患者様控

同 意 書

大阪市立大学大学院医学研究科長　殿

私は、「小児神経伝達物質病の診断基準の作成と患者数の実態調査に関する研究」について説明を受けました。

1．被験者として選ばれた理由
2．この試験の目的、意義
3．方法、期間
4．期待される利益
5．起こりうる危険並びに必然的に伴う不快な状態
6．危険並びに必然的に伴う不快な状態が起こりうる場合の補償等の対応
7．試験にかかる費用及び資金源
8．利害の衝突及び研究者等の関連組織との関わり
9．研究から生じる知的財産権とその帰属先
10. プライバシーは守られること
11. 個人情報の取扱い
12. 資料の保存、使用方法、保存期間、研究終了後の利用又は廃棄方法
13. 代諾者から同意を受ける場合、研究の重要性、必要不可欠性

上記の内容を承知した上で本試験に参加することに同意します。

(西暦)　　年　　月　　日

本人署名：

代諾者署名：　　本人との関係（　　）

上記の方に対する試験内容については、私が説明し、同意されたことを確認致しました。

(西暦)　　年　　月　　日

説明者署名：

〈この書類は複写式になっています。3枚目のコピーは患者様用の控えです〉

小児神経伝達物質病研究 画像記録の説明文書

瀬川病やAADC欠損症などの疾患は、大脳などの中枢神経で神経情報を伝達するドーパミンやセロトニン、ガンマアミノ酪酸（GABA）などの「神経伝達物質」の先天的異常によって起こることがわかってきました。これらの疾患は主に小児期に発症するため、「小児神経伝達物質病」という新しい病気のグループに含められています。

これらの病気は遺伝性であり、多くはジストニアなどの異常な体の動きを伴います。また、血液、髄液および尿などの体液の異常も伴いますが、この異常は特殊な検査を行わないとわからないため、一般の病院で行われる検査だけでは診断できないことが普通です。

そのため、この「小児神経伝達物質病」を疑い、診断するためにはそれぞれの病気で見られる特徴的な体の動き（不随意運動）を見つけることが必要です。しかしながら、これらの動きは教科書の文章や写真だけでは十分に理解できないため、病気の症状が出ていても多くの専門家が正しく診断することが難しいのが現状です。

今回、あなた（もしくはあなたのお子様）は神経伝達物質病であると診断されました。あなた（もしくはあなたのお子様）が示している様々な運動症状は、病気による特徴的な動きが含まれていますので、その動きについて記録・編集したものを診断の助けとなるような教材として全国の専門家に配布する予定です。そうすることでこの病気に気づくのが早くなり、まだ診断されていない同じ病気の人達が早期に適切な治療を受けられるようになることが期待されます。もし研究に参加することをご承諾いただけるようでしたら、主治医または研究担当者があなた（もしくはあなたのお子様）の示す運動症状をビデオで記録致します。

この研究では個人情報の保護のため匿名化を行ないます。このため、目や顔など、個人の判別が可能となる部分は隠されます。しかし、目や顔の表情に特徴的な動きが現れる場合、許可をいただいてその映像を使用することがあります。当然、提供者や家族の氏名は明らかにならないように保護されます。

あなた（もしくはあなたのお子様）がこの研究に映像等を提供しても出演料等の経費は要求できません。この研究について特許権などが生じる可能性がありますが、その権利は研究遂行者に属し、あなたには属しません。またその特許権などをもととして経済的利益が生じる可能性がありますが、あなたはこれについて権利がありません。

この研究への参加は完全に任意であり、一度参加の意思を伝えていたとしてもいつでも参加を取り消すことができます。しかし、研究結果がすでに公表されていた場合にはその結果などを廃棄することはできません。

研究代表者用

同 意 書

私は「小児神経伝達物質病」研究に関する運動症状の記録と提供について説明を受けました。

下記項目にチェックを入れてください。

1，顔や目の症状に特徴的な表情が現れる場合

□映像をモザイク化したり隠したりせずに使用することを承諾します

□映像をモザイク化したり隠したりせず使用することを承諾しません

2，研究終了後の映像資料の取扱に関する条件

本研究が終了したら、

□ 速やかに資料を廃棄し、本研究以外に使用しない

□ 本研究終了後も長期間保存し、本学倫理委員会が認定した研究に連結匿名化して使用してもよい

内容を承知した上で、運動症状を記録し提供することに同意します。

（西暦）　　年　　月　　日

本人署名：

代諾者署名：　　本人との関係（　　）

住　　所：

電　　話：

上記の方に対する試験内容については、私が説明し、同意されたことを確認致しました。

（西暦）　　年　　月　　日

説明者署名：

〈この書類は複写式になっています。3枚目のコピーは患者様用の控えです〉

主治医控

同 意 書

私は「小児神経伝達物質病」研究に関する運動症状の記録と提供について説明を受けました。

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内容を承知した上で、運動症状を記録し提供することに同意します。

（西暦）　　年　　月　　日

本 人 署 名：

代諾者署名：　　本人との関係（　　）

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説明者署名：

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患者様控

同 意 書

私は「小児神経伝達物質病」研究に関する運動症状の記録と提供について説明を受けました。

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内容を承知した上で、運動症状を記録し提供することに同意します。

