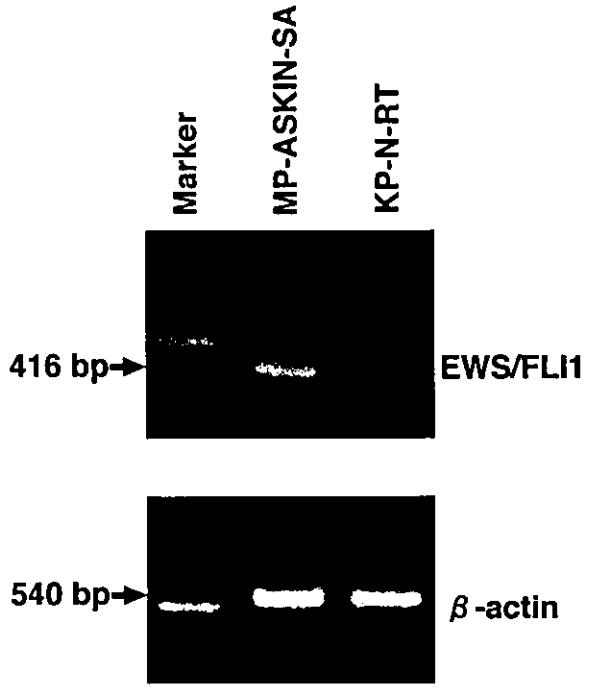

Fig. 5. Detection of the *EWS/FLI1* transcript in the MP-ASKIN-SA cell line by RT-PCR. The MP-ASKIN-SA cells had an *EWS/FLI1* transcript of approximately 420 bp. The neuroblastoma KP-N-RT cell line was used as a negative control. The amplification of β-actin was observed in each sample, confirming the RNA quality.

3.5. c-myc *mRNA expression*

The *c-myc* mRNA of the MP-ASKIN-SA cell line and the HL60 cell line was highly expressed (Fig. 7). In contrast, *c-myc* mRNA from the peripheral lymphocytes of a healthy volunteer was not highly expressed.

3.6. FAK *mRNA expression*

Expression of FAK mRNA was 12-fold higher in the MP-ASKIN-SA cell line than in the fibroblasts of a healthy volunteer. Expression of FAK mRNA was also high in other ESFT cell lines, ranging between 5 and 28 times the expression level in the negative control (Fig. 8; Table 2). Neither the neuroblastoma cell line SJ-N-KP nor the undifferentiated sarcoma cell line A204 expressed high levels of FAK.

4. Discussion

Only a few Askin tumor cell lines have been well documented [18,19]. We established a new Askin tumor cell line, MP-ASKIN-SA, from the thoracic metastatic tissue of a 13-year-old Japanese boy, who presented with a relapsed tumor.

Differentiating ESFT from other small round tumors by morphology alone is difficult. In these cases, immunohistochemical and genetic studies can lead to an accurate diagnosis. Immunohistochemical studies have demonstrated that HBA71 has a striking specificity for ESFT. The t(11;22)(q24;q12) is identified at the karyotypic level in approximately 80% of the cases of ESFT [23,24]. Conventional chromosomal analysis, however, did not demonstrate this characteristic translocation in the MP-ASKIN-SA cells.

This translocation generates an *EWS/FLI1* chimeric transcript that is comprised of the 5′ EWS region and the 3′ FLI1 region [2]. This chimeric transcript has been molecularly identified in approximately 90% of ESFT cases [2,3,25]. Using RT-PCR, the chimeric transcript was detected in the MP-ASKIN-SA cells, indicating that detection of this chimeric gene is a more sensitive diagnostic method. The existence of the chimeric *EWS/FLI1* transcript identified this cell line as ESFT. At least 18 *EWS/FLI1* transcript types have been identified on the basis of the exact fusion exon sites between EWS and FLI1. The fusion of exon 7 of EWS with exon 6 of FLI1, which was revealed to occur in this cell line, is called an *EWS/FLI1* type 1 transcript and accounts for approximately 65% of the cases of *EWS/FLI1* fusion [26]. The resulting chimeric protein probably functions as a constitutive transcriptional activator and is likely to cause the initiation of ESFT tumorigenesis [4]. Only a few studies, however, have investigated the genetic aberrations that cause

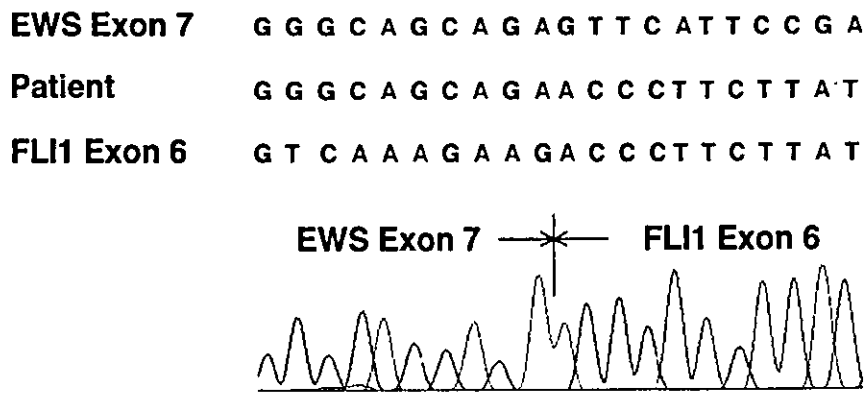

Fig. 6. Nucleotide sequence of *EWS/FLI1* junctions in the MP-ASKIN-SA cell line. Sequencing of the amplified cDNA confirmed that EWS exon 7 fused to FLI1 exon 6.

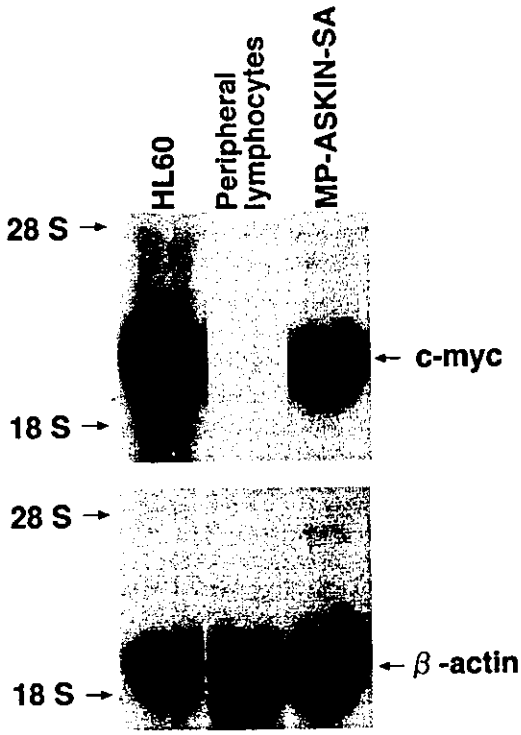

Fig. 7. *c-myc* expression. *c-myc* mRNA of the MP-ASKIN-SA cell line was greatly overexpressed, as compared with the negative control. The *β-actin* gene was used for an internal control.

the malignant progression of ESFT. These studies have implicated mutations of the *TP53* gene [14], INK4A deletions [27], and increased serum intracellular adhesion molecule-1 levels [28] in the malignant progression of ESFT.

ESFT is a systemic disease. Even though the majority of patients have no clinical evidence of metastatic disease upon diagnosis, it must be assumed that every patient has microscopic metastasis. To elucidate the molecular biologic mechanism of spreading and malignant progression in ESFT, we investigated the expression degree of two genes in the MP-ASKIN-SA cell line. One gene is *c-myc*, which is known to be related to the malignant progression of various cancers [6]. Sollazo et al. [5] suggested that *c-myc* is related to malignant progression in Ewing sarcoma clinical samples. In our experiment, a high level of *c-myc* mRNA was detected by Northern blot analysis, although the possibility that this occurred during in vitro culture cannot be excluded. Taken together, these findings suggest that *c-myc* overexpression is strongly associated with poor prognosis in ESFT.

