年齢と薬物動態：　新生児を除くと年少児ほど代謝は早いので，半減期は短く，血中濃度のピーク時間は早く，同じ血中濃度を得るのに要する用量(mg/kg)は多く，頻回分服投与を要する．思春期以降は成人と同様になる．乳幼児は血中濃度が上がりにくい．高齢者では薬物代謝が低下し，半減期は長くなるので，通常量では血中濃度が上がりすぎ，副作用がおこる恐れがあり，低用量にする必要があり，またピーク時間も遅くなる．

血中濃度：　治療域の血中濃度(有効血中濃度)は個人により異なり，低くても発作が抑制されていれば増やす必要はなく，副作用がなければ治療域を超えて増量可能．測定時間により異なるので，半減期とピーク時間を考慮し，有効性の判断には血中濃度の底値を，副作用の判断には頂値を測定．

副作用との関連：　用量(初期量，維持量)，半減期，治療域の血中濃度，ピーク時間との関係が重要．量が多い，血中濃度が高い，血中濃度のピーク時におこる現象は副作用の可能性があるが，逆の場合はそうではない可能性が高い．

半減期(T 1/2)：　ピーク濃度から半減する時間(消失半減期)であり，投与後血中濃度が半減する時間はピーク時間－半減期．多剤併用時，半減期は相互作用で血中濃度が低下する組み合わせでは短縮，上昇する組み合わせでは延長．半減期により分服回数を決める(半減期が短いものは分3，長いものは分2，時に分1)．

定常状態と抗てんかん薬の除去：　半減期の約5倍で，開始時にはほぼ定常状態に至り，減量・中止時には約97%除去される．連用時はこれより遅くなる．ただし，CBZは自己誘導のため，定常状態になるのに2～6週間かかる．開始・増量時の効果判定，減量・中止時の影響の評価にはこの時間を待つ必要がある．半減期が短いものは1週間ごとに増量可能だが，長いものは2週間ごとかそれ以上で増量．

非直線的な血中濃度の上昇：　血中濃度は投与量に対し直線的に増加するが，PHTは対数増加．血中濃度が5 μg/ml前後まではほぼ直線的に増加するがなかなか上昇せず，それ以降は対数的に急上昇するので，増量幅に注意．始めなかなか血中濃度が上がらずに痙攣抑制が不良で，多くなると増量時にふらつき等の副作用が出やすいので，多めに開始し，血中濃度が上昇したら増量幅を減らす．CBZの血中濃度は開始後3～4日(成人10日以内)は急に上昇，以後，代謝酵素の自己誘導により徐々に下降し，2～6週間で定常状態になる．開始，増量時に有効でも1カ月前後で痙攣が悪化する場合は血中濃度低下のためであり，増量すればよい．開始，増量時に眠気等が出やすいが，3～4日待てば改善．

剤型による血中濃度，ピーク時間の変化：　PHTは錠剤＞10倍散＞錠剤粉砕の順に血中濃度が上がるので，剤型変更時は痙攣の悪化と副作用に注意．VPAのピーク時間は，シロップ＜細粒＜錠剤の順で，空腹時は食後より早い．徐放剤は，空腹時より食後が早い．

抗てんかん薬間の相互作用(36頁を参照)：　抗てんかん薬を追加・変更時に，他の抗てんかん薬の血中濃度上昇による効果増強や副作用，または低下による痙攣増加がおこりうる．ある薬を加えて発作が増えたら血中濃度を下げ合う組み合わせになっていないか，眠気やふらつきなどの副作用が出たら血中濃度を上げる組み合わせになっていないかをチェックする．神経系の副作用に関しても増強する場合とそうでない場合がある．

抗てんかん薬と抗生物質との相互作用：　CBZはマクロライド系抗生物質(クラリスロマイシン，エリスロマイシン等)で血中濃度が上昇，ふらつき，眠気．VPAはパニペネム・ベタミプロン，メニペネム，イミペネム・シラスタチンで血中濃度が激減し，発作頻発．

合理的な多剤併用：　それぞれの発作型に対する薬を組み合わせるが，抗てんかん薬の相互作用を考慮し，可能なら作用機序の異なる薬を組み合わせ，また個々の薬の血中濃度を十分に上げる．あまり多剤では効果も相互作用もわからなくなるので，なるべく少ない種類にとどめる．

開始，中止時に注意すべき薬剤：
① 始めから維持量を使うと眠気・ふらつきなどの副作用がおこりやすい：CBZ，CZP，CLZ，CLB，NZP，GBP，TPM
② 発作が増加することがある：CBZ，CZP
③ 急な中止や減量速度が速すぎると痙攣の増加や重積(離脱発作)がおこりやすい：CZP，CLZ，NZP，AZM
④ 耐性を生じやすい：CLZ，NZP，CLB，CZP，AZM

(須貝[5]より改変)

1．抗てんかん薬を開始したときの定常状態でのベースライン濃度の確認
2．抗てんかん薬を増量，変更あるいは追加したときのそれぞれの薬剤の濃度の確認
3．発作を抑制できないとき，効果が乏しいのは投与量が少ないためか否か
4．副作用がみられたとき，過量のためか否か，その薬によるものか否か
5．多剤併用時の薬剤の相互作用の影響の確認
6．薬剤の剤型を変更したとき
7．血中濃度に変化を与えそうな身体的な変化がおこったとき
　妊娠，肝障害，腎障害，薬剤の吸収に影響を与えそうな消化器症状(胃潰瘍など)
8．妊娠前あるいは妊娠中で，痙攣のコントロールと催奇形性を予防するため
9．コンプライアンス不良が疑われるときの服薬状況の確認
10．濃度の変動が大きい薬剤，治療域と中毒域の間が狭い薬剤の投与量の決定
　非直線的な上昇を示すPHTなど

(Johannesenら[6]より作成)

F．相互作用

抗てんかん薬同士の相互作用だけでなく，抗てんかん薬以外の薬により血中濃度が上昇あるいは低下する(詳細は36頁を参照)．

G．非直線的な血中濃度の上昇

通常は，血中濃度は投与量に対し直線的に増加するが，PHTは対数増加をする(図2)．血中濃度が5 μg/ml前後まではほぼ直線的に増加するがなかなか上昇せず，それ以降は対数的に急上昇するので，増量幅に注意を要する．

CBZの血中濃度は開始後3～4日は急に上昇(成人では10日くらいまで上昇するという報告もある)，代謝酵素の自己誘導がおこり血中濃度が徐々に下降し，2～6週間で定常状態になる(図3)．

3．臨床上重要な抗てんかん薬の薬理動態のまとめ

治療効果を高め，副作用を防ぐために重要な項目をまとめる(表4)．多剤併用時には各抗てんかん薬間の相互作用に注意し，また抗てんかん薬以外の薬と併用するときは，他の薬が抗てんかん薬に及ぼす影響と，抗てんかん薬が他の薬に及ぼす影響を考慮する(36頁を参照)．特に，抗生剤の併用時に注意する．

なお，注意すべき抗てんかん薬として臨床的に問題となるのは，おもに開始・増量時のCBZおよびベンゾジアゼピン系薬剤の副作用と痙攣増悪，減量・断薬時のベンゾジアゼピン系薬剤およびアセタゾラミド(AZM)の痙攣増悪(離脱発作)，長期使用時のベンゾジアゼピン系薬剤および

AZMの耐性，そしてCBZ，PHTの非直線的な血中濃度の変動である(表4)．

血中濃度モニター

一般には，薬剤の血中濃度は治療効果および副作用と関連(用量反応関係)があるので，血中濃度測定は臨床上有益である．ただし，上述したように，ベンゾジアゼピン系薬剤は血中濃度があまりあてにならないなど，全ての抗てんかん薬で血中濃度測定が有用なわけではない(表3)．

また，いわゆる「有効血中濃度」と呼ばれるものは，その範囲の濃度では多くの患者で副作用がなくて発作抑制効果があるという血中濃度の範囲(治療域の血中濃度)を指しており，すべての患者に当てはまるわけではない．「有効血中濃度」には個人差があり，「有効血中濃度」以下の濃度でも発作が抑制されていれば，投与量を増やす必要はなく，逆に副作用がなければ「有効血中濃度」より高い濃度まで増量してもよい．

1．いつ，どんな場合に検査すべきか

外来で，血中濃度を測らなくてよいのか，定期的に測らなくてよいのか，毎月測らなくてよいのか，という質問をよく受ける．しかし，血中濃度のモニターは目的もなくただ定期的に行うのではない．

血中濃度モニターは表5のような場合に行い，特に，副作用がみられたとき，発作抑制効果がないとき，服用状況確認が必要なとき，他の薬剤との相互作用の可能性のあるとき，妊娠予定，妊娠中，肝障害，腎障害合併時などのときには必要であり，有用である．

2．測定時期と時間

A．測定時期

定常状態に至るまでは血中濃度は変化するので，半減期の5倍以上たってから測定する．ただしCBZは例外で，投与後服用を開始して3〜4日後にもっとも高い血中濃度になり，代謝酵素の自己誘導により濃度が徐々に低下して2〜6週間後に定常状態になるので，濃度測定は投与開始後1ヵ月以上してから行うのが望ましい(図3)．

B．どの時間に測定するか

できれば一定の時間が望ましいが，入院では可能であるが，外来では患者に多大な不便を強いることになるので無理である．服薬時間と検査時間の関係が重要であり，個々の薬の半減期とピーク時間を考慮して結果を解釈する．すなわち，それが高い時点で検査したか低い時点で検査したかであり，そのためには服薬時間と検査時間を明記することが重要である．

治療効果を検討するためには底値(trough)が有用で，それには次の薬を服用する直前が望ましく，一方，副作用を検討するにはピーク値が有用で，それには個々の薬のピーク時間か副作用発現時に測定するのが適当である．

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BRIEF COMMUNICATION

STXBP1 mutations cause not only Ohtahara syndrome but also West syndrome—Result of Japanese cohort study

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Summary

We performed *STXBP1* mutation analyses in 86 patients with various types of epilepsies, including 10 patients with OS, 43 with West syndrome, 2 with Lennox-Gastaut syndrome, 12 with symptomatic generalized epilepsy, 14 with symptomatic partial epilepsy, and 5 with other undetermined types of epilepsy. In all patients, the etiology was unknown, but *ARX* and *CDKL5* mutations were negative in all cases. All coding exons of *STXBP1* were analyzed by direct-sequencing. Two de novo nucleotide alterations of *STXBP1* were identified in two patients with Ohtahara and West syndrome, respectively. No de novo or deleterious mutations in *STXBP1* were found in the remaining 84 patients with various types of symptomatic epilepsies. This is the first case report showing that *STXBP1* mutations caused West syndrome from the onset of epilepsy. *STXBP1* analysis should be considered as an etiology of symptomatic West syndrome without explainable cause.
KEY WORDS: *STXBP1*, Ohtahara syndrome, West syndrome, Catastrophic epilepsy, Delayed myelination.