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小児神経伝達物質病の診断基準の作成と
患者数の実態調査に関する研究報告書

平成22年3月

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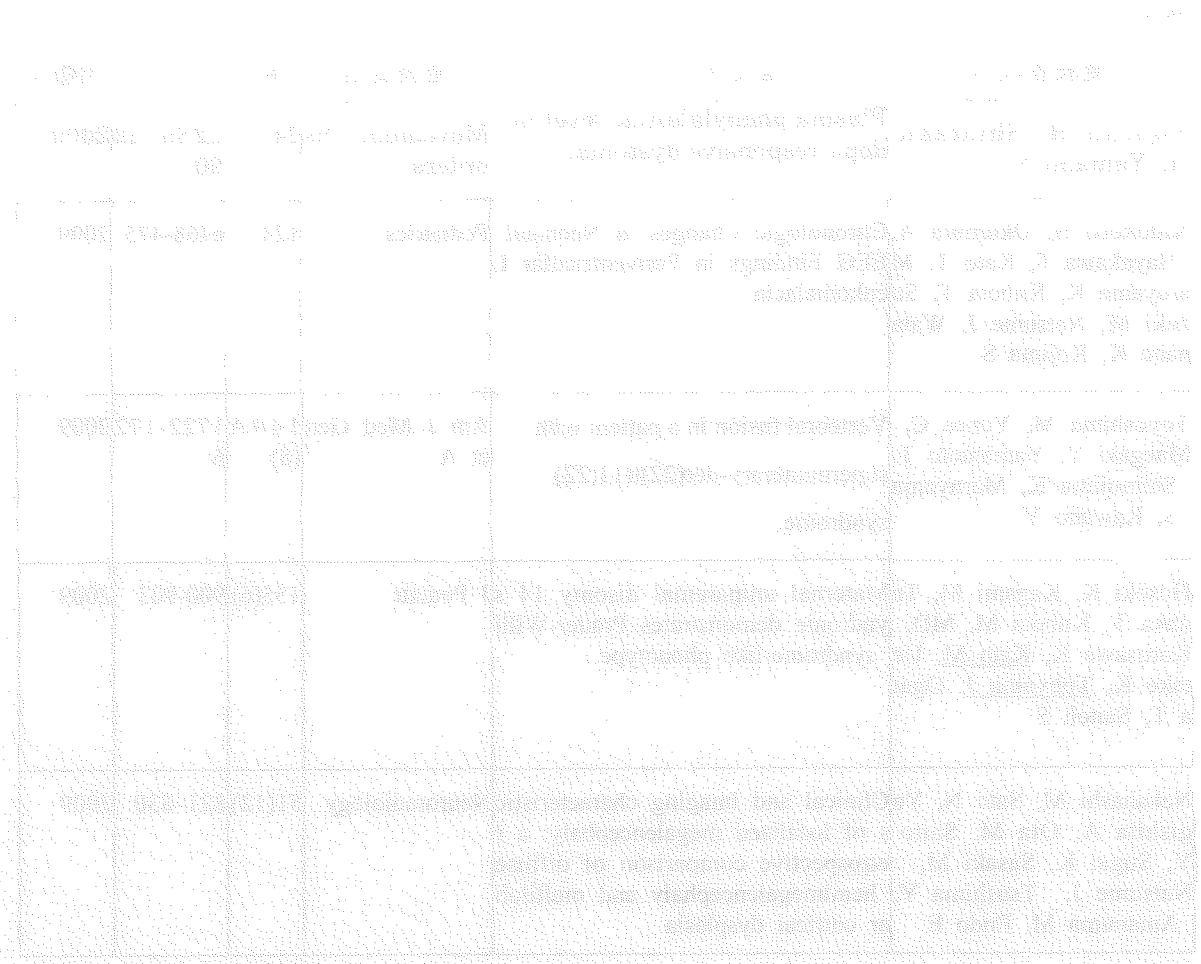
V． 研究成果の刊行に関する一覧表

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Fujioka H, Shintaku H, Yamano Y	Plasma phenylalanine level in dopa-responsive dystonia.	Movement Disorders	24	2289–2290	2009
Kidokoro H, Okumura A, Hayakawa F, Kato T, Maruyama K, Kubota T, Suzuki M, Natsume J, Watanabe K, Kojima S	Chronologic Changes in Neonatal EEG Findings in Periventricular Leukomalacia	Pediatrics	124	e468-475	2009
Toyoshima M, Yonee C, Maegaki Y, Yamamoto T, Shimojima K, Maruyama S, Kawano Y.	Vertebral fusion in a patient with supernumerary-der(22)t(11;22) syndrome.	Am J Med Genet A	149A(8)	1722-1726	2009
Hosoki K, Kagami M, Tanaka T, Kubota M, MD, Kurosawa K, Kato M, Uetake K, Tohyama J, Ogata T, Saitoh S	Maternal uniparental disomy 14 syndrome demonstrates Prader-Willi syndrome-like phenotype.	J Pediatr	155(6)	900-903	2009
Nakahashi M, Sato N, Yagishita A, Ota M, Saito Y, Sugai K, Sasaki M, Natsume J, Tsushima Y, Amanuma M, Endo E	Clinical and imaging characteristics of localized megalencephaly: a retrospective comparison of diffuse hemimegalencephaly and multilobar cortical dysplasia	Neuroradiology	51(12)	821–830	2009