The other gene that we investigated is *FAK*. Increased *FAK* activity correlates with focal adhesion formation and cell migration. *FAK*-null fibroblasts are defective in cell migration [8]. Taken together, these findings indicate that *FAK* is a signaling component that plays a central role in cell migration. A high level of *FAK* mRNA was detected in the MP-ASKIN-SA cell line by Northern blot analysis. To our knowledge, this is the first report of a possible relationship between the *FAK* gene and poor prognosis in ESFT. We also

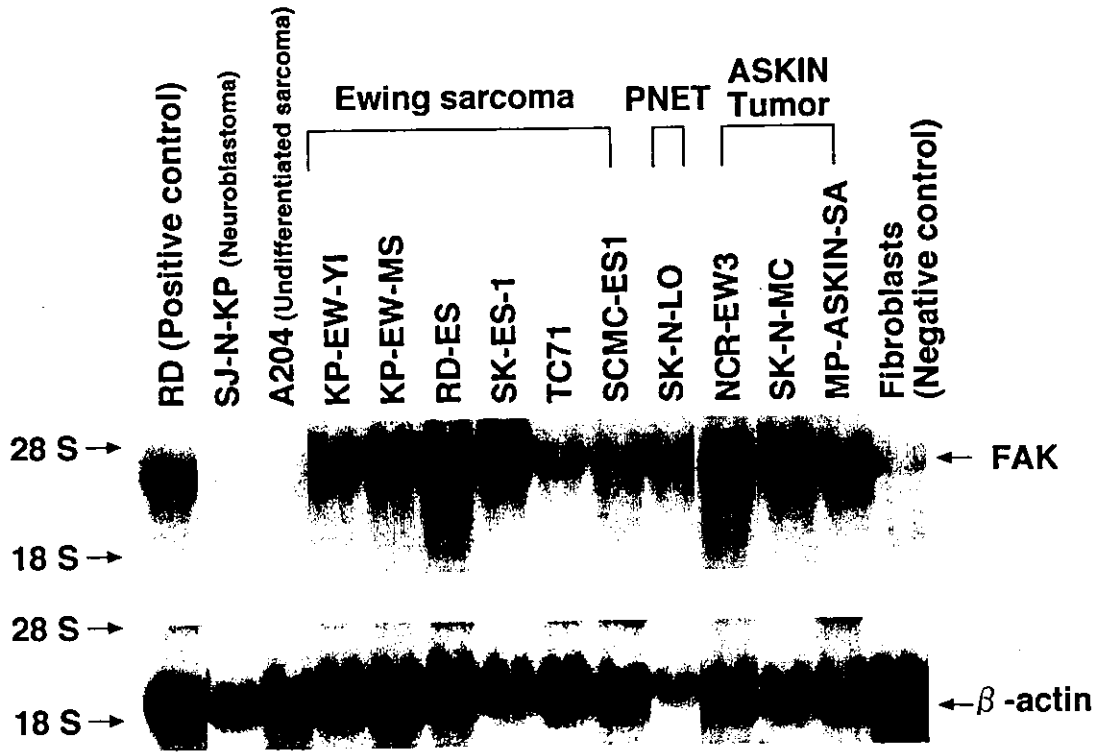

Fig. 8. Focal adhesion kinase (*FAK*) expression. *FAK* mRNA of the MP-ASKIN-SA cell line was highly expressed, as compared with the negative control. *FAK* mRNA was also highly expressed in each of the nine other ESFT cell lines.

Table 2
Quantitative comparison of FAK expression among the RD cell line as a positive control, 10 ESFT cell lines, and fibroblasts of a healthy volunteer as a negative control

Material	Ratio of *FAK* expression
RD cell line (positive control)	100
The ESFT cell lines (mean, $n = 10$)	322 (range: 109–617)
Ewing sarcoma cell lines (mean, $n = 6$)	258 (range: 109–617)
PNET cell line ($n = 1$)	420
Askin tumor cell lines (mean, $n = 3$)	416 (range: 272–506)
Fibroblasts from a healthy volunteer (negative control)	22

found that *FAK* mRNA was highly expressed in nine other ESFT cell lines. Since the *FAK* mRNA was not highly expressed in other representative malignant tumor cell lines, neuroblastoma, and undifferentiated sarcoma, the possibility that this occurred during in vitro culture can be excluded.

FAK is a normal gene with detectable levels of mRNA in all adult tissues [29], and there is no evidence of mutations that would render it a transforming gene [30]. In normal cells, *FAK* might be a sensor of cell adhesion, limiting growth in an anchorage-dependent manner, whereas in transformed cells, overexpression of *FAK* may override this regulation and allow anchorage-independent growth in the absence of cell adhesion. The *EWS/FLI1* fusion protein acts as a transactivator of the *c-myc* gene promoter, suggesting that the *EWS/FLI1* fusion gene affects upregulation of *c-myc* expression [31]. In the future, it is important to elucidate whether *FAK* expression in ESFT is the result of *EWS/FLI1* action, the result of some other alteration in the tumors, or a basic expression feature of the cellular environment.

Both the c-*myc* and *FAK* genes are located on chromosome 8. The most frequent secondary change is trisomy 8, followed by +12, +2, +5, +9, +15, and gain of material from the long and short arms of chromosome 1 [25]. Trisomy 8 has been detected in more than half of ESFT cases [26]. It is possible that these additional copies of the chromosomes increase the function of particular genes located on this chromosome. *FAK* may be an ideal target for therapeutic selection of ESFT. First, in vitro introduction of *FAK* antisense oligonucleotides results in attenuation of *FAK* transcription, loss of cell adherence, and ultimate apoptosis [32]. Second, normal cells treated with *FAK* antisense oligonucleotides are not as sensitive to apoptosis as tumor cells [32]. Further investigation of *FAK* as a therapeutic target and as a clinical tumor marker appears to be warranted.

Acknowledgments

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1．けいれんの診療

4．けいれんと脳波

大塚頌子*
Yoko Ohtsuka

Key words：脳波，てんかん発射，脳侵襲

小児のけいれんの原因は多彩であり，基盤となる病変の病態生理に基づき，急性けいれんと慢性反復性けいれんに分類される。脳波検査はけいれんの診断，治療のための有力な手段であるため，日常診療に脳波検査をどのように応用するかを熟知する必要がある。

【急性けいれん】

1．急性脳侵襲と脳波

急性けいれんでは原因が何であれ，急性脳侵襲の程度と脳波所見の間に，図1のような関係があるといわれる[1]。ここでいう突発波はてんかんでみられるてんかん発射と意義は異なり，急性脳侵襲に反応性の突発波と考えられるが，波型から両者を区別することは難しい。そこで，急性けいれんの急性期に突発波が認められたときには，反応性の突発波の可能性と急性脳侵襲の前から存在したてんかん発射の可能性がある。前者であれば，一過性で，経過を追うと消失し，後者では急性期を過ぎても同様に存続する。また，急性期に突発波はなく，のちに出現するときには，後遺症としてのてんかん発射と考えられる。

2．有熱時けいれん

初めての有熱時けいれんの場合の診断，治療に関する脳波の意義について考えたい。この状況では一般的には以下のような可能性がありうる。①熱性けいれん，②急性脳炎・脳症など中枢神経感染症の初期症状，③てんかんの初発発作，である。

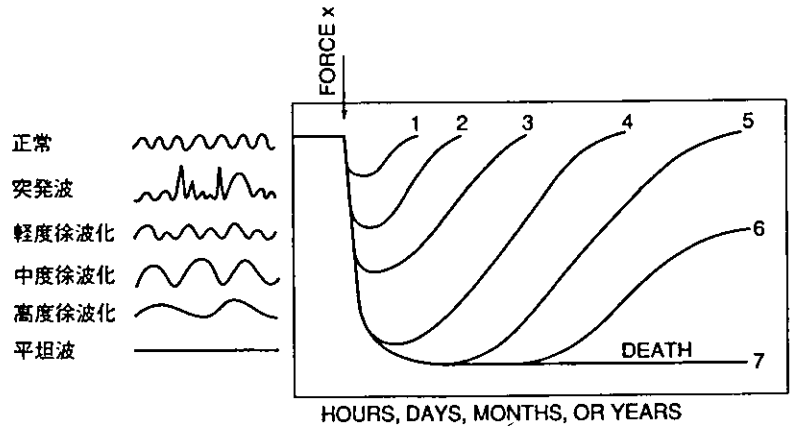

図1 脳侵襲と脳波所見（Gibbs, Gibbs[1] 1951より一部改変）
図左は侵襲の強さに応じた脳波所見（下にいくほど程度が強い）。図右は侵襲の加わったときの脳波所見の程度と回復過程を示した。矢印のところで侵襲が加わった。

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1）熱性けいれん

熱性けいれんが短時間でその後の回復が速やかな場合には，脳波では左右差や，徐波の著明な増加はなく，正常所見を呈する。ただし，発作直後であれば，単純性熱性けいれんでも徐波の全般的な増加はある程度ありうる。しかし，発作後24時間以上経過しても不相応に徐波が多い場合には，急性脳炎・脳症の可能性も念頭に経時的変化をみる必要がある。