Ohtahara syndrome (OS), otherwise known as early infantile epileptic encephalopathy with suppression-burst (EIEE), and West syndrome are representative infantile-onset catastrophic epilepsies, causing marked deterioration of psychomotor development. Although extensive pre-, peri-, and postnatal damage causes symptomatic West syndrome, the precise etiology in many patients remains largely undetermined despite advances in neuroimaging modalities and searches for metabolic disorders (Dulac & Tuxhorn, 2005). Recently, molecular biologic approaches to identify genes responsible for development of the brain have progressed, and mutations closely related to specific structural abnormalities of the brain have been identified. Among these, *CDKL5* and *ARX* mutations have been identified as linked to the underlying cause of West syndrome, and the latter has also been linked to OS, mainly found in boys with abnormal genitalia, although the incidences of these syndromes are rare (Bahi-Buisson et al., 2008; Kato et al., 2003, 2007; Archer et al., 2006). The former produce mainly Rett syndrome-like phenotype and early onset seizure disorders including West syndrome, affecting only girls. Most recently, Saitsu et al. (2008) demonstrated, using an array-based comparative genomic hybridization technique, that de novo *STXBP1* mutations harboring chromosome 9q34.11 were responsible for OS in five children. Then, Hamdan et al., (2009) reported that two children with severe psychomotor retardation and nonsyndromic complex partial epilepsy also had *STXBP1* mutations, indicating that the gene can also cause another type of epilepsy. At this time, we herein reported two patients with symptomatic West syndrome and OS, respectively, carrying *STXBP1* mutations. This is the first case report that *STXBP1* mutations caused West syndrome from the onset of epilepsy, not through transition from OS.

Materials and Methods

After obtaining informed consent from each patient or their legal guardian based on a permission approved by the institution's ethical committee, peripheral blood samples were obtained from 86 patients with epilepsy (49:37: male to female), which included 10 patients with OS, 43 patients with West syndrome, 2 patients with Lennox-Gastaut syndrome, 12 patients with symptomatic generalized epilepsy, 14 patients with symptomatic partial epilepsy, and 5 patients with other undetermined types of epilepsy. All patients were "etiologically unknown" and

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shown to have negative *ARX* and *CDKL5* mutations (data not shown).

In cases of the *STXBP1* mutations, parents' samples were obtained to analyze whether those mutations were de novo. Genomic DNAs were extracted from peripheral blood samples using the QIAquick DNA extraction kit (Qiagen, Valencia, CA, U.S.A.). All of the 20 coding exons were amplified with polymerase chain reaction (PCR) using originally designed primers located in both neighboring intronic sequences according to the standard method (Table S1). All amplicons were subjected to direct sequencing using the BigDye Terminator Cycle Sequencing kit (Applied Biosystems, Foster City, CA, U.S.A.). Sequencing reactions were analyzed with a 3130xl Genetic Analyzer (Applied Biosystems).

Results

STXBP1 mutations

Two nucleotide alterations were identified in two patients. Patient 1 showed 4-bp (ACTC) deletion in exon 4, which caused a frame-shift (Fig. 1A). Patient 2 showed a missense mutation, c.1654T>C (C552R), in exon 18 (Fig. 1B). These mutations were negative in both parents of both patients, indicating de novo occurrence.

No control samples derived from 100 individuals showed c.1654T>C

Descriptions of patients

Patient 1 is a 1-year 11-month-old boy, the only child of his parents, conceived through the use of in vitro fertilization embryo transfer. There is no family history of seizure disorders. Delivery was at 25 weeks of gestation, with weight of 870 g. He had received artificial ventilation for 9 days. Thereafter, he had been well without any complications until 4 months of (corrected) age, when he was found to be retarded. He underwent brain magnetic resonance imaging (MRI), electroencephalography (EEG), and chromosomal study without significant abnormalities at 5 months of age (Fig. S1A). He developed epileptic spasms (ES) in clusters at 6 months of age, and was diagnosed as having symptomatic West syndrome based also on hypsarrhythmic EEG pattern (Fig. S1B). He underwent adrenocorticotropic hormone (ACTH) therapy with only a transient effect. He was referred to our hospital at 9 months of age. He demonstrated 10–15 clusters of ES and 10–30 ES in each cluster. Interictal and ictal EEGs demonstrated hypsarrhythmia, and diffuse electrical decremented EEG patterns, respectively. On neurologic examination, he had no head control, visual attention, or social interaction. He showed markedly decreased muscle tone without exaggerated tendon reflex. He had no gross anomalies or coarse facial appearance. Abnormal slow eye movement mainly in a downward direction and poorly differentiated visual evoked potential pattern suggested cortical blindness. Brain MRI demonstrated hypoplastic thin corpus callosum, delayed myelination of the cerebral white matter, and moderate atrophy of the bilateral frontal lobes, but no findings of periventricular leukomalacia (Fig. 2A). ^{123}I-iomazenil-single photon emission computed tomography (IMZ-SPECT) study showed reduced asymmetrical IMZ receptor distribution in the middle frontal lobe. Trials of thyroxin-releasing hormone (TRH) injection, topiramate, and lamotrigine

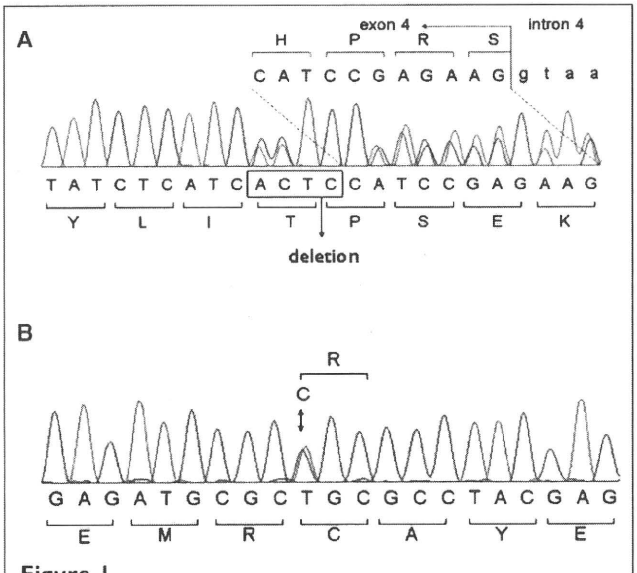

Figure 1.
Mutation analyses of *STXBP1*. Direct-sequencing analysis of PCR-amplified *STXBP1* fragments demonstrated a 4-bp deletion in exon 4 in patient 1 (**A**) and a missense mutation in exon 18 in patient 2 (**B**).
Epilepsia © ILAE

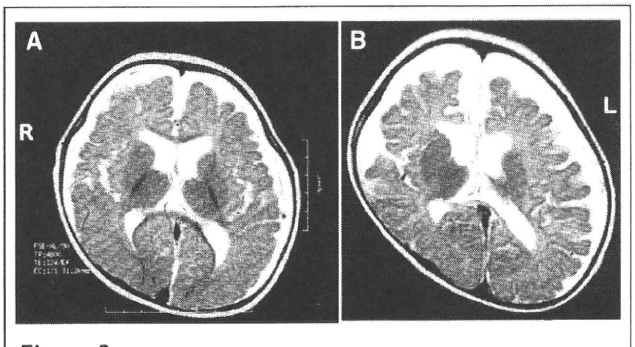

Figure 2.
Brain MRI of the two patients. (**A**) Brain MRI T_2-weighted axial images of Patient 1 obtained at 8 months of age. Hypoplastic thin corpus callosum, delayed myelination of the cerebral white matter, and moderate atrophy of bilateral frontal lobes were apparent. (**B**) Brain MRI T_2-weighted axial images of Patient 2 at 11 months of age. Hypoplastic thin corpus callosum, delayed myelination of the cerebral white matter, and atrophy of the bilateral frontal lobes were more pronounced than those of Patient 1.
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failed to improve either ES or EEG. Because his parents strongly hoped to alleviate his catastrophic state, he underwent corpus callosotomy at 1 year and 1 month of age. Postoperatively, he has remained free from seizures and epileptic EEG abnormality to date. Although he remains unable to sit or see, the social response has improved to the level of exhibiting elementary emotional feelings.

Patient 2 was a 2-year and 0-month-old girl. The infant was born uneventfully at 37 weeks of gestation, and weighed 2,865 g. At 1 month of age, she started to have tonic spasms, and was admitted to a local hospital. At 2 months of age, tonic spasms lasting 5 s occurred every 15–20 s. The interictal EEG showed a suppression-burst EEG pattern, and a diagnosis of OS was made (Fig. S2). At 8 months of age, brain MRI showed frontal-dominant moderate diffuse brain atrophy (Fig. 2B). She showed severe hypotonia with poor head control, visual attention, and ocular pursuit.

Discussion

We identified new *STXBP1* mutations in the two patients with symptomatic West syndrome and OS, respectively, among a cohort of 86 patients with various types of symptomatic epilepsies. These mutations were found in 2 of 86 patients overall (2.3%), 1 of 10 patients with OS (10%) and 1 of 43 patients with West syndrome (2.3%), although the precise figure of the prevalence awaits further prospective study. *STXBP1* mutations have previously been shown to cause OS and also nonsyndromic complex partial epilepsy (Saitsu et al., 2008; Hamdan et al., 2009). This is the first case report showing that *STXBP1* mutations caused West syndrome from the onset of epilepsy. Therefore, our findings indicate that *STXBP1* disruption has the potential to cause a wider spectrum of epileptic disorders in association with severe mental retardation.

Despite the presumed polyetiology of symptomatic West syndrome and OS, these two syndromes are generally considered to result from a primary structural abnormality of the brain or a malformation of cortical development. The transition from OS to West syndrome that is characterized by ES in clusters, arrest of psychomotor development, and hypsarrhythmia on EEG, occurs in 75% of patients with OS and a common pathologic mechanism between them has been suggested (Ohtahara & Yamatogi, 2003). In this sense, it is reasonable to expect that *STXBP1* mutations would cause not only OS but also symptomatic West syndrome.