VI. 研究成果の刊行物・別刷



Movement Disorders
Vol. 24, No. 15, 2009, pp. 2289–2308

Letters to the Editor Related to New Topics

Plasma Phenylalanine Level in Dopa-Responsive Dystonia

DYT5 is a condition characterized by levodopa (L-dopa) responsive dystonia (DRD) that shows childhood onset and marked diurnal fluctuation. Patients with DYT5 have heterozygous mutations in the GCH1 gene, which codes for GTP cyclohydrolase I (GTPCH), a rate-limiting enzyme in tetrahydrobiopterin (BH_4) synthesis.[1] BH_4 is a cofactor for aromatic amino acid hydroxylases including tyrosine hydroxylase (TH), phenylalanine hydroxylase (PAH), and tryptophan hydroxylase.[2] In patients with DYT5, production of dopamine is suppressed due to the decrease of BH_4 because TH is a rate-limiting enzyme in dopamine synthesis. The lack of BH_4 may also affect the activity of PAH, and patients with complete GTPCH deficiency show hyperphenylalaninemia. However, hyperphenylalaninemia has not been reported in patients with DYT5.[3] Therefore, we examined blood phenylalanine levels in patients with DYT5 compared with controls to determine whether the decrease of BH_4 in DYT5 affects PAH activity.

Blood samples for analysis of amino acids were obtained from seven patients with DRD[4] and heterozygous mutations of GCH1, 24 patients with dopa nonresponsive dystonia (non-DRD), and 12 controls. The samples were collected in a tube containing EDTA, and plasma was obtained for analysis of phenylalanine and tyrosine levels using an auto-amino acid analyzer (HS-3000; Hitachi, Tokyo, Japan). All data are expressed as means ± SD. The data were analyzed by analysis of variance (ANOVA) with multiple comparison using the Bonferroni method. A significant difference was defined as a P value < 0.05.

The phenylalanine and tyrosine levels in the plasma of patients with DYT5, patients with non-DRD, and controls are shown in Figure 1. The phenylalanine levels in the DYT5 (81.1 ± 26.6 μmol/L), non-DRD (60.5 ± 14.5 μmol/L), and control (58.7 ± 9.1 μmol/L) groups were all within the normal range. However, the phenylalanine level in patients with DYT5 was significantly higher than those in the other groups ($P = 0.027$ by ANOVA). Multiple comparison also indicated that the level of plasma phenylalanine in patients with DYT5 was significantly higher than those in patients with non-DRD ($P = 0.043$) and in controls ($P = 0.040$). There was no significant difference in the plasma phenylalanine levels between patients with non-DRD and controls. There were no significant differences in plasma tyrosine levels among all the groups.

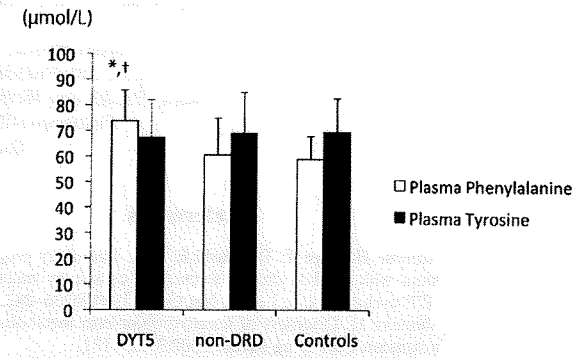


FIG. 1. Plasma phenylalanine and tyrosine levels. The plasma phenylalanine levels (open boxes) and tyrosine levels (closed boxes) are shown for patients with DYT5, patients with non-DRD, and controls. Error bars indicate standard deviations. *$P < 0.05$ (DYT5 vs. non-DRD). †$P < 0.05$ (DYT5 vs. controls).

BH_4 deficiency causes hyperphenylalaninemia and a decrease of dopamine production, because it suppresses the activity of PAH and TH. Patients with a homozygous mutation in the GCH1 gene are reported to show hyperphenylalaninemia, in addition to DRD. Patients with DYT5 having only a heterozygous mutation in GCH1 also show symptoms of DRD, but do not have hyperphenylalaninemia. Our results indicated that blood phenylalanine levels in patients with DYT5 are within the normal range, but are higher than those in controls, which suggests that the activity of PAH is partially affected by the decrease in BH_4 in DYT5.

GTPCH is regulated by BH_4 itself and phenylalanine via GTPCH feedback regulatory protein (GFRP).[5] An increase of phenylalanine induces GFRP to upregulate GTPCH activity, whereas an increase of BH_4 downregulates GTPCH activity via GFRP. Hyland et al. has reported prolonged hyperphenylalaninemia after oral phenylalanine loading in patients with DRD,[6] which suggests that decreased BH_4 production due to mutations in GTPCH restrict the catalysis of excessive phenylalanine by PAH. However, a defect in GFRP or in the interaction between GTPCH and GFRP would cause the same results. Our results indicate that the phenylalanine level in patients with DYT5 differs from those in controls without phenylalanine loading, which suggests that a partial defect of GTPCH affects the activity of PAH.