複雑性熱性けいれんでは，けいれんに左右差が認められる場合には，発作直後の脳波で左右差が認められる可能性がある。また，けいれんが長時間持続したときには，脳波でそれに相応する徐波の増加が予想される。そのような場合には，とくに急性脳炎・脳症との鑑別が重要であるが，脳波所見そのものに特異性はなく，症状の全体像と症状と脳波の関連や脳波の経時的変化により，包括的に診断する。すなわち，脳波の徐波や左右差が意識障害を伴って数日続くときは急性脳炎・脳症の可能性を考慮すべきである。

2）急性脳炎・脳症など中枢神経感染症

急性脳炎・脳症の脳波所見は基本的には高振幅徐波の出現であり，意識障害が強ければ，覚醒・睡眠の変化も認められず，睡眠に特有な紡錘波などの波型も認められない。通常，脳炎・脳症では脳波に左右差は乏しいが，脳圧亢進によりテント切痕ヘルニアが起これば，脳波に左右差が出現することがある。急性脳炎・脳症では徐波の程度はけいれんの程度より意識障害の程度に相関が強い。そこで，けいれん自体は軽いのにその後の意識障害が強く，また長引き，脳波でも高振幅徐波が強いときには，単に熱性けいれん後の徐波ではなく，脳炎・脳症を示唆する所見と考えられる。

急性脳炎・脳症は後遺症としてのてんかんを発症することがあるが，急性期から間隔をおかず難治てんかんに移行する特異な病型が知られている[2]。この場合は脳炎・脳症の一般的症状とともに，急性期にけいれんが頻発するのが特徴で，脳波では広汎性，または左右差を示す高振幅徐波の持続に部分発作の発作時脳波が挿間する。

3）てんかんの初発発作

てんかんの初発発作が有熱時に起こることも多い。乳児期の有熱時けいれんでは，乳児重症ミオクロニーてんかんがよく知られている。基本的にはてんかんでは脳波にてんかん発射を認めるが，てんかんであっても必ずしも全例にてんかん発射が認められるとはかぎらない。たとえば，乳児重症ミオクロニーてんかんでは，乳児期には，とくに発熱時にけいれんが頻発するが，1歳頃までは脳波にてんかん発射は検出しにくいことが特徴的であり，注意を要する[3]。また，一般的にけいれん直後にはてんかん発射が出現しにくいため，てんかん発射の有無を判定するには，けいれん後少なくとも2週間以降に検査するのがよい。ただし，発作直後にてんかん発射が出やすい症例もあり，発作後早期と2週間以降の両方の時に検査できればよりよい。

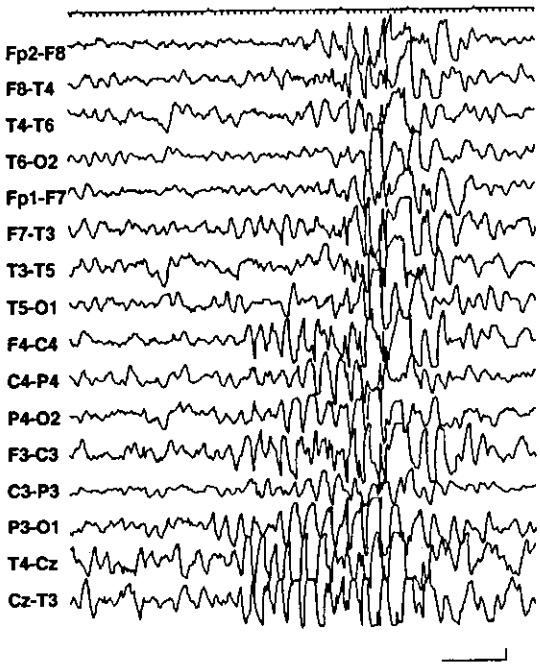

図 2　Pseudo petit mal discharge

棘波を伴った3〜5 Hz広汎性不規則徐波群発で，睡眠段階1と2のみにみられ，完全に覚醒しているときには認められない。棘波は中心部に最も強い。1歳未満と8歳以上ではほとんどみられず，1〜2歳に出現のピークがある。図に熱性けいれんの1歳11か月の男児の睡眠時にみられたpseudo petit mal dischargeを示した。較正標は1秒，50 μV

熱性けいれんとてんかんの鑑別では狭義のてんかん発射の出現を見定める必要がある。熱性けい

れんではしばしばpseudo petit mal discharge, hypnagogic paroxysmal spike-wave activity[4]が出現するが，これは狭義のてんかん発射ではないので注意深く区別しなくてはならない（図2）。

初めての有熱時けいれんで脳波検査を行い狭義のてんかん発射が認められたときの対応については，必ずしも一定の見解はない。てんかん発射に基礎波の左右差や著明な徐波化など脳障害を示唆する所見を伴うとき，また発達遅滞や神経学的異常を伴うときは，のちに無熱性けいれんを発症する可能性が高くなる。また，狭義のてんかん発射を有する熱性けいれんの症例ではてんかん発射のない症例より，のちにてんかんを発症する率が高いというデータも示されており[5]，てんかん発射を認める場合には，注意深い経過観察を要する。

3．急性代謝障害

小児では低血糖，電解質異常，脱水，水中毒などの代謝異常でけいれんが出現しやすい。個々の病態に特有の脳波所見はないが，一般に徐波の増加が認められ，とくに低血糖では高振幅徐波が出現する。小児の低血糖ではケトン性低血糖症がよく知られている。

電解質異常によるけいれんは新生児けいれんでよくみられ，低Ca血症，低Mg血症によるけいれんが多い。この場合も脳波の徐波化がみられるが，そのほかに突発性波型の出現も経験される。低Na血症や水中毒でも高振幅徐波や突発性波型が出現するといわれる。

このように，急性代謝異常では脳波の徐波化とともに突発性波型の出現が報告されている。そこで，急性期にてんかん発射を認める場合には，その意義を慎重に考慮しなければならない。すなわち，てんかん発射はそれ以前から存在した可能性と，急性期の一過性の反応の可能性がある。前者の場合にはローランド発射や光突発反応などの素因性波型のことと，もともとの器質性病変を反映した波型の可能性がある。対応としては，まず経過観察により一過性の反応であることがわかれば，抗てんかん薬持続投与は不要である。持続的に出現する場合には，臨床的・脳波学的に経過観察し，必要に応じて抗てんかん薬の持続内服を行うこともある。

4．ウイルス感染による良性けいれん

最近ロタウイルスなどのウイルス感染により，下痢に伴いけいれんが頻発する状態が報告されている[6]。これは必ずしも電解質異常や脱水をきたさず出現し，その予後は良好であることが知られている。このような状態のとき一般的には発作間欠時にてんかん発射は認められない。急性期にはけいれんが頻発するため，抗てんかん薬の投与は急性期のけいれんの治療としては適切であるが，長期予後が良好であることから，抗てんかん薬の持続内服は行わず，慎重に経過観察すればよい。

5．頭部外傷

小児の急性けいれんのなかで頻度が比較的高いのは頭部外傷による急性けいれんである。けいれんを起こす頭部外傷の種類は脳振盪，脳挫傷，頭蓋内出血があり，脳振盪では脳波は全般性の徐波化がみられるが，脳挫傷，頭蓋内出血では病変部位や病変の性質により，全般性の徐波化以外に左右差や局在性の徐波や低振幅がみられる。現在では神経画像診断が手軽にどこでもできるようになったが，画像検査はあくまで構造的異常を反映するにすぎないので，機能異常を反映する脳波検査を組み合わせて頭部外傷の病変の性質や部位を判定することが重要である。

さて，頭部外傷の急性期にてんかん発射が認められることは例外的で，その場合にはもともと存在した可能性が高い。とくに，前述の素因性の波型が検出された場合は頭部外傷とは無関係である。なお，頭部外傷で急性期にけいれんが起きた場合にはのちに外傷後てんかんを発症する率が高いといわれており[7]，急性期以後の脳波の経時的追跡が必要である。

【慢性反復性けいれん】

1．てんかんとてんかん発射

慢性反復性けいれんの代表的な疾患はてんかんである。てんかん性の確認のためには臨床的には発作の常同性，反復性が重視されるが，客観的指

表　初診時脳波検査におけるてんかん発射検出率

てんかん分類	症例数	てんかん発射（+）	てんかん発射出現率（%）
局在関連性てんかん	183	131	71.6
特発性	18	18	100
症候性	50	31	62
潜因性	115	82	71.3
全般性てんかん	115	97	84.3
特発性	79	63	79.7
潜因性/症候性	25	25	100
症候性	11	9	81.8
未決定てんかん	6	5	83.3
分類不能	4	0	0
計	308	233	75.6