Our Patient 2 developed OS at 2 months of age, which later evolved to nonspecific generalized epilepsy. In the original description, four of the five patients with *STXBP1* mutations evolved from OS to symptomatic West syndrome over time (Saitsu et al., 2008). Comparisons of the neuroimaging findings among the five patients with OS that they reported with those of our two patients demonstrated that three of the former group and our two patients displayed moderate frontal dominant cerebral atrophy, thin corpus callosum, and delayed myelination of the white matter. In the remaining two patients in the Saitsu series, MRI findings during infancy were not described. Myelination is one of the most important factors influencing brain maturation and epileptogenesis (van der Knaap et al., 1991). Although the delayed myelination itself in those with West syndrome does not appear to be specific for the underlying etiology (Takano et al., 2007; Tohyama et al., 2008), it may offer a clue to approach the diagnosis of *STXBP1* mutations among infants with epileptic spasms and nonexplainable severe psychomotor retardation.

Most recently, α-II spectrin mutation has also been found to cause West syndrome with severe cerebral hypomyelination (Saitsu et al., 2010).

Further study to search for the characteristic MRI features in infants with *STXBP1* mutation is needed when cerebral MRI data in those with etiologically determined West syndrome are accumulated.

Hamdan et al. (2009) found two patients with truncating *STXBP1* mutations exhibiting severe mental retardation, muscle hypotonia, complex partial epilepsy, and either normal brain computed tomography (CT) or MRI findings, despite that they were ambulatory. These two patients appeared milder in phenotypic expressions than the Saitsu series and our two cases, including five with missense mutations, most of whom showed profound mental retardation, infantile epileptic encephalopathy, and lack of ambulatory function. Therefore, phenotype and genotype correlation may not be clear based on the mutation type, although it is too premature to refer to this correlation in this small number of patients with *STXBP1* mutations.

In conclusion, *STXBP1* mutations cause not only OS, but also symptomatic West syndrome from the onset of epilepsy. A further larger study is needed to estimate the incidence of *STXBP1* mutation causing directly symptomatic West syndrome.

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Disclosure

We certify that we have read the Journal's position regarding issues pertaining to ethical publication, and affirm that this report is consistent with those guidelines. There are no conflicts of interest, related to this manuscript.

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Supporting Information

Additional supporting information may be found in the online version of this article:

Figure S1. Interictal sleep EEGs before (**A**) and after (**B**) the occurrence of epileptic spasms.

Figure S2. An interictal sleep EEG at 2 months of age.

Table S1. Primers used for PCR and direct sequencing.

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Review article

Treatment of benign focal epilepsies in children: When and how should be treated?

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Abstract

Benign focal epilepsies represent almost one-fourth of all childhood epilepsies and are a frequent occurrence in clinical practice. They include benign infantile seizures (BIS), Panayiotopoulos syndrome (PS), and benign childhood epilepsy with centrotemporal spikes (BCECTS) in this order of the onset age. Because the prognosis is always excellent in patients with benign focal epilepsies, we must consider the risks and benefits of chronic antiepileptic drug (AED) administration. AED treatment is usually not recommended for the patients with a first attack, but should be considered for those with a second or third attack. A choice of AED has been based on the expert opinion. Carbamazepine (CBZ) is recommended for both acute and chronic treatment of seizure clusters in patients with BIS. Valproic acid (VPA), CBZ or clobazam (CLB) appears to be a first option of AED for patients with PS. A common first choice for BCECTS is CBZ in the USA and Japan, and VPA in the EU. The treatment period should be as short as possible without waiting for EEG normalization, possibly within 2 years after the initiation of AED. We must remember that some patients with BCECTS may have an "atypical evolution". In conclusion, when and how to treat this benign condition should be determined in an individual manner based on the length and frequency of seizures, circadian rhythm of the attacks, interictal EEG findings, cognitive and behavioral functions in daily life and the attitude of the parents toward seizure recurrences and AED side effects.

Keywords: Antiepileptic drug treatment; Benign focal epilepsies; Benign infantile seizures; Panayiotopoulos syndrome; Benign childhood epilepsy with centrotemporal spike

1. Introduction

Benign focal epilepsies represent almost one-fourth of all childhood epilepsies and are most frequently encountered not only in the clinical setting of pediatric neurology, but also in pediatric emergency medicine [1]. Compared to children with intractable epilepsy, those with benign focal epilepsies are believed to enter remission without antiepileptic drug (AED) treatment until adolescence [1–4]. The risks associated with chronic AED treatment might outweigh the risks seizure recurrences because the patients may experience only a few such recurrences. Thus, the issue of when and how to treat the patients has been a matter of debate for many years [2,3,5]. Consensus has been generally established in the context of the treatment of the child with a first unprovoked seizure in that patients without specific risk factors are recommended to postpone AED treatment at least until a second seizure [6]. In addition, there have been few evidence-based studies for the treatment of benign focal epilepsies, which makes it difficult to develop a formulated treatment policy [3,7]. In this article, I focus on the treatment of following three representative benign focal epilepsies, benign infantile seizures (BIS), Panayiotopoulos syndrome (PS) and benign childhood epilepsy with

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centrotemporal spikes (BCECTS), because the prognosis of Gastaut type late-onset childhood occipital epilepsy has been shown to be unpredictable and the term "benign" is not included in this descriptive terminology [1].

2. Treatment for BIS

The concept of benign infantile convulsions (BIC) was first described by Fukuyama in 1963 [8]. He identified a group of previously normal infants who experienced one or a few clusters of generalized tonic-clinic seizures (GTCS), and later, the infants did not develop epilepsy. However, there was no progress for the concept of BIC until 1981 when Morooka reported 22 infants between 6 months and 2 years and 6 months of age who experienced a cluster of GTCS during periods of gastroenteritis with mild diarrhea [9]. This new syndrome received attention because of the close relationship between the seizures and rota gastroenteritis as well as the high incidence of this syndrome. In contrast, Watanabe et al. studied BIC with focal onset or secondarily generalized seizures from 1987 to early 1990's and proposed the concept of benign partial epilepsy in infancy, which was finally recognized as BIS in the 2001 International League Against Epilepsy (ILAE) classification [10]. At the same time, the syndrome of benign familial infantile convulsions (BFIS) proposed by Vigevano et al. was also recognized [11]. In the 2006 ILAE classification proposal, these two syndromes were combined and unified into one entity called BIS. Most recently, a new form of benign focal epilepsy termed benign familial neonatal-infantile seizures (BFNIS) has been established clinically and genetically, with an onset age between 2 days and 3.5 months of age, which nosologically link BIS to benign familial neonatal convulsions [12].

Thus, BIC as originally proposed by Fukuyama, came to include BIS and BIC with mild diarrhea, the latter of which has been recently re-designated as BIC with mild gastroenteritis (BICMG) and categorized as "chanced epilepsy". BICMG has not been recognized world-wide despite the fact that these seizures are the most common form of BIC in Japan. Sakauchi previously studied 56 infants with BIC, who showed two distinct peaks of onset age [13]. The earlier onset group was 2–11 months old, and they tended to have recurrent seizures or clusters of seizures that indicated BIS. In contrast, the later onset group was 1–2 years of age, and they experienced only one episode or one cluster of seizures, which indicated BICGM. Thus, the onset age and the association of mild diarrhea appear to be important for distinguish both conditions. The historical changes in the concept and terminology of BIS are shown in Fig. 1.

The treatments for BIS and BICMG can be categorized as acute or chronic (Table 1). Because the patients experience a cluster of seizures for several days, acute

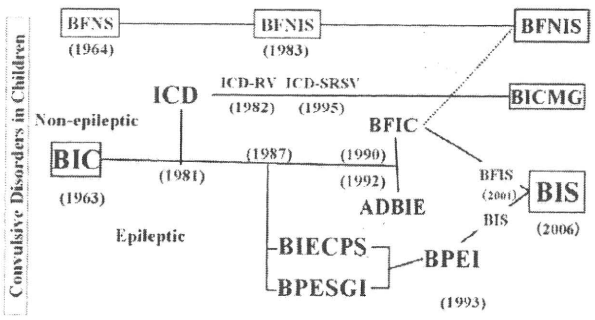

Fig. 1. Changes in the concept and terminology of benign infantile seizures (BIS)** by courtesy of Dr. Sakauchi. Abbreviations: BIC, benign infantile convulsions; ICD, infantile convulsions with diarrhea, ICD-RV, ICD with rotavirus infection; FCD-RV, febrile convulsions with diarrhea due to RV; BFIC, benign familial infantile convulsions; ADBIE, autosomal dominant benign infantile epilepsy; BPEI, benign partial epilepsy in infancy; BIECPS, benign infantile epilepsy with CPS; BPESGI, benign partial epilepsy with SG in infancy; BFNIS, Benign familial neonatal–infantile seizures; BICMG, Benign infantile convulsions with mild gastroenteritis.

treatment is urgent. There have been no control studies regarding the acute treatment for either syndrome. Intravenous or rectal diazepam therapy has been shown to be ineffective for seizure clusters [14–16]. There have been no systematic studies regarding rectal phenobarbital suppositories or intravenous phenytoin therapy. Intravenous lidocaine infusion therapy has been shown to suppress seizures effectively in a few open studies [14,15]. Most recently, single, low-dose oral CBZ has been shown control a cluster of seizures in patients with both BIS and BICGM. As such, CBZ appears to be the safest and easiest treatment option [16]. Although the evidence is limited, a single oral dosage of CBZ and an intravenous lidocaine infusion are currently recommended for the acute treatment of these seizures.

As for chronic prophylactic treatment, it is not generally recommended for patients with BICMG because the seizures seldom recur. In contrast, seizures in infants with BIS generally continue for months or years. The best AED and the best treatment duration have not been determined, although there was one open study recommending the use of low-dose CBZ in patients up to 2–3 years of age [16]. There were no available data for other agents such as PB or VPA, which have also been frequently used for infants with recurrent seizures. Thus, CBZ appears to be a first choice not only for the acute treatment of BICGM, but also chronic treatment of BIS.

3. Treatment for PS

PS is a benign age-related focal seizure disorder that occurs in early and mid-childhood. The onset age of epilepsy ranges from 1 to 14 years of age, with three-quarter of the cases occurring between 3 and 6 years. Clinical

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Table 1
Antiepileptic drug (AED) treatment for benign focal epilepsies.