Author Roles: Hiroki Fujioka, MD, PhD: correcting samples, Performing statistical analysis. Haruo Shintaku, MD: correcting samples, supervising. Satoshi Kudo, PhD: measuring amino acid concentration. Tsunekazu Yamano, MD: supervising.

Potential conflict of interest: Hiroki Fujioka received the Grants-in-Aid for Scientific Research by the Ministry of Education, Culture, Sports, Science and Technology of Japan (No. 20790771). Hiroki Fujioka and Haruo Shintaku received Grants-in-Aid for Scientific Research by the Ministry of Education, Culture, Sports, Science and Technology of Japan (No. 17591109).

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Hybrid Cars May Interfere with Implanted Deep Brain Stimulators

Clinicians and patients are always concerned about potential interference between external electromagnetic fields and implantable pacemaker devices. In a recent *New York Times* article, concern was raised about emitted "magnetic fields" from hybrid cars and association with various diseases such as childhood leukemia.[1] We report a case of a patient with deep brain stimulator placement for Parkinson's disease who developed unusual symptoms possibly related to stimulator malfunction while riding in a hybrid car.

A 73-year-old man with history of tremor-dominant Parkinson's disease (PD) underwent bilateral subthalamic nucleus deep brain stimulator (STN DBS) placement. One month later, initial stimulator programming was performed, and he complained of symptoms of severe nausea, dizziness, and palpitations while driving the 4- to 5-hour journey home in a 2008 hybrid Toyota Prius car. The patient's wife had to stop the car multiple times as he felt so ill. Prior to initial programming, the patient was able to drive and ride in the Prius without any problems. After stimulator activation, the patient complained of reproducible symptoms of nausea, dizziness, lightheadedness, and cardiac palpitations when sitting in the front passenger seat. He noticed that the symptoms worsened when both the gasoline engine and electric motor were running or when the car battery was charging. The symptoms spontaneously resolved when he exited the car and never occurred when he was in his truck, which is a nonhybrid vehicle. The symptoms also improved when he manually turned off his stimulator while inside the Prius or when he moved to the back seat. These symptoms did not occur at any other time. On interrogation of his stimulator 4 weeks after initial DBS programming, seven activations were noted with only two that were accounted by the patient turning the pulse generator off and on manually. The internal pulse generators (IPGs), however, had been on 99% of the time.

The patient experienced the worst symptoms when sitting in the front seat of the Prius and when the car battery was being charged, suggesting that the electromagnetic field emitted might be interfering with his neurostimulator settings. There were multiple unaccounted activations on interrogation of the stimulator, although the IPGs were on 99% of the time. He did not get symptoms in a nonhybrid car or in the Prius when his IPG was off. We have observed similar symptoms when the voltage of an STN neurostimulator was increased rapidly. We hypothesize that the device was turning off and on rapidly, with voltage surges, thus causing the patient's symptoms. This is the first documented case of a hybrid vehicle, potentially interfering with the IPG settings in a subject with PD and STN DBS. There has been controversy over the effect of electromagnetic fields generated by hybrid vehicles on cardiac pacemakers and implantable defibrillators. Patients with cardiac pacemakers have complained of similar symptoms as the ones which our patient experienced when inside a hybrid car or near its smart key device (internet message boards).[2] In the Prius owner's manual, Toyota warns that people with implanted pacemakers or cardiac defibrillators should keep away from the vehicle smart entry and start system antennas.[3] Currently, the manual does not comment specifically about DBS. We recommend that such patients should not drive a Prius or other hybrid vehicle until more research and data are available for theirs and others safety. Whether they are safe as passengers remains to be proven. Further investigation should include measurement of all electromagnetic fields and frequencies generated in hybrid and electric cars, including the Toyota Prius, and evaluating for deep brain stimulator device interference or malfunction.

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Potential conflicts of interest: The authors report no conflict of interest.
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Chronologic Changes in Neonatal EEG Findings in Periventricular Leukomalacia

Hiroyuki Kidokoro, Akihisa Okumura, Fumio Hayakawa, Toru Kato, Koichi Maruyama, Tetsuo Kubota, Motomasa Suzuki, Jun Natsume, Kazuyoshi Watanabe and Seiji Kojima

Pediatrics 2009;124;e468-e475; originally published online Aug 10, 2009;
DOI: 10.1542/peds.2008-2967

Chronologic Changes in Neonatal EEG Findings in Periventricular Leukomalacia

WHAT'S KNOWN ON THIS SUBJECT: Many studies have reported the usefulness of PRSWs in EEG recordings for early detection of PVL. Chronologic changes in neonatal EEG findings according to the severity of PVL have never been documented.

WHAT THIS STUDY ADDS: EEG findings in PVL differed according to the severity of PVL and the time of recording. To evaluate brain injury in PVL, ≥2 EEG recordings are recommended, 1 within 48 hours and 1 in the second week of life.

abstract

OBJECTIVE: This study sought to clarify chronologic changes in neonatal electroencephalographic (EEG) findings in periventricular leukomalacia (PVL).