標としては発作間欠時脳波のてんかん発射の確認が重要である。小児てんかんではてんかん発射の出現率が比較的高率であり，診断上重視される。表に岡山大学小児神経科で加療したてんかん患者のてんかん症候群別の初診時のてんかん発射の出現率を示した[8]。

てんかんのなかには発作間欠時のてんかん発射の検出しにくいものもある。その原因の一つはてんかん原性焦点部位に関連することである。Penfield と Jasper[9]によると，前頭葉傍矢状溝などの深部にある場合，抑制系が賦活される場合，高振幅放電の代わりに低振幅速波活動が出現する場合には頭皮上脳波では変化を検出しにくく，electrically silent seizure となるという。このような場合には診断確定のため，発作時脳波の検討を要するため，ビデオ・脳波・筋電図同時記録による発作時脳波を施行する。

てんかんであってもてんかん発射が検出しにくいもう一つの要因として，年齢要因があげられる。けいれん準備性は幼児期に最も高く，乳児期前半と成人では低い。そこで，小児てんかんでは乳児期や年長児にてんかん発射が検出されない場合，それのみでてんかんを除外しにくく，診断は臨床像を含め総合的に行う。

また，てんかん発射が検出される場合にも，乳児期に有熱時けいれんなどを発症し，その時点でてんかん発射がなく，脳波検査を経時的に行うと，数年後に発作はないのにローランド発射などの年齢依存性のてんかん発射が出現することがある。このような場合には，てんかん発射が認められたからといって，以前のけいれんがてんかん性であったとはいい難い。

2．脳波検査の条件，賦活法

てんかん発射の検出には脳波検査の条件も重要で，覚醒・自然睡眠を含めた完全記録によって判定する必要がある。また，各種賦活を駆使することも重要で，発作の誘因などの病歴を詳しく調査し，光，図形，ゲームに関連する発作では光刺激，図形賦活を十分行ったり，実際にゲームをしながら脳波記録をすることが重要である。

若年性ミオクロニーてんかんや覚醒時大発作てんかんでは通常の脳波記録でてんかん発射がでにくい場合でも，断眠賦活が有効なことがある。

もやもや病など脳血管不全を基盤にしたてんかんの可能性のあるとき，または脳血管不全の虚血発作とてんかん発作の鑑別が必要な場合には，過呼吸賦活を注意しながら行い，rebuild-up の有無を検討することが重要である。ただし，脳血管不全の診断が確定した後には，むやみに過呼吸賦活をして不必要な負荷をかけることのないように注意する。

また，小児欠神てんかんでは過呼吸賦活を十分行い，発作の誘発とてんかん発射の誘発を検討することは周知のことである。

3．てんかん発射とそれ以外の波型の鑑別

最後に，てんかん発射の診断には，熱性けいれんで出やすい pseudo petit mal discharge や狭義のてんかん発射に属さない wave-spike phantom,

positive spikes, psychomotor variant, small sharp spikes などの波型を狭義のてんかん発射と正確に区別する必要がある。

4．てんかんと非てんかん性発作現象の鑑別

原則的には非てんかん性発作現象では発作間欠時にはてんかん発射が認められない。しかし，小児期にはてんかん発作がなくても，素因と関連する良性のてんかん発射を示す症例や，非てんかん性発作現象とは無関係に脳障害の徴候としてんかん発射が認められることがある。このような場合にはてんかん発射があるために，非てんかん性発作現象をてんかん発作と診断してしまうことがある。

また，急性けいれん，慢性反復性けいれんを問わず，てんかん以外の病態で起こるけいれんであっても，それが脳起源のけいれんであれば，発作時脳波ではてんかん発作と類似の変化を呈するので，発作時脳波のみで鑑別はできない。

このように脳波は有力な検査法であるが，常に臨床症状や，他の検査所見とも関連づけて，総合的に判断することが重要である。また，脳波検査をいつ，どのように施行すべきか，その所見をどう解釈すべきかよく考えて行う必要がある。

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Original article

Paroxysmal movement disorders in severe myoclonic epilepsy in infancy

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Abstract

We report on the electroclinical findings and the results of a molecular genetic study of a patient with typical severe myoclonic epilepsy in infancy (TSME) and three with borderline SME (BSME) who showed paroxysmal movement disorders, such as choreoathetosis, dystonia and ballismus, during their clinical course. BSME was defined as a clinical entity that shares common characteristics with TSME but lacks myoclonic seizures associated with ictal EEG changes. When the paroxysmal movement disorders were first observed, all the patients in this study were being treated with polytherapy including phenytoin (PHT), and these abnormal movements disappeared when PHT was discontinued or reduced. However, on other occasions, two of our cases also showed the same abnormal movements even when not being treated with PHT. One patient with TSME and two of the three patients with BSME had *SCN1A* gene mutations that lead to truncation of the associated protein. We conclude that paroxysmal movement disorders seen in SME patients were closely related to their AED therapy, especially the use of PHT. It is thought that patients with both TSME and BSME have some predisposition toward paroxysmal movement disorders, and that this predisposition is partly related to sodium channel dysfunction, although some other factors might influence the occurrence of this phenomenon.

Keywords: Severe myoclonic epilepsy in infancy; Paroxysmal movement disorder; Phenytoin; Antiepileptic drug; *SCN1A* mutation; Sodium channel

1. Introduction

Severe myoclonic epilepsy in infancy (SME) is an epileptic syndrome that is characterized by prolonged generalized or alternating hemiconvulsions beginning in infancy [1]. Later on, patients begin to suffer myoclonic seizures and/or atypical absences with eyelid myoclonias. Some researchers, ourselves included, have noted the existence of patients who appear to have SME but lack myoclonic seizures associated with ictal EEG changes [1–5]. Since most of these atypical cases have erratic and segmental myoclonias that are not associated with ictal EEG changes, many other researchers do not differentiate these atypical cases from typical SME cases and diagnose all of them as having SME. In this paper, we refer to typical SME cases as typical SME (TSME) and the above-mentioned atypical cases as borderline SME (BSME). The relationship between TSME and BSME has not yet been fully elucidated. Recently, molecular genetic studies have been performed on patients with SME, and a high rate of mutations in the voltage-gated sodium channel α1-subunit (*SCN1A*) gene has been reported [6,7]. We also performed a genetic study on patients with SME, which included TSME and BSME, and found a high rate of mutations in the *SCN1A* gene [8].

Recently, Saito et al. reported phenytoin-induced choreoathetosis in patients with SME [9]. We also observed similar movement disorders in one patient with TSME and three patients with BSME. We report herein on the electroclinical findings on these patients, as well as the results of a molecular genetic study we performed on these patients. Finally, we discuss the possible causes of their involuntary movements.

2. Case reports

2.1. Case 1

This patient is a male with BSME, 14 years and 2 months old. At 11 years, 6 months of age (August 9, 1999), he was

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admitted to our hospital because of an increase in convulsive seizures and segmental myoclonias without ictal EEG changes. On admission, he was being treated with 1200 mg/day of valproate (VPA) and 1500 mg/day of potassium bromide (KBr). Although he did not have definite hemiparesis, he had tended to avoid using his left hand since he was about 8 years old. Phenytoin (PHT) therapy was started on August 24, 1999. On September 3, 1999, 3 days after we had increased the dosage to 200 mg/day (serum level: 9.5 μg/ml), he suddenly started to exhibit involuntary movements in the left upper and lower limbs. At this time, he was placed on 200 mg/day of PHT, 1000 mg/day of VPA and 1300 mg/day of KBr. During episodes of involuntary movements lasting from about 20 min to several hours, his left upper and lower limbs became tonic and his left arm was flexed at the elbow, accompanied by choreoathetosis involving his left fingers and left toes. He became agitated, and hyperhidrosis was observed. These episodes occurred every several days, mainly in the afternoon or evening. EEGs during these episodes of involuntary movements showed no significant ictal changes. A thorough investigation into the cause of these involuntary movements revealed a close relationship between the appearance of the movements and PHT serum levels. After many trials, it was found that he was free from involuntary movements at PHT serum levels of less than 7.5 μg/ml. PHT was discontinued and carbamazepine (CBZ) was started on October 15, 1999. On November 4, 7 days after the dosage of CBZ was increased to 500 mg/day, he showed the same type of involuntary movements again from one to several times a day for 3 days. At this time he was placed on 500 mg/day of CBZ (serum level: 10.5 μg/ml), 1600 mg/day of VPA (serum level: 113.2 μg/ml) and 0.6 mg/day of ethyl loflazepate. Each episode lasted for about 30 min. When CBZ was discontinued his involuntary movements rapidly disappeared. He is now being treated with 800 mg/day of KBr, 1300 mg/day of VPA, 90 mg/day of phenobarbital (PB) and 350 mg/day of zonisamide (ZNS), and his choreoathetosis has not recurred during the 2-year-4-month follow-up period. However, the patient often keeps his left arm in an abnormally flexed position and it does not move naturally while he is walking. Although he can walk without help, his gait is very ataxic. He speaks only some simple sentences.