1. Treatment of benign infantile seizures (with or without mild gastroenteritis)
   (1) Acute AED treatment for a cluster of seizures: Administration of low-dose CBZ (5 mg/kg) once orally or through a nasogastric tube if infant is asleep.
   Intravenous infusion of lidocaine is an effective alternative if CBZ cannot be used or is not effective.
   Intravenous phenobarbital, phenytoin, and midazolam may be effective treatment
   Diazepam (i.v. or rectal usage) is not effective for a cluster of seizures.
   (2) Chronic AED treatment
   Benign infantile seizures with mild gastritis: Not required
   Benign infantile seizures: Low-dose CBZ (5 mg/kg) is recommended for use up to 2–3 years of age
2. Treatment of Panayiotopoulos syndrome
   (1) First seizure
   Prescribe a rectal diazepam suppository or solution for the next seizure and then postpone AED administration until at least a second seizure has occurred
   (2) Second or third seizure
   Start an AED if caregivers agree.
   VPA, CBZ or CLB is recommended.
   Those with frequent seizure recurrences* may require AED adjustment (e.g. high-dose VPA, CLB), *5–10% of patients, especially those with mild neurobehavioral disorders
   (3) Period of treatment
   Two to three years after the last seizure then discontinue AED without waiting for the disappearance of epileptic EEG spikes
3. Treatment of benign childhood epilepsy with centrotemporal spikes
   (1) Postpone AED administration until a second seizure occurs.
   (2) For short intervals between the first 3 seizures, a younger age of onset (less than 4 years), recurrent GTCS, or the presence of diurnal seizures are considered to be risk factors for seizure recurrences, thereby recommending the early initiation of AED
   (3) Selecting AEDs
   CBZ or VPA is recommended. Sulthiame, GBP and CLB are second options.
   (4) Period of treatment
   One to two years after the last seizure, AED should be discontinued without waiting for the disappearance of rolandic spikes
4. Treatment of atypical evolution of benign focal epilepsies (Atypical benign partial epilepsy of childhood)
   (1) Discontinue CBZ if it appears to provoke atypical evolution
   (2) Try ESM for spike-and-wave related absence seizures or epileptic negative myoclonus

seizures are characterized by sudden-onset autonomic symptoms including emesis, vomiting, and paleness of the face and the deviation of both eyes. These symptoms evolve to generalized tonic-clonic (generalized, unilateral), or prolonged atonic seizures, which are designated as ictal syncope. The seizures occur during sleep in two-third of all cases. Seizure duration is usually longer than 10 min, and 44% of patients develop status epilepticus lasting longer than 30 min. Interictal EEG shows high amplitude sharp or sharp-slow complexes recorded initially with posterior predominance, and shifting in localization or becoming multifocal along with an age progresses [1]. Some cases later show centro-temporal EEG foci, which are reminiscent of the foci shown in BCECTS. Other cases exhibited synchronous and asynchronous epileptic EEG foci between the frontopolar and parieto-occipital regions, which we have designated as the "Fp-O pattern" [17]. The prognosis of PS is excellent. Remission often occurs within one to two years after onset, and always occurs before 12 years of age. Roughly 5–10% of the patients may experience recurrences of either brief or prolonged autonomic attacks more than 6–10 times that are refractory to conventional AED therapy.

Fig. 2 illustrates the ages of 106 children with PS at the time of their first and last seizures [18]. The age range for the first seizure was from 1 to 10 years of age with a peak at 3–5 years of age. The ages at last seizures ranged from 3 to 10 years. A total of 77% of cases entered remission within 3 years from onset. Fifteen percent of the patients had only had a single seizure. However, 17 of the 106 cases (17%) had more than 10 seizure recurrences despite AED treatment. In our previous study, most of the latter cases had mild neurobehavioral abnormalities, which may have contributed to the refractoriness of seizures because the abnormalities were found before the onset of epilepsy [19]. However, all of the cases ultimately entered remission until 12 years of age.

Treatment of PS has not yet been well studied because of the condition's excellent prognosis. AED treatment is usually not recommended. However, a rectal diazepam suppository or solution should be better to be prepared for a next prolonged seizure. There have been no control studies nor open trials specifically for AED treatment of PS. There were two control studies for the newly diagnosed form of childhood epilepsy enrolled mostly patients with idiopathic focal epilepsy, thereby demonstrating the equal effectiveness between CBZ and VPA in one study, and also among phenobarbital (PB), phenytoin (PHT), CBZ and VPA in the other study [20,21]. Independent expert-consensus studies were conducted in the USA, EU and Japan in which

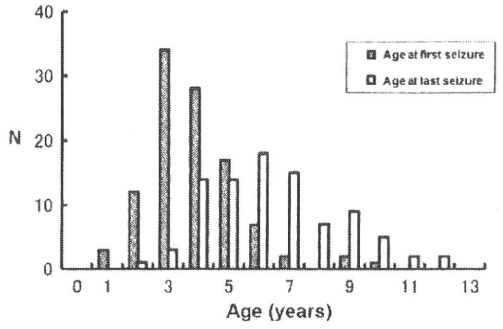

Fig. 2. The ages at the first and last seizures for 106 children with Panayiotopoulos syndrome followed-up at Tokyo Women's Medical University. The peak incidences of epilepsy onset and remission were 3–4 years and 5–7 years of age, respectively in the study cohort [18].

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the treatment choice for children with cryptogenic complex partial epilepsy was oxcarbazepine (OXC) and CBZ, CBZ and OXC, and CBZ and zonisamide (ZNS), respectively [22–24]. In this regard, the choice of AED has to be determined based on the side-effect profiles of these agents. Thus, CBZ or VPA is usually recommended when AED is introduced in PS patients [25]. In rare instances, CBZ may paradoxically induce seizures and cause EEG exacerbation [26]. Most recently, Hirano et al. investigated the effectiveness of AEDs on seizures in 26 PS patients with more than six seizure recurrences. The effectiveness of both VPA, especially high-dose, and CLB appeared to be better than that of CBZ [27].

In conclusion, the prognosis of PS is excellent except for 5–10% of patients who have many seizure recurrences. AED treatment is usually not recommended for the patients with a first seizure. After a second or third seizure, it would be better consider treating patients with VPA, CLB or CBZ, depending on the length of seizures, the association of mild neurobehavioral disorders and whether parents are more concerned about seizure recurrences or chronic AED side effects.

4. Treatment for BCECTS

BCECTS is a prototype of idiopathic focal epilepsies and has been extensively studied with clinical, electrophysiological and genetical methods, although the molecular approach has not yet been successful. BCECTS, which comprises 15–20% of all childhood epilepsy cases, is the most common epileptic syndrome in children [1]. The onset age of epilepsy ranges from 3 to 13 years of age with peak incidence occurring between 9 and 10 years of age. Typical seizures are characterized by short-lasting focal motor or sensory seizures that occur exclusively during sleep. An EEG typically shows biphasic sharp wave discharges arising from centro-temporal regions during sleep (rolandic spikes). The prognosis is excellent. The seizures enter remission always before 10–12 years of age, and the rolandic spikes disappear before 15–16 years of age.

Bouma et al. conducted a meta-analysis of 20 publications for a total of 794 patients with BCECTS [5]. The study demonstrated that seizures occurred only once in 15.6% of the patients, two to five times in 62.1%, 6 to 15 times in 17.3% and more than 15 times in 5.3%. Thus, 77% of the patients had less than five seizure recurrences, similar to the figures for PS. Secondary GTCS occurred in 43.5% of the patients. A follow-up was successfully conducted without AED in 18.4% of the patients. AED treatment was successfully discontinued in 87.8% of the patients and seizure recurrences after AED discontinuation were found in 14.2% of the patients. Finally, seizure remission was confirmed in 97.7% of all patients. In conclusion, the authors stated that early prediction of seizure outcome in a new patient with BCECTS cannot be determined with certainty based on these meta-analyses. In other words, it is difficult to predict which patients have possible few seizure recurrences without requiring chronic AED treatment at the time of their first seizures.

Conversely, there have been several risk factors that suggest a longer duration of the active seizure period and frequent seizure recurrences. If short intervals exist between the first three seizures, a younger age of onset (less than 4 years), or a presence of recurrent GTCS and diurnal seizures, these characteristics indicate the need for early AED treatment [2,4,5].

Although the ultimate prognosis of BCECTS is excellent, recent neuropsychological studies using more sophisticated tests showed that rolandic spikes could interfere with specific cognitive and behavioral functions in children with BCECTS. Between 28% and 53% of children with BCECTS displayed neuropsychological abnormalities during the active phase of the epilepsy, including cognitive dysfunction such as difficulties with auditory-verbal, and visuospacial memory and executive function tasks as well as language impairment, attention disorders, learning disabilities, and behavioral disturbances [28]. However, we do not know whether the neuropsychological abnormalities are a consequence of persistent rolandic spikes or already existed before the onset of epilepsy. Whether chronic AED treatment could prevent these neuropsychological dysfunctions is also unknown.

The choice of AED for those with BCECTS is mostly based on expert opinions without any control studies. It is now generally accepted that AED administration should be postponed until at least a second seizure occurs. CBZ is recommended as a first-line AED in both USA and Japan, whereas VPA is the first-line AED in EU according to expert-consensus studies [22–24]. Sulthiame and gabapentin are AEDs effective for those with BCECTS as demonstrated by a randomized control study [3,7]. Sulthiame is not only effective for BCECTS seizures but also for rolandic spikes, although the effect may not be lasting long. Thus, CBZ or VPA is the best choice for clinical practice. Sulthiame and GBP are good second options (Table 1). Some authors recommend clobazam (CLB) or clonazepam (CZP) taken once before going to sleep, which can suppress not only seizures but also rolandic spikes [29]. However, the development of tolerance and sedative side effects remains a problem for these benzodiazepines. Although newly introduced AEDs including lamotrigine (LTG), OXC, topiramate (TPM) and levetiracetam (LEV) are also potentially effective and have fewer side effect, a large scale study is needed to determine whether they have superior effects compared to AEDs that have previously been described. For the time being, these medications should be considered as a second or third choice depending on the

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side-effect profiles. AED treatment should be kept as short as possible. Usually the treatment lasts for 1–2 years after the last seizure, and then the treatment is discontinued without waiting for a disappearance of rolandic spikes.

5. Treatment for atypical forms of benign focal epilepsies

Benign focal epilepsies, especially, PS and BCECTS, occasionally show atypical features including severe aggravation of epileptic manifestations as well as transient or persistent impairments of cognitive, behavioral and language functions. Fejerman designated these forms of epilepsy as "atypical evolution" of benign focal epilepsies [25]. Although Landau-Kleffner syndrome and continuous spike-and-wave during slow sleep (CSWS) syndrome have nosologically been placed within a conceptual framework of begin focal epilepsies, the treatment of all of these ILAE-recognized epileptic syndromes is beyond the focus of this paper. However, the following two forms of "atypical evolution" are important.

