyridoxine or TPM in a certain group of IS patients might be possible. Future precision treatment may improve the outcome of these patients, and avoid the delayed treatment caused by trying pyridoxine or TPM in non-responsive patients.

Author contributions JX contributed to study design, collection, evaluation and interpretation of the data, and drafting and writing of the manuscript. PQ, HL, YW, HX and YZ contributed to collection, evaluation and interpretation of the data. ZY contributed to study design, collection, evaluation and interpretation of the data, and revised the manuscript and approved the final version.

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Compliance with ethical standards

Ethical approval This study was approved by the Ethical Committee of Peking University First Hospital. The individuals' parents in this manuscript had given written informed consent to publish these cases details. All data were analyzed anonymously.

Conflict of interest The authors declare that they have no conflict of interest.

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