2.2. Case 2

This patient is a 7-year-11-month-old male with BSME. It was noticed that he did not move his right arm naturally while he was running since he was 3 years of age. He was admitted to our hospital at 5 years, 9 months of age (January 20, 2000) because of frequent hemiconvulsions and generalized clonic or tonic–clonic convulsions, which occurred mainly during sleep, clustered into several occurrences a day. On admission, he was treated with 1000 mg/day of VPA, 1100 mg/day of KBr, 120 mg/day of primidone and 50 mg/day of PHT. Because of frequent convulsive seizures, we increased the dosage of PHT to 200 mg/day. On February 2, 2000, 10 days after this increase, choreoathetosis appeared in his right upper arm. At this time, he was being treated with 200 mg/day of PHT, 900 mg/day of VPA and 1000 mg/day of KBr. These involuntary movements were often observed just after throwing a ball with his right hand or while he was handling a toy with his right hand. These episodes occurred suddenly and lasted for about 1 h, especially in the evening before bedtime. EEGs during these involuntary movements showed no significant changes. The sudden appearance of involuntary movements seemed to be related to the increased PHT dosage. An analysis of the relationship between choreoathetosis and PHT serum levels revealed that choreoathetosis occurred only at levels of 17.6 μg/ml or higher. After reducing the PHT dosage (serum level: < 16 μg/ml), choreoathetosis has not recurred during the 2-year-1-month follow-up period. However, he still does not move his right arm naturally while he was running and tends to avoid using his right hand. Although he can walk without help, his gait is ataxic. He speaks only single words.

2.3. Case 3

This patient is a 22-year-9-month-old male with BSME. At 10 years of age, the patient's mother noticed that, about once a month, the boy assumed a strange posture that lasted from about 1 h to almost an entire day. During these episodes, his body stooped to the left, with the left arm flexed and the left fingers overextended, and he repeatedly twisted his body to the left. Although he could stand, walk and move his left arm during these episodes, all his movements were slow and awkward. He looked vacant and unusually quiet. Upon examination, he was found to have mydriasis, tachycardia and hyperhidrosis. He underwent an EEG, which showed no significant ictal changes. At this time, he was being treated with 200 mg/day of PHT, 1200 mg/day of VPA and 100 mg/day of CBZ. The PHT serum level was 17.1 μg/ml. Although he had been taking PHT (dosage: 130–200 mg/day; serum level: 4.3–26.6 μg/ml, mostly less than 10 μg/ml) since 3 years of age, the dosage of PHT had been increased from 175 to 200 mg/day at 9 years, 7 months of age, about 4 months before the onset of these episodes. The dosage of PHT was not changed until 10 years, 7 months of age. Then it was stopped at the age of 11 years, 3 months. He sometimes manifested these episodes until 10 years, 6 months of age. Five years later, when he was 15 years, 11 months old, he again showed the similar stooping posture to the left, lasting for several days without any precipitating factors. At this time, he was placed on 1400 mg/day of VPA, 280 mg/day of ZNS, 7 mg/day of diazepam and 4000 mg/day of vigabatrin. This episode spontaneously disappeared and he has had no recurrences during the 6-year-10-month follow-up period. Although he

Table 1
Clinical findings of four patients

Case (gender/diagnosis)	Age at onset of seizures (months)	Generalized seizures	Alternating hemiconvulsions	Complex partial seizures	Myoclonic seizures and atypical absences with eyelid myoclonias	Status epilepticus	Precipitation by fever	Segmental myoclonias
1 (male/BSME)	5	(+)	(+) L > R	(+)	(−)	(+)	(+)	(+)
2 (male/BSME)	7	(+)	(+) R > L	(+)	(−)	(+)	(+)	(+)
3 (male/BSME)	4	(+)	(+) L > R	(+)	(−)	(+)	(+)	(+)
4 (female/TSME)	3	(+)	(+)	(+)	(+)	(+)	(+)	(+)

BSME, borderline severe myoclonic epilepsy in infancy; TSME, typical severe myoclonic epilepsy in infancy; R, right side of the body; L, left side of the body. Myoclonic seizures were associated with ictal EEC changes. Segmental myoclonias were erratic myoclonias which were not associated with ictal EEG changes.

can walk without help, his gait is ataxic. He speaks only a few simple sentences.

2.4. Case 4

This patient is a 37-year-old woman with TSME. At 18 years, 7 months of age, she began to have strange episodes of irregular and violent writhing or flinging movements involving the right upper and lower limbs. These episodes occurred every several days and lasted for several hours, sometimes almost all day. During these episodes, she looked agitated, or was drowsy but unable to sleep. She could neither eat nor drink, and hyperhidrosis was observed. Although these involuntary movements occurred solely on the right side of her body on most occasions, they sometimes spread over her entire body. They rarely occurred mainly on the left side of her body. These episodes have occurred once every several days, mainly in the late afternoon to evening, until the time of writing.

Based on our experiences with our other cases, we suspected that her involuntary movements were related to PHT. However, she had been taking PHT in addition to other antiepileptic drugs (AEDs) without any involuntary movements since 15 years, 8 months of age. Before the involuntary movements appeared, there was no change in her AED regimen, which was a polytherapy, consisting of 100 mg/day of PHT (serum level: 2.4 μg/ml), 50 mg/day of PB, 400 mg/day of CBZ and 900 mg/day of VPA. She has continued to take PHT (dosage: 100–200 mg/day) until the time of writing. During the past 10 years, her serum levels of PHT have ranged from 3.3 to 17.0 μg/ml, mostly less than 7 μg/ml. Because we suspected that her involuntary movements might be caused by PHT, we reduced the dosage of PHT from 150 to 100 mg/day when the patient was 36 years, 4 months of age. After the reduction of PHT, her episodes of involuntary movements completely disappeared for 3 weeks. However, because generalized tonic seizures during sleep increased markedly, we had to increase the dosage of PHT to 150 mg/day, and her episodes of involuntary movements recurred. Although she could speak some meaningful words and walk during childhood, she cannot speak any words and cannot walk without help at present.

Tables 1 and 2 summarize the electroclinical and neuroimaging findings of the four patients discussed above. Table 3 summarizes paroxysmal movement disorders seen in these patients and their AED therapy.

3. Molecular genetic study

Written consent was obtained from all participants for the molecular genetic study. Genomic DNA was extracted from peripheral blood leukocytes by the standard method. All coding exons of the *SCN1A* gene were amplified with the intronic primers. All PCR products were reacted with the Big Dye Terminator FS Ready-Reaction Kit (Applied Biosystems, Foster City, CA), and analyzed on an ABI 3100 automated sequencer (Applied Biosystems, Foster City, CA). Table 3 shows the *SCN1A* gene mutations found in these patients. Two out of the three patients with BSME

Table 2
Electrical and neuroimaging findings of four patients

Case	Diffuse spike-waves	Multifocal spikes	Photosensitivity	Multifocal spikes at appearance of PMD	Neuroimaging (MRI/CT)
1	(+) rarely	(+)	(−)	Mainly R. F	Slight cortical atrophy
2	(−)	(+)	(−)	Mainly B. F	Normal
3	(+) rarely	(+)	(−)	Mainly B. F	Normal
4	(+)	(+)	(+)	Mainly B. F	Normal

PMD, paroxysmal movement disorders; R.F., right frontal; B.F., bilateral frontal. Diffuse spike-waves and photosensitivity had disappeared by the time of appearance of paroxysmal movement disorders. In all patients, interictal EEGs at the time of appearance of paroxysmal movement disorders showed only mutifocal spikes.