5.1. Atypical benign partial epilepsy of childhood

During the clinical course of BCECTS, some patients develop frequent atonic drop attacks (mostly epileptic negative myoclonus) and display nearly continuous diffuse spike-and-wave during sleep which mimics CSWS, at times following the CBZ administration. The spike-and-wave related atonic or absence attacks may resolve spontaneously after stopping CBZ treatment but often continue over years if proper treatment is not introduced. We have recommended the early introduction of ethosuximide (ESM), and adrenocorticotropin (ACTH) or steroid therapy if ESM is insufficient [30].

5.2. Status of BCECTS

During the clinical course of BCECTS, some patients also develop frequent focal status epilepticus involving the oro-motor area, which leads to transient drooling, dysphasia, dysarthria or even aphasia. Some other children may develop the same symptoms along with worsening of EEGs associated with a few oro-motor seizures. Shafrir and Prensky recognized the latter condition as a new entity that was distinct from Landau-Kleffner syndrome and designated it as acquired epileptiform opercular syndrome [31]. In this condition, direct clinical or indirect electrical interference in the bilateral paraopercular regions has been suggested to inhibit the neuronal activity of the cortex integrating oro-motor functions. AED treatment has been shown to be difficult during the active phase of the epilepsy. Most recently, von Stulpnagel et al. reported a promising LEV effect for these atypical rolandic epilepsies [32].

6. Worsening of idiopathic focal epilepsies from CBZ treatment

There have been many case reports regarding the worsening of seizures and epileptic EEG abnormalities in children with idiopathic focal epilepsies shortly after the introduction of CBZ, as we previously described [33]. Because CBZ is always the first choice for the treatment of idiopathic and symptomatic focal epilepsies regardless of age, the paradoxical reactions of CBZ should always be considered. CBZ can potentially increase not only generalized spike-and-wave activity leading to aggravation of absence seizures but also accelerate the secondary bilateral synchrony producing CSWS in children with idiopathic focal epilepsies. Thus, CBZ is not recommended for patients with BCECTS that shows frequent spike-and-wave discharges while the patient is asleep or while the patient is awake.

7. Discussion

Because the prognosis has been shown to be excellent in patients with benign focal epilepsies, we must consider a balance between the risks and benefits of chronic AED treatment [1]. Treatment with AEDs has risks of acute and chronic side effects and is an economic burden. However, parents may be overly concerned about the recurrence of seizures if their child is not treated. In addition, recent studies have clarified a risk of potential cognitive and behavioral impairments caused by epileptic EEG spikes in children with benign focal epilepsies, which could be treated with AEDs [28]. However, it is not known whether AED treatment can effectively suppress epileptic EEG abnormalities without side-effects or even of the resulting decreases in the epileptic EEG abnormalities can reasonably improve cognitive and behavioral functions.

The attitudes of parents and physicians about whether we should treat or not treat a patient change depending on the circumstances of the individual patient because the epileptic conditions in children with benign focal epilepsies are not always homogeneous. Some cases have few seizure recurrences and rare epileptic EEG abnormalities, and other cases have several or more seizure recurrences and abundant epileptiform EEG abnormalities. Thus, rigid treatment recommendations are not always helpful for patients with benign focal epilepsies. Ultimately, the best goal for children with benign focal epilepsies is to make them a free from restrictions as possible so that they can lead a normal school life irrespective of AED treatment. Thus, when and how to treat this benign condition should be determined in an individual manner based on the length and frequency of seizures, circadian rhythms of the attacks,

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the attitudes of the patients' parents toward seizure recurrences and AED side effects, interictal EEG information, and finally cognitive as well as behavioral functions in daily life.

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ELSEVIER

Atypical Benign Partial Epilepsy: Recognition Can Prevent Pseudocatastrophe

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To characterize and distinguish atypical benign partial epilepsy of childhood among various epileptic syndromes, we conducted a clinical and electroencephalogram study. Seventeen children with atypical benign partial epilepsy of childhood were followed at our hospital. They all underwent a video/polygraphic study of characteristic daily seizures, facilitating a diagnosis of atypical benign partial epilepsy of childhood. Their clinical and electroencephalogram features were retrospectively analyzed. A video/polygraphic study indicated negative motor seizures including epileptic negative myoclonus, atonic absence seizures, or atonic seizures corresponding to spike-and-wave complexes arising from centro-parieto-temporal regions. Early in the clinical course, these seizures appeared every 4 ± 2 months, and lasted 1-3 months. Interictal sleep electroencephalograms, initially localizing in the centro-parieto-temporal regions, became widespread and displayed continuous, diffuse, spike-and-wave complexes, although the spike-wave index did not exceed 85%. Negative motor seizures responded to ethosuximide, corticotropin, and high-dose steroid, whereas other antiepileptic drugs were much less effective. All patients ultimately entered remission before age 12 years. Patients with atypical benign partial epilepsy of childhood exhibited a characteristic clinical course, and responded favorably to antiabsence treatment. Atypical benign partial epilepsy of childhood should be recognized as a discrete epileptic syndrome. Its early diagnosis leads to the prevention of pseudocatastrophe.

Fujii A, Oguni H, Hirano Y, Osawa M. Atypical benign partial epilepsy: Recognition can prevent pseudocatastrophe. Pediatr Neurol 2010;43:411-419.

Introduction

Atypical benign partial epilepsy of childhood is a special type of epileptic syndrome first described by Aicardi and Chevrie in 1982, characterized by an age of onset between 2.5-6 years, multiple seizure types (including focal motor seizures, atypical absence, or myotonic seizures), focal epileptic electroencephalogram abnormalities during wakefulness, generalized continuous slow spike-and-wave electroencephalogram complexes during sleep, the persistence of normal neurologic and mental functions throughout the course, and an ultimately favorable prognosis in terms of seizure [1-3]. Aicardi and Chevrie stressed the close similarity of clinical and electroencephalogram manifestations to those of Lennox-Gastaut syndrome and myoclonic-astatic epilepsy, and referred to the differential diagnosis of these two syndromes [4]. Since then, a number of studies have mostly given special attention either to the peculiar seizure type (termed "epileptic negative myoclonus"), or to the nosologic relationship with benign epilepsy of childhood with centrotemporal electroencephalogram foci [5-8]. Atypical benign partial epilepsy of childhood has not been accepted by the International League Against Epilepsy as an independent and distinct epileptic syndrome, in part because it is recognized as an atypical evolution of benign epilepsy of childhood with centrotemporal electroencephalogram foci or special types of epilepsy with continuous spike-and-wave complexes during slow sleep [4]. We have long studied patients with atypical benign partial epilepsy of childhood, giving special attention to the neurophysiologic mechanism of epileptic negative myoclonus and its treatment response to various antiepileptic drugs, because epileptic negative myoclonus appears to be resistant to those treatments effective in focal epilepsy [9-12]. Recent advances in epilepsy surgery prompted us to consider its indication when seizures are resistant to all appropriate antiepileptic

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drugs for at least 2 years. Patients with atypical benign partial epilepsy of childhood may have manifested a "pseudocatastrophic" clinical course when the treatment strategy proved inappropriate [2,3,13]. Here, we stress that atypical benign partial epilepsy of childhood is a discrete epileptic syndrome with a characteristic age-specific clinical course and electroencephalogram picture, and that it favorably responds to anti-absence antiepileptic drugs.

Patients and Methods

Subjects included 17 patients who underwent detailed examinations, and were followed at Tokyo Women's Medical University since 1980. They fulfilled several clinical characteristics: (1) no gross developmental delay before the onset of epilepsy, (2) age of onset for epilepsy between ages 2.5-6 years, (3) a combination of focal seizures and daily atypical absence or myotonic seizures confirmed by an ictal polygraphic study, and (4) interictal electroencephalograms displaying both focal and generalized epileptic discharges.

We retrospectively reviewed the patients' medical records, neuroimaging data, electroencephalograms, and other laboratory data. The 17 patients all underwent long-term ictal video-polygraphic or polygraphic studies. Surface electromyogram activity data were collected from the trapezius, sternocleidal mastoideus, and deltoid muscles, and also from the quadriceps femoris, biceps femoris, and tibialis anterior of the lower limbs if they were involved. Electroencephalograms were recorded with a time constant of 0.1 second and a high-frequency cutoff of 70 Hz. On electromyograms, the filter was set with a time constant of 1.5 and a high-frequency cutoff of 3000 Hz. In addition, routine waking and asleep electroencephalogram studies were performed every 6 months during the follow-up period.

To confirm that early effective treatment is important in mental prognoses, we selected 10 of the 17 patients. These 10 patients underwent the same intelligence quotient test battery before and after the remission of their seizures, and we compared active seizure periods between those with and without decreasing points of intelligence quotients. For statistical analysis, the unpaired Student's t test was used for comparisons between the two groups. $P < 0.05$ indicated a significant difference.

Results

Prenatal and perinatal histories were unremarkable in all 17 patients. Developmental milestones had all been passed before the onset of epilepsy. However, in the detailed clinical histories, clumsiness, hyperactivity, and slow acquisition of language were implied in four patients (22%). Regarding a family history of seizure disorders, seven patients, two patients, and two patients demonstrated a history of epilepsy, epilepsy as well as febrile seizures, and febrile seizures, respectively. Thus, 53% of the patients demonstrated a family history of epilepsy within third-degree relatives (Table 1).

Clinical Seizure Manifestations

INITIAL SEIZURE TYPES A total of 16 patients experienced the onset of epilepsy with nocturnal focal motor seizures at an age range of 2.5-8 years (mean age, 5 years and 2 months) (Table 1). The remaining patient began with diurnal atonic seizures. Seizures manifested with twitching of the unilateral face and arm in 12 patients, tonic posturing of the leg in two patients, versive seizures in two patients, unilateral clonic seizures in one patient, and secondarily generalized tonic-clonic seizures in 10 patients.

NEGATIVE MOTOR SEIZURES Atypical absence or myotonic seizures developed approximately at the same time, or up to 3 years and 6 months after the onset of the focal seizures (mean time, 16 ± 11 months). Detailed seizure analyses via video polygraphic or polygraphic studies demonstrated that 15 patients manifested epileptic negative myoclonus, atonic absence seizures, and atonic seizures. Four patients experienced frequent atonic seizures leading to injuries. The remaining two patients manifested atypical absence seizures only. No patients exhibited myoclonic or myoclonic-atonic seizures. Thus, we designated these attacks as negative motor seizures in this study. In the ictal polygraphic recordings of epileptic negative myoclonus, sudden interruptions of ongoing electromyogram activity, ranging from 100-300 ms, were confirmed in all patients. Epileptic negative myoclonus involved the right arm in seven patients, left arm in two patients, both arms asymmetrically in four patients, the right leg in one patient, and both legs asymmetrically in three patients. The neurophysiologic characteristics of negative motor seizures in some patients were previously described in detail [10]. The frequencies of these attacks increased up to hundreds per day in all patients. Three patients exhibited mild dysarthria and mild weakness of the ipsilateral face and arm during periods when negative motor seizures were frequent.