METHODS: We obtained serial EEG findings for all premature infants who were admitted to our hospital at gestational age of ≤33 weeks between 1997 and 2006. EEG recordings were obtained on days 1 to 4, 5 to 14, 15 to 28, 29 to 56, and 57 to 84. Abnormal EEG findings were classified as acute-stage abnormalities (ASAs) or chronic-stage abnormalities (CSAs) and were subclassified as mild, moderate, or severe. PVL was classified as noncystic, localized cystic, or extensive cystic. The final diagnosis of PVL was made through neurologic assessment and MRI findings at 24 months.

RESULTS: Fifty-five infants were diagnosed as having PVL, including 23 with noncystic PVL, 9 with localized cystic PVL, and 23 with extensive cystic PVL. ASAs were observed most frequently on days 1 to 4 and were observed rarely thereafter in all groups. CSAs were observed most frequently on days 5 to 14, were most severe on days 5 to 14, and then resolved within 1 to 2 months in all groups. CSAs in patients with extensive cystic PVL were more severe and persisted longer, compared with other groups. ASA and CSA severity was correlated with PVL severity.

CONCLUSIONS: EEG findings in PVL differed according to the severity of PVL and the time of recording. To detect PVL, ≥2 EEG recordings are recommended, 1 within 48 hours after birth, to detect ASAs, and 1 in the second week of life, to detect CSAs. *Pediatrics* 2009;124:e468–e475

CONTRIBUTORS: Hiroyuki Kidokoro, MD,[a,b] Akihisa Okumura, MD,[c] Fumio Hayakawa, MD,[d] Toru Kato, MD,[d] Koichi Maruyama, MD,[e] Tetsuo Kubota, MD,[a] Motomasa Suzuki, MD,[e] Jun Natsume, MD,[b] Kazuyoshi Watanabe, MD,[f] and Seiji Kojima, MD[b]

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KEY WORDS

periventricular leukomalacia, electroencephalography, preterm infants

ABBREVIATIONS

PVL—periventricular leukomalacia
EEG—electroencephalographic
PRSW—positive rolandic sharp wave
CUS—cranial ultrasonographic
ASA—acute-stage abnormality
CSA—chronic-stage abnormality

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Despite advances in neonatal medicine, periventricular leukomalacia (PVL) is a common disease that occurs in 5% to 15% of premature infants. Affected infants seem to be in neurologically normal condition except for mild lower-limb weakness during the neonatal period, although they have motor and cognitive impairments later in life. Detecting PVL during early neonatal life is difficult without cranial ultrasonographic (CUS) evaluations or other neuroimaging modalities.

Electroencephalographic (EEG) findings play an important role in the understanding of pathophysiologic features of PVL. In particular, many reports have referred to the usefulness of positive rolandic sharp waves (PRSWs) for early detection of PVL, with high prognostic values.[1–6] Some studies suggest that the sensitivity of PRSWs is insufficient, however, because they rarely detect PVL in mildly affected infants.[7,8] Moreover, unless EEG recording is performed within 2 weeks after birth, PVL is rarely detected through PRSWs. Understanding the differences in EEG findings according to the severity of PVL and the chronologic changes in EEG findings is important for determining the best time for EEG recording. This study sought to clarify the chronologic changes in EEG findings in PVL during the neonatal period, especially for PVL of different severities. In addition, we determined an appropriate time for EEG studies to detect PVL.

METHODS

Study Group and PVL Definitions

To investigate the chronologic changes in EEG findings in PVL during the neonatal period, we obtained serial EEG recordings for all premature infants who were admitted to our hospital at a gestational age of ≤33 weeks between April 1997 and August 2006. Seven hundred twenty-three of those infants were monitored after discharge until corrected age of ≥24 months. Of those, we enrolled infants with a diagnosis of PVL in this study. The diagnosis of PVL was based on both characteristic MRI findings and clinical signs of spastic diplegia or quadriplegia at corrected age of 24 months. The definition of PVL on the basis of MRI findings was taken from previous studies.[9] Pediatric neurologists performed neurologic assessments during the follow-up period. The degree of motor disability was classified into 5 groups by using the Gross Motor Function Classification System.[10] Impairment in cognitive ability and IQ were evaluated by using the Wechsler Intelligence Scale for Children III at 5 years of age or the new K-form developmental test at 2 years of age when the score was ≤69. In addition, follow-up MRI findings obtained at ≥2 years of age were classified into the following 3 categories according to the location of white matter loss: posterior only, posterior and middle only, or posterior, middle, and anterior. The MRI findings were judged by 2 of us (Drs Kidokoro and Kubota).

To investigate the differences in the severity of PVL, we divided the subjects with PVL into noncystic, localized cystic, and extensive cystic PVL groups on the basis of CUS findings obtained during the neonatal period (Fig 1), as in a previous study.[11] We routinely performed CUS evaluations almost every day during the first week of life and thereafter at least twice per week until discharge. On CUS scans, cystic PVL was defined when bilateral multiple cysts of >3.0 mm in diameter were observed in the deep white matter, localized cystic PVL when cysts were localized in the deep white matter around the trigone of the lateral ventricles, and extensive cystic PVL when cysts extended beyond the trigone toward the body and the frontal horn of the lateral ventricles. Infants who had transient periventricular densities but no cystic lesions throughout the neonatal period were included in the noncystic PVL group.