Table 3
SCN1A mutations, paroxysmal movement disorders and AED therapy

Case	*SCN1A* mutations	Age at follow-up	Age at appearance of PMD	Nature of PMD	AEDs at appearance of PMD	PHT therapy
1	R501fsX543	14 years 2 months	11 years 7 months	Choreoathetosis	PHT, VPA, KBr	11 years 6 months–11 years 7 months
			11 years 9 months	Choreoathetosis	CBZ, VPA, ethyl loflazepate	
2	K547fsX570	7 years 11 months	5 years 10 months	Choreoathetosis	PHT,VPA, KBr	3 years 10 months*
3	(−)	22 years 9 months	10 years 0 months–10 years 6 months	Dystonia	PHT, VPA, CBZ	3 years 7 months–11 years 3 months
			15 years 11 months	Dystonia	VPA, ZNS, DZP, vigabatrin	
4	R854X	37 years 0 months	18 years 7 months-present	Choreoathetosis, ballismus	PHT, PB, CBZ, VPA	15 years 8 months*

* PHT therapy has continued until the time of writing in cases 2 and 4.

and one patient with SME had *SCN1A* gene mutations. These mutations lead to truncation of the associated protein.

4. Discussion

Patients with TSME and BSME share some characteristic symptoms in addition to epileptic seizures, such as erratic and segmental myoclonias without ictal EEG changes, ataxia and appearance of psychomotor retardation after early normal development [1]. The patients discussed here can be clinically characterized as suffering from TSME (case 4) and BSME (cases 1–3). Thus, it appears that paroxysmal movement disorders are another common characteristic shared by both TSME and BSME. Other researchers also reported involuntary movements during the clinical course of TSME [9] and BSME [10], and theorized that they were induced by PHT. Our patients also showed paroxysmal movement disorders that seemed to be related to PHT. However, CBZ also induced these types of movements in our case 1. The same type of movement disorder was also observed in our case 3 while he was not being treated with PHT or CBZ. In cases 2–4, the movement disorders did not appear for many years even while they were being treated with PHT, but when they did appear, they disappeared after a discontinuation or reduction of PHT. Furthermore, the serum levels of PHT that induced the movement disorders were relatively low in our cases and other symptoms of acute PHT toxicity were not observed in any of our cases. Therefore, these movement disorders are not merely a symptom of PHT overdose.

Although it has been reported that PHT and CBZ can induce involuntary movements in patients with epilepsy [11–13], the precise frequency of this occurrence is not clear. It is thought that patients with TSME and BSME manifest involuntary movements much more often than those with other types of epilepsies. The four patients discussed herein were all patients who suffered paroxysmal movement disorders while undergoing AED therapy drawn from among all the epilepsy patients seen in our hospital to date, except for some patients with paroxysmal kinesigenic choreoathetosis and epilepsy. It is very likely that patients with TSME and BSME have a predisposition for paroxysmal movement disorders, and it appears that these movement disorders are mainly induced by PHT and sometimes by other AEDs or other factors.

Mutations in the *SCN1A* gene have often been detected in patients with SME [6–8]. In this study, three of the four patients had mutations in the *SCN1A* gene. Recently, the relationship between paroxysmal movement disorders and epilepsy has attracted attention, and it has been proposed that ion channel dysfunction may be the basis of the association between seizures and paroxysmal movement disorders [14,15]. Thus, mutations in the *SCN1A* gene might be linked to the occurrence of involuntary movements in SME. It has also been reported that this type of sodium channel subunit isoform occurs not only in the cerebral cortex but also in the brainstem, substantia nigra and caudate in mammals [16]. It is thought that some AEDs act by modulating the ion channels (Na^+, Ca^{2+}, K^+) [17]. The principal pharmacological action of PHT, CBZ and ZNS involves modulation of voltage-dependent ion channels, such as sodium channel. Thus, these AEDs might induce paroxysmal movement disorders through their action on ion channels. However, all TSME and BSME patients with mutations in the *SCN1A* gene did not necessarily show involuntary movements while they were being treated with this class of AEDs. Moreover, one of our patients with BSME did not have any *SCN1A* gene mutations. Therefore, some other factors might also influence the occurrence of these movement disorders.

Regarding the nature of paroxysmal movement disorders, cases 1, 2 and 4 mainly had choreoathetosis, but case 4 showed more violent flinging movements, which resembled ballismus. Case 3 manifested dystonia. In all our cases, movement disorders appeared unilaterally on most occasions. Before the appearance of their paroxysmal movement disorders, cases 1 and 2 had shown persistent

slight motor disturbances on the same side of the upper limb as that which suffered the involuntary movements, without focal MRI abnormalities. These motor disturbances continued after the disappearance of the paroxysmal movement disorders. They appeared to be an extrapyramidal sign, namely, abnormal muscle tone or a disturbance of coordination. Additionally, in cases 1–3, seizures were seen more often on the same side of the body. Accordingly, it is thought that the motor circuit involving the cortex (including the supplementary motor area, the primary motor area, and the precentral motor area) and the basal ganglia has some functional disturbance in these patients [18,19]. The fact that interictal EEGs of all four of our patients showed frontal spikes at the time of appearance of paroxysmal movement disorders might support this hypothesis.

The causes of paroxysmal movement disorders in TSME and BSME are still poorly understood. However, at the very least, the physician should carefully monitor the appearance of this symptom during patients' clinical courses. At the first appearance of involuntary movements, precipitating factors, especially the AED therapy, should be thoroughly investigated. Furthermore, the frequent appearance of this symptom in TSME and BSME might shed some light on the pathophysiological and genetic mechanisms of these disorders.

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Original article

Is phenotype difference in severe myoclonic epilepsy in infancy related to *SCN1A* mutations?

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Abstract

We classified 28 patients with severe myoclonic epilepsy in infancy (SME) according to the presence or absence of myoclonic seizures and/or atypical absences. Eleven of the patients had myoclonic seizures and/or atypical absences, and we refer to this condition as 'typical SME (TSME)'. Seventeen of the patients had only segmental myoclonias, and we refer to this condition as 'borderline SME (BSME)'. We then analyzed the electroclinical and genetic characteristics of these two groups. Ten of the 11 TSME patients had a photoparoxysmal response at some time during their clinical course, while none of the BSME patients showed this response. TSME and BSME showed a significant difference in regard to gender ratio: female dominance in TSME and male dominance in BSME ($P = 0.008$). The detection rate of the voltage-gated sodium channel α1-subunit (SCN1A) gene mutations was 72.7 and 88.2% in TSME and BSME, respectively. There was no difference in the type or rate of mutation between TSME and BSME. We conclude that TSME and BSME show distinct differences in photoparoxysmal response and gender, which might be caused by some genetic mechanism(s) other than the SCN1A gene mutation.

Keywords: Severe myoclonic epilepsy in infancy; Generalized epilepsy with febrile seizures plus; SCN1A; Phenotype

1. Introduction

Severe myoclonic epilepsy in infancy (SME) was first described by Dravet in 1978 [1]. This epileptic syndrome is characterized by generalized or unilateral prolonged seizures in the 1st year of life, often associated with fever. Between the ages of 1 and 4 years, patients begin to have myoclonic seizures and/or atypical absences. These myoclonic seizures and atypical absences disappear by around 10 years of age in most patients, while convulsive seizures persist throughout the clinical course.

Some investigators, ourselves included, have noticed cases which have some of the typical characteristics of SME but have neither distinct myoclonic seizures nor atypical absences. Although these atypical cases do not have myoclonic seizures which are associated with ictal electroencephalograph (EEG) changes, they have segmental myoclonias without ictal EEG changes. Therefore, there are many researchers who do not differentiate these atypical cases from typical SME cases. It has been long debated whether myoclonic seizures associated with epileptic discharges on ictal EEGs are essential feature for the diagnosis of SME.

Based on our previous study of SCN1A mutations in patients with SME [2], we decided to investigate the correlation between the electroclinical and genetic characteristics of SME.

2. Patients and methods

Twenty-eight patients with SME, 12 males and 16 females, were recruited from patients with epilepsy who

Abbreviations: SME, severe myoclonic epilepsy in infancy; GEFS +, generalized epilepsy with febrile seizures plus; TSME, typical SME; BSME, borderline SME.

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were seen at Okayama University Hospital from 1969 to 2001. All patients with SME satisfied the diagnostic criteria of the International League Against Epilepsy classification [3]. The age at the initial examination ranged from 4 months to 5 years, 4 months. The age at the last visit ranged from 4 to 36 years. The follow-up period ranged from 13 months to 34 years (average: 10 years, 6 months). All patients were admitted, and ictal EEGs, including EEGs at the time of segmental myoclonias, were repeatedly performed. Seizure manifestations were intensively observed by child neurologists and/or EEG technologists at the time of EEG examinations before 1981. Since 1981, simultaneous video-EEG-electromyography (EMG) monitoring was performed as well. During follow-up, EEG was basically performed once a year on an outpatient basis. Whenever new types of seizures were noticed, we made every effort to record ictal EEGs by means of long-term simultaneous EEG-EMG recordings. Myoclonic seizures were distinguished from segmental myoclonias without epileptic discharges on ictal EEG by means of ictal simultaneous EEG-EMG recordings.