PERIODIC APPEARANCE OF FOCAL SEIZURES AND NEGATIVE MOTOR SEIZURES The focal and negative motor seizures appeared and subsided in a periodic fashion during an early period of the clinical course (Fig 1). In 14 children, the periodic appearance of these attacks was evident every 4 ± 2 months, and subsided within a few months, regardless of various antiepileptic drug trials. In the remaining three patients, precise information on seizure recurrence was not available because of late introduction of the patients to our hospital. During each episode, focal seizures were followed by bouts of negative motor seizures within 1 or 2 weeks. Thus, seizures in all patients did not initially exhibit a progressive worsening, but a more protracted waxing and waning pattern.

Interictal Electroencephalogram Characteristics

The waking electroencephalograms in all patients indicated a mild, diffuse slowing of background activity and, at times, a clear accentuation over both centro-parieto-temporal areas. Epileptiform discharges were all recorded during the initial electroencephalogram examination at our hospital, displaying the right, left, and bilateral centro-parieto-temporal regions in eight, six, and three patients, respectively. The evolutional electroencephalogram changes observed after the onset of epilepsy in six patients demonstrated that centro-parieto-temporal spike discharges gradually became widespread, involving both hemispheres in a bilaterally synchronous fashion during sleep, from ages 5-8 years. When negative motor seizures developed, sleep electroencephalograms always indicated

a diffuse, semicontinuous pattern that became localized to the centro-parieto-temporal regions again after they subsided. In eight patients undergoing an all-night sleep electroencephalogram study, the spike-and-wave index during slow-wave sleep reached 65% on average (S.D., 10%), and none of them exceeded 85%.

Neuroimaging Study

Cranial computed tomography scans produced normal results in 13 patients. Cranial magnetic resonance imaging was performed in 10 children, one of whom exhibited a small, increased signal intensity lesion in the left coronal radiate. Another patient manifested a suspected malrotation of the right hippocampus. The remaining eight patients manifested normal findings of cranial magnetic resonance imaging. One patient underwent cerebral arteriography because of a suspicion of cerebrovascular accident without abnormality. Interictal ^{99m}Tc-ethyl cysteinate dimer-single photon emission computed tomography (SPECT) and ^{123}I-iomazenil SPECT were performed in five patients and one patient, respectively. In two of these five patients, the SPECT lesion corresponded to that of the predominant epileptic electroencephalogram focus.

Magnetoencephalography was performed in one patient to identify the precise anatomic region responsible for the sharp-and-slow waves in the centroparietal regions. The equivalent current dipole for the magnetic field first appeared at the primary sensorimotor cortex of the hand area, and then moved to the area where the central sulcus and sylvian fissure crossed. The area corresponded to the primary sensory cortex (S1) and the secondary sensory cortex (S2) of the facial and oral areas.

Prognosis

MENTAL PROGNOSIS Intelligence quotients during patients' first (n = 17) and last (n = 12) examinations at our hospital ranged from 61-115 with a mean of 72, and from 50-100 with a mean of 70, respectively (Table 1). The Wechsler Intelligence Scale for Children and a modified Binet test battery were performed in 7 and 3 patients, respectively, before and after the remission of seizures (Table 1). The mean active negative motor seizure period lasted 15.5 months (S.D., 6.4 months) in four patients with decreasing intelligence quotients (range, 4 to 28 points), and 5.5 months (S.D., 3.5 months) in the remaining six patients with increasing intelligence quotients (range, 0-12 points). The mean active negative motor seizure period was significantly longer in the former than in the latter group, indicating that early control of negative motor seizures was important for mental prognoses ($P < 0.05$). In addition, performance intelligence quotient changes appeared more predominant than verbal intelligence quotient changes in five of seven patients undergoing the Wechsler Intelligence Scale for Children test battery (with an increase in performance intelligence quotient in three patients, and a decrease in performance intelligence quotient in two patients).

SEIZURE PROGNOSIS Ages of occurrence for the last focal and negative motor seizures ranged from 6 years to 11 years and 11 months with a mean of 96 ± 22 months, and from 5-12 years with a mean of 93 ± 20 months, respectively. In eight patients, negative motor seizures were controlled earlier than focal seizures, whereas both seizure types were suppressed at the same time in the remaining nine patients. In one patient receiving ethosuximide early in the clinical course, negative motor seizures were immediately controlled at age 6 years and 2 months, whereas infrequent focal motor seizures continued until age 11 years and 11 months. The active seizure period, as estimated from the onset of epilepsy to final seizures, ranged from 7-83 months with a mean of 35 ± 22 months in focal seizures, and from 1 to 64 months with a mean of 23 ± 21 months in negative motor seizures. Twelve patients had successfully discontinued antiepileptic drugs during their final follow-up period. Thus, all patients demonstrated a remission of seizures before age 12 years.

Treatment

Because negative motor seizures were resistant to various antiepileptic drugs, ketogenic diet therapy, corticotropin, and oral high-dose steroids were used in three patients, two patients, and one patient, respectively. Corticotropin and oral high-dose steroid treatment produced excellent seizure control in all three patients, whereas ketogenic diet therapy led to excellent seizure control in one patient, a favorable transient effect in one patient, and insufficient control in the remaining patient.

During their clinical course, carbamazepine was administered to nine patients, none of whom exhibited improvement. Furthermore, negative motor seizures appeared in three of nine patients shortly after the introduction of carbamazepine. Finally, ethosuximide proved most effective, leading to an excellent negative motor seizure response in all 13 successive patients, with serum levels between 28-143 μg/mL (mean, 88 μg/mL) (Table 1).

Case Reports

Patient 14

The patient was a 20-year-old woman. Her birth was uneventful, and she achieved normal developmental milestones. She developed seizures, characterized by initial tonic posturing followed by unilateral clonic convulsions, at age 6 years and 4 months. An interictal electroencephalogram revealed spike-and-wave complexes in both centrotemporal regions. She received various antiepileptic drugs, including valproic acid, without success. Negative motor seizures developed at age 7 years, and they increased in frequency up to 100 times a day. A detailed description of negative motor seizures in this patient was

Table 1. **Demographic data of the 17 patients**

Patient No.	Sex	Age of Onset for FS	Age of Onset for NMS	Follow-Up Period (mo)	Previous History	FH of Epilepsy	Type of FS	Type of NMS
1	F	2 yr, 10 mo	6 yr, 2 mo	98	Transient hemiparesis		Nocturnal Sylvian seizures, GTCS	ENM of Lt upper ext, AA
2	M	3 yr, 0 mo	4 yr, 0 mo	9	FC		Sylvian seizures	ENM of lower ext, AA
3	M	3 yr, 6 mo	7 yr, 0 mo	243	FC	Epi, FC	Nocturnal Sylvian seizures, SGTCS	ENM of Rt and Lt upper ext, AA
4	F	3 yr, 10 mo	4 yr, 5 mo	115		FC	Sylvian seizures, GTS	ENM of Rt upper and lower ext
5	F	3 yr, 10 mo	5 yr, 4 mo	42			Nocturnal hemiconvulsions	ENM of Rt upper ext, AA
6	F	4 yr, 5 mo	4 yr, 6 mo	26	FC	Epi	Sylvian seizures	ENM of Rt upper and lower ext, AA
7	F	5 yr, 0 mo	5 yr, 11 mo	92			Nocturnal Sylvian seizures and adversive seizures, GTS	ENM of Rt upper ext, AA
8	F	5 yr, 1 mo	6 yr, 8 mo	58		Epi	Nocturnal Sylvian seizures	ENM of Rt and Lt upper and lower ext, AA
9	M	5 yr, 7 mo	6 yr, 7 mo	181			Nocturnal Sylvian seizures	AA
10	M	5 yr, 9 mo	6 yr, 3 mo	263			Nocturnal adversive seizure, GTS	ENM of Rt upper ext, AA
11	F	6 yr, 0 mo	7 yr, 9 mo	83			Sylvian seizures and adversive seizures, GTCS	ENM of Rt upper ext, AA
12	M	6 yr, 2 mo	6 yr, 2 mo	31			Nocturnal Sylvian seizures	ENM of Lt upper ext, AA
13	F	6 yr, 2 mo	7 yr, 6 mo	9		Epi + MR, FC	Nocturnal Sylvian seizures, GTCS	ENM of Rt and Lt upper ext AA
14	F	6 yr, 4 mo	7 yr, 0 mo	222		FC	Nocturnal Sylvian seizures, SGTCS	ENM of Lt upper ext, AA
15	F	6 yr, 6 mo	7 yr, 6 mo	102	FC		Nocturnal Sylvian seizures, GTCS	ENM of Rt upper ext
16	M	6 yr, 8 mo	7 yr, 9 mo	17			Nocturnal Sylvian seizures, SGTCS	AA
17	F	8 yr, 2 mo	8 yr, 4 mo	76			Nocturnal Sylvian seizures, GTS	ENM of Lt and Rt upper and lower ext

Abbreviations:

AA = Atonic absence seizures
ACTH = Adrenocorticotropic hormone
AEDs = Antiepileptic drugs
CP = Centro parietal
CTP = Centrotemporoparietal
CZP = Clonazepam
EEG = Electroencephalogram
ENM = Epileptic negative myoclonus
Epi = Epilepsy
ESM = Ethosuximide
ext = Extremity
F = Female
FC = Febrile convulsion
FH = Family history
FIQ = Full intelligence quotient
FS = Focal seizures
GTCS = Generalized tonic-clonic seizures
GTS = Generalized tonic seizures
IQ = Intelligence quotient
Lt = Left
M = Male
mo = Months
MR = Mental retardation
mT = Midtemporal
mT-C = Midtemporal-central
mT-CP = Midtemporal-centroparietal
mT-P = Midtemporal-parietal
NMS = Negative motor seizures
PIQ = Performance intelligence quotient
PTO = Parietal-temporal-occipital
pT-P = Posterior temporal-parietal
Rt = Right
SGTCS = Secondary generalized tonic-clonic seizures
SI-IV = Sleep stages I-IV
Sylvian seizures = FS involving the ipsilateral face, tongue, and upper extremity
VIQ = Verbal intelligence quotient
yr = Years

reported elsewhere [11]. She underwent ketogenic diet treatment, which partly controlled her seizures, but the negative motor seizures again increased in frequency at age 7 years and 9 months. Finally, she was successfully treated with high-dose hydrocortisone. She has been seizure-free since age 8 years and 10 months and free of epileptic electroencephalogram abnormalities since age 15 years. Her modified Binet intelligence quotient at age