EEG Recordings

EEG recordings were obtained routinely. Generally, the first recording was obtained on the day after birth; if that day was a weekend day or a holiday, then EEG recording was performed as soon as possible (ie, on the third or fourth day of life). The second recording was obtained between days 5 and 14 of life, the third recording between days 15 and 28 of life, and subsequent recordings at 4-week intervals until discharge. The EEG findings were recorded polygraphically at the

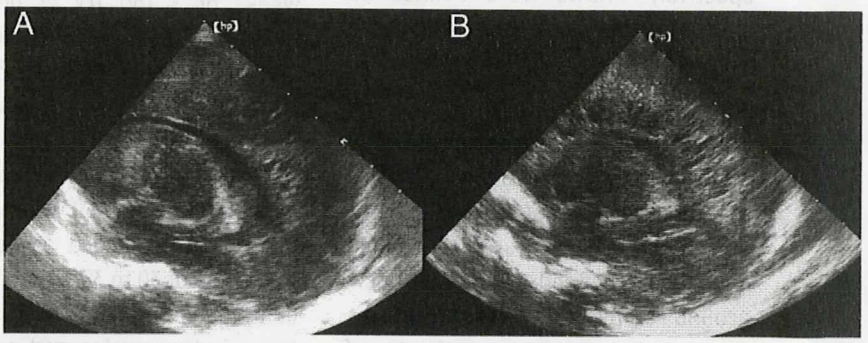

FIGURE 1

Localized cystic and extensive cystic PVL on CUS scans. A, Perisagittal section of localized cystic PVL at day 21 of life. Cysts were observed only in the white matter around the trigone of the lateral ventricles. B, Perisagittal section of extensive cystic PVL at day 16 of life. Cysts were observed not only in the occipital white matter around the trigone but also in the middle and frontal white matter.

bedside for ≥40 minutes and included both active and quiet sleep, with 8 electrodes placed at AF3, AF4, C3, C4, O1, O2, T3, and T4, by using the international 10–20 system. AF3 and AF4 were located halfway between Fp1 and F3 and between Fp2 and F4, respectively. The time constant was 0.3 seconds, and the paper speed was 3.0 cm/seconds.

EEG Assessments

To evaluate the chronologic changes in EEG findings, an understanding of the 2 types of background EEG abnormalities defined in our previous reports, that is, acute-stage abnormalities (ASAs) and chronic-stage abnormalities (CSAs),[12] is essential. ASAs were diagnosed as present when decreased continuity, lower amplitude of background activities, or both were observed. CSAs in PVL were strongly associated with a disorganized pattern, which was diagnosed as present when deformed δ waves were observed with or without frontal and/or occipital sharp waves, PRSWs, and abnormal brushes that were cogwheel-shaped, spiky, and of high amplitude, compared with normal brushes.[13,14] Frontal and occipital sharp waves were defined as sharp waves of positive polarity in the frontal regions with amplitudes of >100 μV and those of negative polarity in the occipital regions with amplitudes of >150 μV, respectively. PRSWs were defined as sharp waves of positive polarity in the rolandic regions with amplitudes of >100 μV.

In this study, the severity of ASAs and CSAs was categorized as mild, moderate, or severe. These grades are defined in our previous reports.[8,12,15] Mild ASAs were defined when the background amplitude was mildly suppressed but normal continuity of background activity was observed, moderate ASAs when the EEG amplitudes were moderately suppressed and continuity was decreased, and severe ASAs when continuous patterns disappeared completely (burst-suppression pattern). Mildly low voltage refers to δ waves of <200 μV before postconceptional age of 30 weeks or <150 μV at postconceptional age of 30 to 33 weeks. Moderately low voltage refers to δ waves of 20 to 50 μV. Decreased continuity refers to a continuous pattern occupying <10% of the entire record at postconceptional age of <30 weeks or <30% of the entire record at postconceptional age of 30 to 33 weeks. An absent continuous pattern is associated with loss of sleep cycles and reactivity. A mild disorganized pattern (ie, CSAs) was defined when a disorganized pattern without PRSWs was observed intermittently, a moderate disorganized pattern when a disorganized pattern without PRSWs was observed continuously, and a severe disorganized pattern when a disorganized pattern with PRSWs was observed continuously. Samples of these abnormal findings are shown in Figs 2 and 3. Two expert neonatal neurologists evaluated all EEG recordings independently, with blinding with respect to CUS findings. EEG findings were judged as abnormal when both analysts agreed. When ≥2 recordings were obtained in the same period, we used the one with the most-severe findings.