We divided the patients into two groups, according to the presence or absence of myoclonic seizures and/or atypical absences, which were confirmed by ictal EEG-EMG recordings. In this study, we refer to cases having myoclonic seizures and/or atypical absences with myoclonic components as 'typical SME (TSME)' and cases having only segmental myoclonias as 'borderline SME (BSME)'. When the patients had doubtful history of myoclonic seizures, we classified them into the group of BSME, if we could not confirmed myoclonic seizures by repeated ictal EEG-EMG recordings.

The methods of the molecular genetic study were described in our previous study [2].

Fisher's exact test was used for statistical analysis.

3. Results

3.1. Electroclinical study

Among 11 patients with TSME, four had both myoclonic seizures (Fig. 1a) and atypical absences, five had only myoclonic seizures and the remaining two had only atypical absences (Table 1). These atypical absences were associated with eyelid myoclonias (Fig. 1b) and/or myoclonic components of the shoulders and the neck. In addition, myoclonic seizures and atypical absences were associated with spike-and-wave complexes on ictal EEGs. The other 17 patients with BSME had only segmental myoclonias without epileptic discharges on ictal EEGs (Fig. 2). Both groups shared the same clinical features except for the presence or absence of myoclonic seizures and atypical absences, as shown in Table 1. All patients with TSME also had segmental myoclonias. Moreover, all 28 patients had mental retardation and frequent generalized or hemiconvulsive status epilepticus during infancy, often associated with fever. In addition, all but four patients (patients 8, 16, 20, and 26) had various degrees of ataxia.

Interestingly, TSME and BSME showed a significant difference with regard to gender: females tended to suffer from TSME, while males tended to suffer from BSME ($P = 0.008$) (Table 1). Regarding EEG characteristics, ten of the 11 patients with TSME (90.9%) had photoparoxysmal response (PPR) (Fig. 1b) transiently during their clinical course, while no patients with BSME showed PPR. However, all patients in both groups shared the other common EEG characteristics of SME, such as rare or no epileptic discharges in the 1st year of life, followed by the appearance of focal spikes and diffuse epileptic discharges later in life. A positive family history of convulsive disorders, mainly febrile seizures, was observed at almost the same rate in both groups (Table 1).

3.2. Genotype-phenotype correlation

In a previous paper, we reported on a mutation analysis of the *SCN1A* gene in patients with SME [2], including the patients in the present study. Mutations of the *SCN1A* gene were detected in 23 of the 28 patients (82.1%) with SME. The patients with TSME had two nonsense mutations, one frameshift mutation, and five missense mutations in the *SCN1A* gene. The patients with BSME had three nonsense mutations, seven frameshift mutations, four missense mutations and one an amino acid deletion. The detection rate of *SCN1A* mutation was 72.7 and 88.2% in TSME and BSME, respectively. There was no statistically significant difference in the type, location or rate of mutation between TSME and BSME.

4. Discussion

Generalized epilepsy with febrile seizure plus (GEFS +) has recently been described and has been attracting much attention. It is a common childhood genetic epilepsy syndrome characterized by febrile seizures that persist beyond 6 years of age and by the appearance of other types of afebrile seizures [4,5]. GEFS + shows marked phenotype heterogeneity. It is thought that SME might be located in the extended spectrum of GEFS + [6].

Although SME is a well-defined epileptic syndrome, some nosological issues still remain to be resolved. In the 1980s, some researchers, particularly Japanese ones, started reporting cases of BSME [7–10]. Although patients with BSME have neither myoclonic seizures nor atypical absences, they have erratic and segmental myoclonias which are not associated with spike-wave discharges on ictal EEGs. Most typical SME patients also have a similar type of segmental myoclonias. Since myoclonic seizures associated with ictal EEG changes are very minor and transient phenomena in some cases, it is necessary to repeat

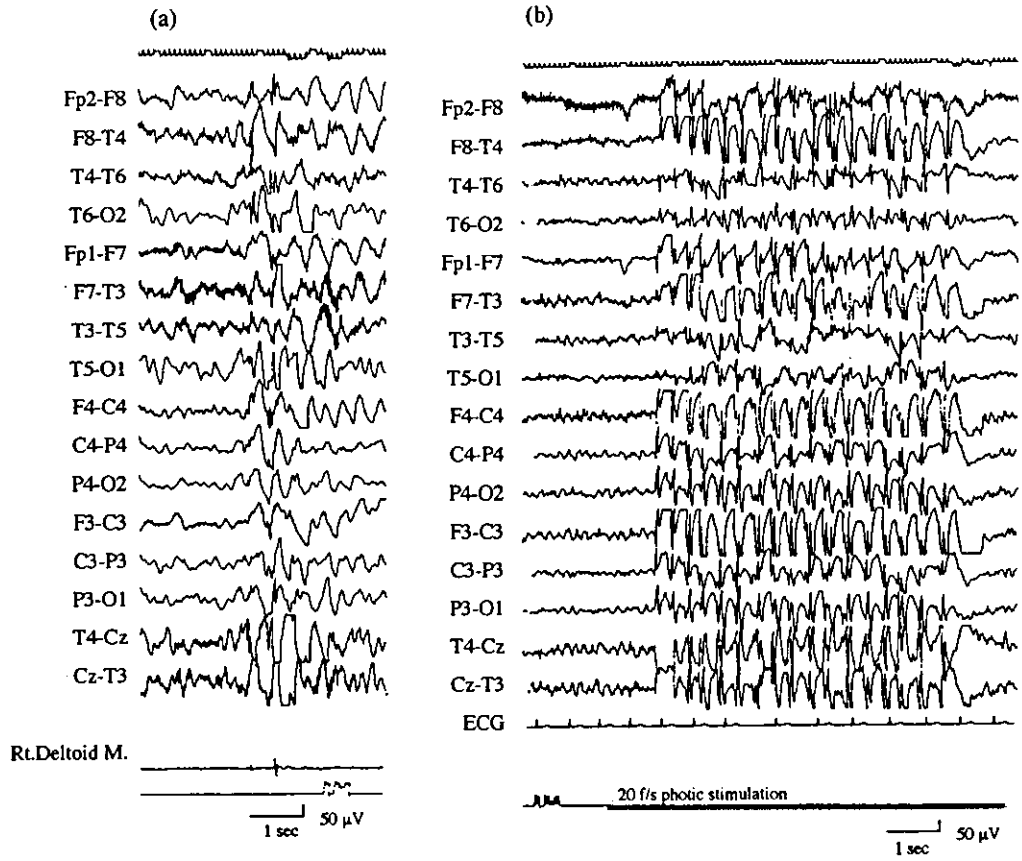

Fig. 1. (a) An ictal EEG of a myoclonic seizure associated with spike-and-wave complexes (patient 5). (b) Atypical absence with eyelid myoclonias provoked by 20 f/s photic stimulation (patient 9).

long-term simultaneous EEG-EMG-video recordings for the detection of myoclonic seizures and to differentiate between myoclonic seizures and segmental myoclonias. Although Dravet et al. reported that 21% of the patients in their series of patients with SME had only segmental myoclonias, they did not clearly describe the significance of the presence of these atypical cases [11]. Based on the current viewpoint, in which SME is located in the extended spectrum of GEFS+, the presence of BSME is intriguing. It is thought that BSME is also located in the extended spectrum of GEFS+. There may be some other cases in this spectrum which share some of the same electroclinical and genetic characteristics with TSME and BSME.

In previous papers [8,12,13], we reported that the presence or absence of myoclonic seizures and atypical absences, and PPR on EEGs, were the main electroclinical differences between TSME and BSME. The present study confirms these findings and reveals a clear gender difference between the two types: female dominance in TSME, and male dominance in BSME. In general, PPR and photosensitive epilepsy are more often observed in females. Therefore, the female dominance in TSME must be meaningful. Regarding the gender of patients with SME, Darvet et al. reported that males are slightly more affected (57%) [11]. We do not know whether this discrepancy is caused by differences in selection criteria of patients or by racial differences.