Active NMS Period (mo)	Age at last NMS	Age at last FS	Most effective AEDs for NMS	Predominant Epileptic EEG Foci	Spike-Wave Index (%)	First IQ	First IQ Test Age	Last IQ	Last IQ Test Age
12	7 yr, 2 mo	7 yr, 6 mo	ESM	Rt mT-CP	SI: 55, SII: 40, SIII: 30, SIV: 40	FIQ, 89 (VIQ, 98; PIQ, 82)	7 yr, 4 mo	FIQ, 101 (VIQ, 101; PIQ, 101)	14 yr, 7 mo
39	7 yr, 3 mo	8 yr, 2 mo	ESM	Bilateral CTP (Lt > Rt)	SI-SIV: 60	FIQ, 76 (VIQ, 79; PIQ, 79)	8 yr, 1 mo		
9	7 yr, 9 mo	7 yr, 11 mo	ACTH	Lt > Rt mT	SI-SIV: 80	63 (modified Binet test)	7 yr, 8 mo	FIQ, 50 (VIQ, 68; PIQ, 45)	8 yr, 1 mo
15	5 yr, 8 mo	6 yr, 8 mo	ACTH	Lt CP	SI-SIV: 65	F101 (VIQ, 99; PIQ, 103)	6 yr, 8 mo	FIQ, 78 (VIQ, 81; PIQ, 79)	14 yr, 8 mo
18	6 yr, 10 mo	6 yr, 10 mo	Ketogenic diet	Lt pT-P		115 (modified Binet test)	5 yr, 8 mo	111	6 yr, 10 mo
20	6 yr, 2 mo	6 yr, 2 mo	ESM	Lt CTP		FIQ, 95 (VIQ, 94; PIQ, 97)	6 yr, 9 mo		–
3	6 yr, 2 mo	11 yr, 11 mo	ESM	Bilateral CTP (Lt > Rt)	SI-SIV: 80	FIQ, 100 (VIQ, 105; PIQ, 104)	6 yr, 2 mo	FIQ, 100 (VIQ, 100; PIQ, 100)	10 yr, 8 mo
20	8 yr, 4 mo	8 yr, 4 mo	CZP	Rt or Lt mT-C	SI: 38, SII: 32, SIII: 65, SIV: 70	97 (modified Binet test)	7 yr, 4 mo		–
4	6 yr, 11 mo	11 yr, 11 mo	ESM	Rt > Lt mT-CP		90 (modified Binet test)	6 yr, 0 mo	95	13 yr, 9 mo
3	6 yr, 6 mo	6 yr, 6 mo	ESM	Lt PTO	SI: 40, SII: 45, SIII: 45, SIV: 72	FIQ, 65 (VIQ, 91; PIQ, 43)	6 yr, 6 mo	FIQ, 78 (VIQ, 83; PIQ, 77)	14 yr, 3 mo
1	7 yr, 10 mo	7 yr, 10 mo	ESM	Lt > Rt mT-C		80 (modified Binet test)	8 yr, 0 mo	FIQ, 66 (VIQ, 69; PIQ, 69)	14 yr, 2 mo
5	6 yr, 7 mo	6 yr, 9 mo	ESM	Rt CP		FIQ, 93 (VIQ, 90; PIQ, 97)	6 yr, 9 mo		–
4	7 yr, 10 mo	7 yr, 10 mo	ESM	Bilateral CP (Rt > Lt)	SI-SIV: 70	FIQ, 78 (VIQ, 72; PIQ, 89)	7 yr, 11 mo	FIQ, 86 (VIQ, 79; PIQ, 97)	9 yr, 5 mo
22	8 yr, 10 mo	8 yr, 10 mo	High-dose steroid	Rt > Lt mT-P	SI: 75, SII: 65, SIII: 65, SIV: 45	101 (modified Binet test)	7 yr, 1 mo	73	10 yr, 0 mo
7	8 yr, 1 mo	9 yr, 5 mo	ESM	Rt > Lt mT-CP		FIQ, 61 (VIQ, 66; PIQ, 63)	7 yr, 10 mo	FIQ, 65 (VIQ, 62; PIQ, 75)	14 yr, 5 mo
17	9 yr, 2 mo	9 yr, 2 mo	Ketogenic diet	Rt > Lt mT-C		91 (modified Binet test)	8 yr, 3 mo		–
7	8 yr, 11 mo	9 yr, 4 mo	ESM	Rt CP		FIQ, 105 (VIQ, 100; PIQ, 111)	8 yr, 9 mo	FIQ, 95 (VIQ, 101; PIQ, 88)	12 yr, 3 mo

10 years of age dropped from 101 to 73 during the first examination. The Wechsler Adult Intelligence Scale-Revised test at age 20 years of age demonstrated a full-scale intelligence quotient of 67.

Patient 7

The patient was a girl aged 13 years and 6 months. Her birth was uneventful, and she achieved normal

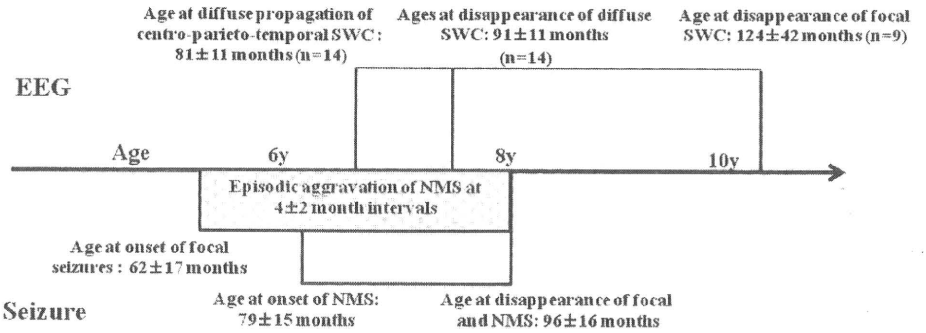

Figure 1. Episodic pattern of seizure aggravation. Fourteen patients exhibited the episodic appearance of both focal and NMS at 4 ± 2 month intervals. The follow-up period ranged from 12-263 months (mean, 98 ± 8 months). EEG: electroencephalogram; NMS: negative motor seizures; SWC: spike-and-wave complexes.

developmental milestones. At age 5 years, she developed a focal motor seizure involving her right eyelids, face, and arm, lasting for 5 minutes during sleep. An interictal electroencephalogram revealed active sharp-and-slow wave complexes in both centroparietal regions synchronously, with a left-sided predominance. The diagnosis of epilepsy was rendered at a local hospital, and carbamazepine was initiated. However, the seizures persisted despite the administration of carbamazepine and then valproic acid. She was referred to our hospital at age 5 years and 11 months, when she manifested frequent epileptic negative myoclonus of the right arm, at times leading to atypical absence seizures (Fig 2). We added ethosuximide to the valproic acid, which fully controlled the epileptic negative myoclonus and led to a marked improvement of the interictal electroencephalogram abnormalities (Fig 3A,B). Since then, she has experienced brief nocturnal focal motor seizures approximately every 3-4 months, despite the combination of zonisamide and phenytoin until age 11 years and 11 months, but she never experienced negative motor seizures after the introduction of ethosuximide. No deterioration of intelligence quotient, as measured by the Wechsler Intelligence Scale for Children-Third Edition test, had occurred when intelligence quotients were compared between age 6 years and 2 months and age 10 years and 8 months. The antiepileptic drug was successfully discontinued at age 13 years.

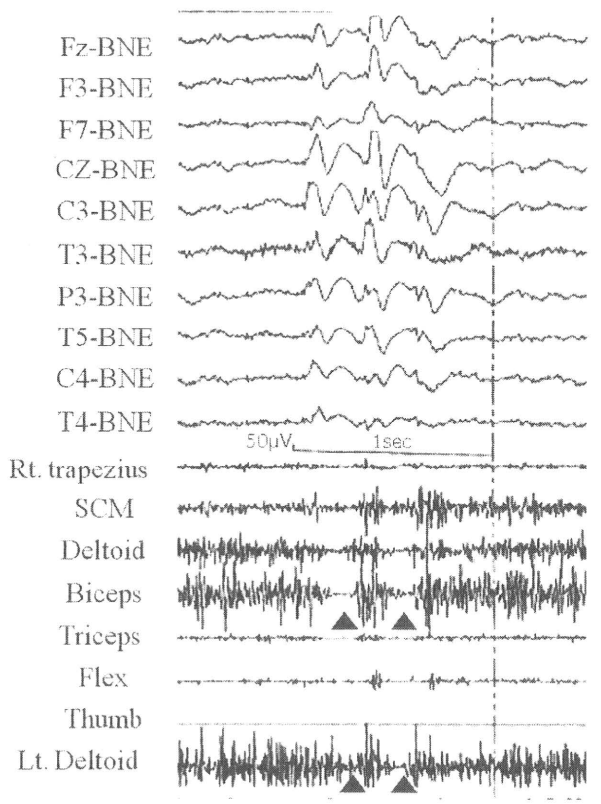

Figure 2. Ictal polygraph of epileptic negative myoclonus in Patient 7 at age 6 years and 2 months. When asked to stretch both arms in front of herself and count numbers, her left arm dropped, and she discontinued counting. On the surface electromyogram, an interruption of the ongoing electromyogram involving the biceps deltoid and triceps muscles of her right arm, lasting 100-400 ms, corresponded to the epileptic negative myoclonus. BNE: balanced noncephalic electrode; Flex: flexor forearm muscles; Lt.: left; Rt.: right; SCM: sternocleidomastoideus.

Discussion

This study revealed that in 12 of our patients, initial focal seizures with atypical benign partial epilepsy of childhood occurred mostly during sleep, and resembled seizures of benign epilepsy of childhood with centrotemporal electroencephalogram foci, involving the orofacial areas and unilateral limbs. However, the remaining five patients manifested either focal tonic seizures involving only one limb, or versive seizures occurring frequently during the daytime, which was unusual in those with benign epilepsy of childhood with centrotemporal electroencephalogram foci. Both focal and negative motor seizures, including epileptic negative myoclonus, atypical absence seizures, and atonic seizures, were resistant to antiepileptic drugs, and appeared every 4 ± 2 months. Negative motor seizures usually developed several months after the onset of focal seizures.