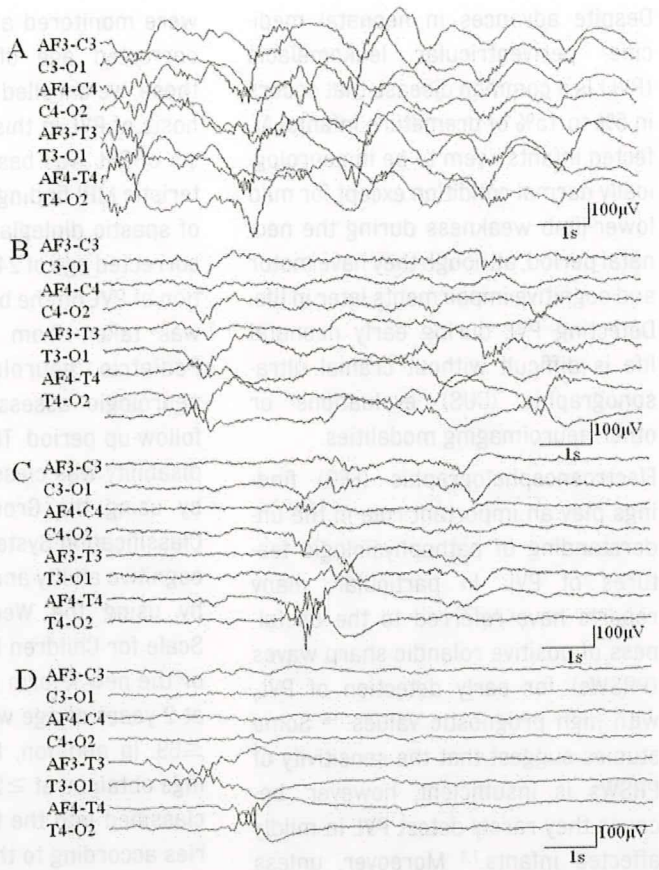

FIGURE 2
EEG samples of various grades of ASAs. A, Normal EEG findings. B, Mild ASAs. The amplitude of the background activities was decreased mildly, but continuity was maintained. C, Moderate ASAs. Continuity was decreased and the amplitude of background activities was reduced moderately. D, Severe ASAs. The continuous patterns were completely absent, indicating a burst-suppression pattern.

Statistical Analyses

Statistical analyses were performed with SPSS 16.0 for Windows (SPSS Inc,

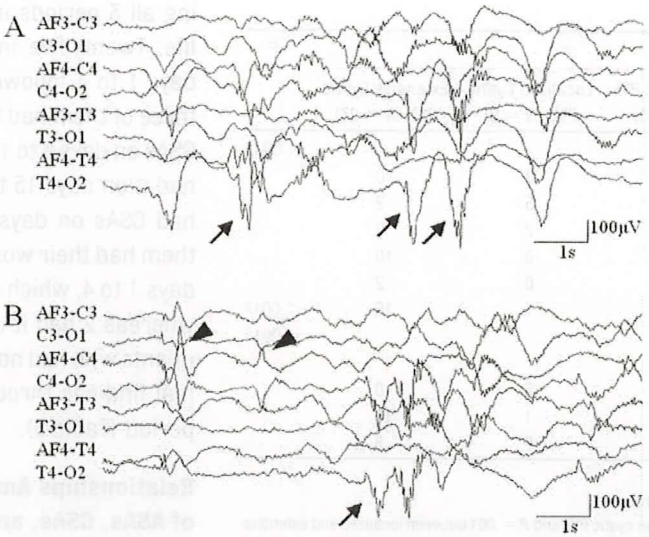

FIGURE 3
EEG samples of various grades of CSAs. A, Moderate CSAs. A disorganized pattern was observed continuously throughout the recordings. Occipital sharp waves and abnormal brushes (arrows) were detected. B, Severe CSAs. PRSWs (arrowheads) were observed, accompanied by a continuous disorganized pattern (arrow).

Chicago, IL) to compare the clinical variables among the 3 groups, by using 1-way analysis of variance for gestational age and birth body weight and the χ^2 test for the other variables. When analysis of variance or the χ^2 test revealed a significant difference, Tukey's test was performed as a posthoc test. Spearman's rank-sum correlation was performed to analyze the correlation among the grading of ASAs and CSAs and the severity of PVL. *P* values of $<.05$ were considered statistically significant.

RESULTS

Patient Characteristics

The sample consisted of 55 infants (7.6%) who were diagnosed as having PVL. The subjects with PVL had a mean gestational age of 29.3 weeks and a mean birth weight of 1292 g. Thirty-two infants were diagnosed as having cystic PVL and 23 infants as having noncystic PVL on the basis of CUS findings. Of the infants with cystic PVL, 9 had localized cystic PVL and 23 extensive cystic PVL. The perinatal characteristics of each group are shown in Table 1.

Thirty of the 32 infants with noncystic or localized cystic PVL had similar findings on MRI scans, consisting of posterior white matter volume loss only. Fifteen infants with extensive cystic PVL had posterior and middle lesions, and 8 had posterior, middle, and anterior lesions. The severity of motor impairment differed markedly among the 3 groups ($P < .001$). Cognitive impairment was observed for 3 of 23 patients with noncystic PVL and 1 of 9 with localized cystic PVL, whereas it was observed for 16 of 23 patients with extensive cystic PVL ($P < .001$) (Table 2).

No infants had CUS abnormalities at birth. Hyperechogenicities were first observed in all infants with cystic PVL between the second and fourth days of life. The mean interval between hyperechogenicities and the appearance of cysts was 18.2 days in localized cystic PVL and 16.0 days in extensive cystic PVL. Two infants experienced intraventriculer hemorrhage during the neonatal period.