Based on molecular/genetic analysis, mutations of the voltage-gated sodium channel β1-subunit *SCN1B* gene [14], the α1-subunit *SCN1A* gene [15–19], the α2-subunit *SCN2A* gene [20] and the *GABRG2* gene [21–23] were detected in patients with GEFS+ and localization-related epilepsy. Escayg et al. reported that the rate of *SCN1A* mutations in GEFS+, including mainly juvenile myoclonic epilepsy and childhood absence epilepsy, was 5.6% [24]. As for SME, *SCN1A* mutations have been detected at a high rate in two studies [25,26] and most of these were nonsense or frameshift mutations which lead to truncation of the associated protein. The authors of these papers indicated that a truncation mutation of the *SCN1A* gene is related to a severe phenotype in the extended spectrum of GEFS+, since all *SCN1A* mutations in GEFS+ were missense mutations. In our previous study, we detected 24 novel mutations (83%) in the *SCN1A* gene of the 29 patients with SME [2]. This was the largest group of SME patients to be studied for genetic mutations until that point, and not only truncation mutations (13 cases) but also missense mutations (nine cases) were detected. The present study showed that both TSME and BSME are highly correlated with mutations of the *SCN1A* gene and that there are no significant differences between the two groups in terms of mutation

Table 1
Summary of electroclinical characteristics and SCN1A mutations[a]

Patients No.	Subgroup	Gender	Age at onset (months)	Seizure type					Ataxia	Precipitating factors	PPR on EEG photo/pattern	Family history	SCN1A mutation	
				GS	Ab	My	Hemi	CPS					Exon	Amino acid change
1	TSME	F	4m	+	+	+	+	−	+	Fe,HB	+/−	−	12	P696fsX703*
2	TSME	F	2m	+	+	+	+	+	+	Fe,HB	−/−	+	12	R701X*
3	TSME	F	3m	+	+	+	+	+	+	Fe,HB	+/−	+	15	R854X*
4	TSME	M	5m	+	−	+	+	+	+	Fe,HB	+/−	−	15	R921C*
5	TSME	F	6m	+	−	+	+	+	+	Fe,HB	+/−	−	19	L1255P*
6	TSME	F	4m	+	−	+	+	+	+	Fe,HB,pattern	−/+	−	22	W1424R
7	TSME	F	3m	+	−	+	+	+	+	Fe,HB,TV	+/+	+	26	R1638C
8	TSME	F	7m	+	+	+	+	+	−	Fe,HB,TV	+/+	−	26	T1899I
9	TSME	F	4m	+	−	+	+	+	+	Fe,HB,TV,SL	+/+	+	Not detected	
10	TSME	F	4m	+	+	−	+	+	+	Fe,HB	+/−	+	Not detected	
11	TSME	F	6m	+	+	−	+	+	+	Fe,HB	+/−	+	Not detected	
12	BSME	M	5m	+	−	−	+	+	+	Fe,HB	−/−	+	10	R501fsX543*
13	BSME	M	7m	+	−	−	+	+	+	Fe,HB	−/−	−	10	K547fsX570*
14	BSME	M	3m	+	−	−	+	+	+	Fe,HB	−/−	+	11	R568X*
15	BSME	F	6m	+	−	−	+	+	+	Fe,HB	−/−	−	11	S607fsX622
16	BSME	M	5m	+	−	−	+	+	−	Fe,HB	−/−	−	15	F891C
17	BSME	F	6m	+	−	−	+	+	+	Fe,HB	−/−	−	15	R921C*
18	BSME	M	4m	+	−	−	+	+	+	Fe,HB	−/−	+	16	A992fsX999*
19	BSME	M	5m	+	−	−	+	+	+	Fe,HB	−/−	+	16	K1017X*
20	BSME	M	7m	+	−	−	+	+	−	Fe,HB	−/−	−	16	T1072fsX1077*
21	BSME	F	5m	+	−	−	+	+	+	Fe,HB	−/−	+	19	W1261X
22	BSME	M	4m	+	−	−	+	+	+	Fe,HB	−/−	+	19	1279delF*
23	BSME	M	7m	+	−	−	+	+	+	Fe,HB	−/−	+	22	A1419fsX1433
24	BSME	M	8m	+	−	−	+	+	+	Fe,HB	−/−	−	23	Q1440R*
25	BSME	F	5m	+	−	−	+	+	+	Fe,HB	−/−	−	26	G1664R*
26	BSME	F	6m	+	−	−	+	+	−	Fe,HB	−/−	−	26	G1870fsX1871
27	BSME	F	6m	+	−	−	+	+	+	Fe,HB	−/−	+	Not detected	
28	BSME	M	4m	+	−	−	+	+	+	Fe,HB	−/−	−	Not detected	

[a] M, male; F, female; GS, generalized seizures include generalized clonic seizure, generalized tonic-clonic seizure, and secondairly generarized seizure; Ab, atypical absence; My, myoclonic seizure; Hemi, hemiconvulsion; CPS, complex partial seizure; Fe, fever; HB, hot bath; TV, television; SL, sunlight; and PPR, photoparoxysmal response. Numbering of the SCN1A mutations started from the initiating ATG codon. (GenBank accession number was AF22S985). *The same mutations are not found in their parents.

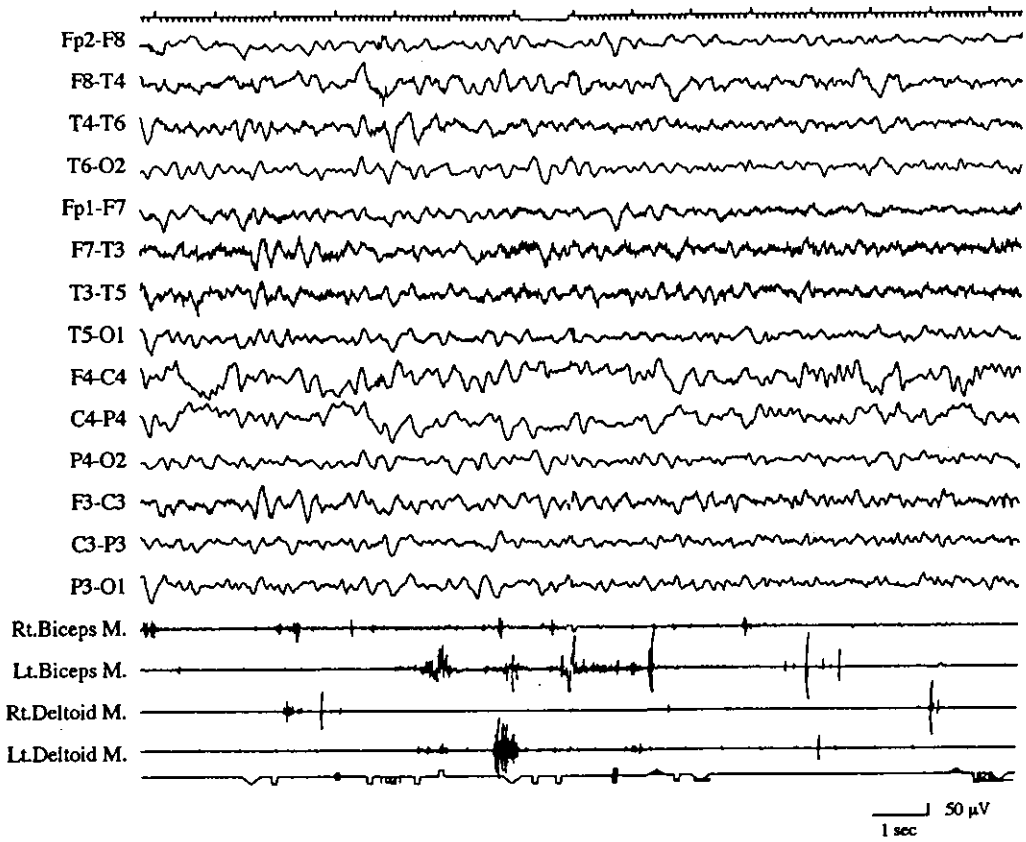

Fig. 2. An EEG at the time of segmental myoclonias without epileptic discharges (patient 22). These segmental myoclonias are not associated with epileptic discharges.

type, location or prevalence. Our findings indicate that both TSME and BSME share common genetic mechanisms. One of the common clinical features is the frequent occurrence of convulsions associated with fever, which sometimes develop into status epilepticus. Since *SCN1A* mutations were detected equally in the both groups, *SCN1A* may be related to a dysfunction of brain neurons exacerbated by high body temperature.

We conclude that TSME and BSME are closely related from an electroclinical and molecular genetic point of view. We believe that it is appropriate that both TSME and BSME are categorized under the term 'Dravet syndrome' [1]. The electroclinical differences between TSME and BSME might be caused by some as-yet-undiscovered molecular genetic differences. Further studies are needed to elucidate the relationship between the phenotypes and the molecular genetic mechanisms underlying these two syndromes.

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