By means of ictal video/polygraphic investigations, we demonstrated that epileptic negative myoclonus, atypical absence seizures, and atonic seizures are primary seizure types in atypical benign partial epilepsy of childhood. The interruptions of ongoing electromyogram activity

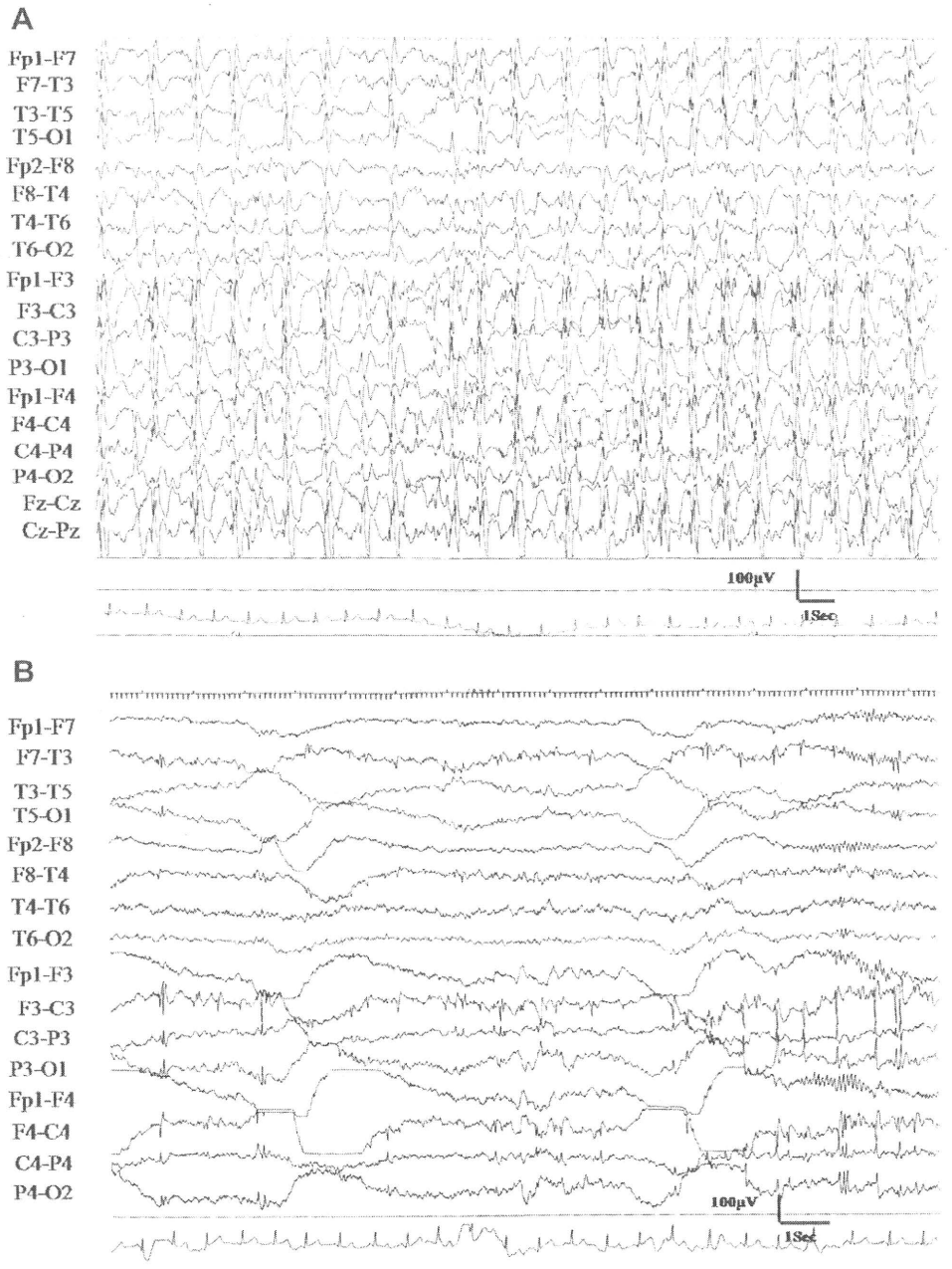

Figure 3. Interictal sleep electroencephalograms before and after the introduction of ethosuximide in Patient 7. (A) Before the administration of ethosuximide, almost continuous, diffuse sharp-and-slow wave complexes were recorded, with maximum accentuation over both centroparietal regions, and with a left-sided predominance. (B) After the introduction of ethosuximide, the sleep electroencephalogram findings dramatically improved, leaving infrequent bilateral centroparietal sharp-and-slow wave complexes with a left-sided predominance.

without any myoclonic component in these attacks led us to designate them as negative motor seizures in this study [9,10,12]. The neurophysiologic mechanism underlying epileptic negative myoclonus has been the subject of speculation [9,10,14-16]. A magnetoencephalographic study strongly suggested that the sensorimotor cortex is a primary focus of the attack. Epileptic negative myoclonus was observed not only in atypical benign partial epilepsy of childhood, but in other symptomatic focal epilepsies with a heterogeneous etiology, and it appears to be pharmaco-resistant despite differences in etiology [17]. Epileptic negative myoclonus sometimes evolved into atonic absence seizures when the sharp-slow discharges became generalized, and were sustained in a rhythmic, successive fashion [10,12]. When these negative motor seizures occurred very frequently, patients appeared dazed and constantly dropped their heads or arms, as previously described in peculiar nonconvulsive status epilepticus by Ohtsuka et al. [18]. In addition, three patients in that study experienced sustained neurologic deficits, including mild dysarthria and ipsilateral facial and arm paresis, when the negative motor seizures were frequent. These neurologic deficits disappeared after successful treatment. These transient

neurologic deficits indicate that negative motor seizures involve the primary sensorimotor cortex, and occur so frequently as to impair mental function and quality of life [10]. Our results suggest that intelligence quotients, and especially performance intelligence quotients, decrease permanently if the period of active negative motor seizures is prolonged, whereas intelligence quotients are maintained if the period of active negative motor seizures is shorter. As described in our Case Reports, intelligence quotients did not deteriorate even if infrequent focal motor seizures persisted.

In a number of reports, carbamazepine potentially induced peculiar myoclonic or atonic seizures during the clinical course of benign epilepsy of childhood with centrotemporal electroencephalogram foci [5-8]. Most recently, the induced seizures were recognized as epileptic negative myoclonus according to a polygraphic study, and were reported to disappear when carbamazepine was discontinued. Because the clinical and electroencephalogram features of these patients were identical to those with atypical benign partial epilepsy of childhood, some authors suggest that atypical benign partial epilepsy of childhood is an atypical evolution of benign epilepsy of childhood with centrotemporal electroencephalogram foci modified by carbamazepine [6]. In our series, three patients developed epileptic negative myoclonus shortly after starting carbamazepine. However, the withdrawal of carbamazepine alone did not lead to a decrease in attacks, and the remaining 14 patients developed epileptic negative myoclonus without any relationship to the administration of carbamazepine. As we previously reported, the pharmacologic responses to carbamazepine and ethosuximide in epileptic negative myoclonus are quite similar to those in absence seizures [9]. Thus, carbamazepine can aggravate epileptic negative myoclonus, but it is not a causal agent in transforming benign epilepsy of childhood with centrotemporal electroencephalogram foci to atypical benign partial epilepsy of childhood. The episodic aggravation of negative motor seizures in a periodic fashion made it difficult to judge the exact pharmacologic response. Corticotropin and high-dose oral steroids appeared more effective than ethosuximide in frequent negative-motor seizures, and ketogenic diet therapy also appeared effective despite our limited number of patients. The introduction of ethosuximide in our 11 patients with atypical benign partial epilepsy of childhood completely controlled the negative motor seizures, and markedly improved the electroencephalogram findings. However, ethosuximide could not alleviate the focal motor seizures appearing in an episodic fashion in the one patient who was treated with ethosuximide immediately after negative motor seizures developed. It is reasonable to suggest that ethosuximide is only effective for absence seizures.

We stress that the early diagnosis of atypical benign partial epilepsy of childhood is important because the wrong treatment strategy (aiming strictly to control focal seizures) can aggravate the seizures, and lead to pseudointractable or even "pseudocatastrophic" epilepsy, with frequent drop attacks for years [3,13]. Moreover, unnecessary surgical interventions may be considered if "pseudocatastrophic" seizures persist for more than 2 years without responding to more than two or three antiepileptic drugs [19].

The nosologic situation of atypical benign partial epilepsy of childhood among various discrete epileptic syndromes has been discussed for a long time, but it is not officially recognized by the International League Against Epilepsy. Here, we demonstrated that atypical benign partial epilepsy of childhood does not fulfill the electroencephalogram criterion of continuous spike-and-wave complexes during slow sleep, and is not caused by inadequate treatment with carbamazepine in those with benign epilepsy of childhood with centrotemporal electroencephalogram foci. Thus, atypical benign partial epilepsy of childhood should not necessarily be considered an atypical form of continuous spike-and-wave complexes during slow sleep or an atypical evolution of benign epilepsy of childhood with centrotemporal electroencephalogram foci.

A limitation of this study may involve the five patients with subnormal intelligence quotients and two patients with a minor magnetic resonance imaging abnormality during their first examination, casting into question the homogeneity of etiologies. Doose et al. proposed the concept of hereditary impairment of brain maturation, which would underlie childhood epilepsies with multifocal sharp waves, including benign epilepsy with occipital paroxysms, benign epilepsy of childhood with centrotemporal electroencephalogram foci, continuous spike-and-wave complexes during slow sleep, Landau-Kleffner syndrome, and atypical benign partial epilepsy of childhood [20]. According to this concept, genetically determined focal cortical hyperexcitability, in combination with other acquired or hereditary factors, can produce a variety of these subsyndromes. In our previous study, patients with early-onset benign epilepsy of childhood with centrotemporal electroencephalogram foci, and with an onset of epilepsy at less than age 5 years, experienced more frequent and resistant seizures despite their ultimate remission before adolescence [21]. Those patients manifested more frequent, mild neurobehavioral disorders than those with Panayiotopoulos syndrome and a comparable age at onset of epilepsy, suggesting that preexisting factors contribute to the genesis of earlier onset seizures in benign epilepsy of childhood with centrotemporal electroencephalogram foci [22]. This hypothesis may also apply to those with atypical benign partial epilepsy of childhood, because over 50% of patients had a family history of epilepsy, and at least 30% manifested borderline developmental problems before the onset of epilepsy. In general, patients with atypical benign partial epilepsy of childhood first develop seizures before age 5 years, and tend to continue focal motor seizures despite the immediate control of negative motor seizures by the introduction of ethosuximide.