Cross-Sectional Aspects of EEG Findings

The cross-sectional aspects of the EEG findings for all infants with PVL are shown in Fig 4. ASAs were observed for 26 (51.0%) of 51 infants on days 1 to 4, 6 (11.3%) of 53 infants on days 5 to 14, and none thereafter. CSAs were observed most often on days 5 to 14. The proportion of CSAs decreased gradually after days 5 to 14. The differences in the chronologic changes in ASAs and CSAs according to the severity of PVL are shown in Figs 5 and 6. To evaluate the frequency of ASAs among the first EEG recordings, we differentiated EEG recordings obtained on days 1 to 2 from those obtained

TABLE 1 Patient Characteristics and Perinatal Complications

	Overall ($N = 55$)	Noncystic PVL ($N = 23$)	Localized Cystic PVL ($N = 9$)	Extensive Cystic PVL ($N = 23$)	*P*
Gestational age, mean ± SD, wk	29.3 ± 2.2	29.0 ± 2.3	30.4 ± 1.3	29.0 ± 2.3	.21
23–26 wk, *n*	4	1	0	3	
27–30 wk, *n*	36	16	5	15	
31–33 wk, *n*	15	6	4	5	
Birth weight, mean ± SD, g	1292 ± 362	1168 ± 342	1512 ± 150	1330 ± 399	.02[a]
Male, *n*	36	15	8	13	.22
Multiple pregnancy, *n*	17	9	3	5	.26
Cesarean section, *n*	48	20	7	21	.59
Prolonged rupture of membranes, *n*	19	7	3	5	.82
Pregnancy-induced hypertension, *n*	6	3	0	0	.11
Tracheal intubation, *n*	44	16	9	19	.14
Respiratory distress syndrome, *n*	38	15	8	15	.37
Hypotension, *n*	4	1	0	3	.34
Treated patent ductus arteriosus, *n*	6	3	0	3	.52
Neonatal infection, *n*	2	2	0	0	.24
Pneumothorax, *n*	1	0	0	1	.49
Necrotizing enterocolitis, *n*	0	0	0	0	1.00

[a] A posthoc test showed $P < .05$ between noncystic PVL and localized cystic PVL.

TABLE 2 Outcomes for Patients in Each Group

	n				*P*
	Overall (*N* = 55)	Noncystic PVL (*N* = 23)	Localized Cystic PVL (*N* = 9)	Extensive Cystic PVL (*N* = 23)	
GMFCS classification					<.001[a]
Grade 1	18	16	2	0	
Grade 2	14	7	5	2	
Grade 3	11	0	2	9	
Grade 4	10	0	0	10	
Grade 5	2	0	0	2	
Cognitive impairment	20	3	1	16	<.001[b] <.001[c]
Lesions of white matter loss on MRI scans					
Posterior only	30	22	8	0	
Posterior and middle only	17	1	1	15	
Posterior, middle, and anterior	8	0	0	8	

GMFCS indicates Gross Motor Function Classification System.

[a] A posthoc test showed significant differences between any 2 groups.

[b] A posthoc test showed $P < .001$ between noncystic and extensive cystic PVL and $P = .001$ between localized and extensive cystic PVL.

[c] A posthoc test showed $P < .001$ between noncystic and extensive cystic PVL and $P < .001$ between localized and extensive cystic PVL.

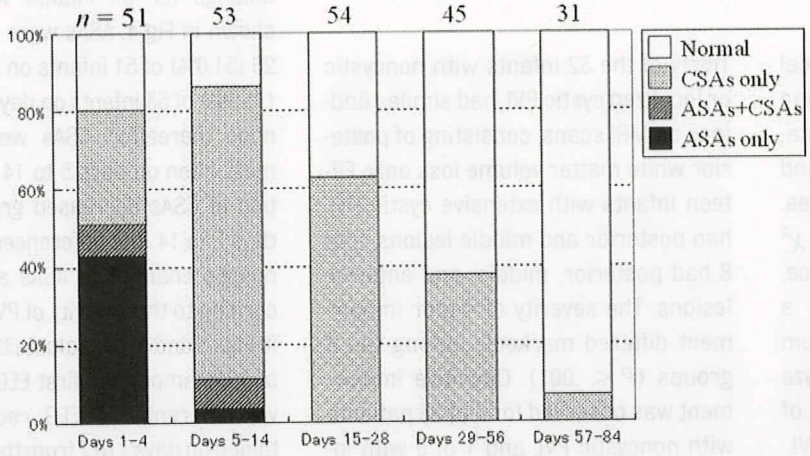

FIGURE 4
Cross-sectional aspects of EEG findings for all infants with PVL. The numbers of patients are indicated above the chart.

on days 3 to 4. ASAs were observed on days 1 to 2 for 41.7% and on days 3 to 4 for 20% of the infants with noncystic PVL, ASAs were observed on days 1 to 2 for 100% and on days 3 to 4 for 50% of the infants with localized cystic PVL, and ASAs were observed on days 1 to 2 for 91.7% and on days 3 to 4 for 30% of the infants with extensive cystic PVL. Severe ASAs were observed exclusively on days 1 to 2 among infants with extensive cystic PVL.

CSAs in the extensive cystic PVL group were most severe and persisted longest among the 3 groups. CSAs were most frequent and severe on days 5 to 14 in all groups. Severe CSAs (ie, PRSWs) were observed for 14 (25.5%) of 55 infants with PVL; all except 1 infant had extensive cystic PVL. Severe ASAs were first observed on days 1 to 4 for 2 infants and on days 5 to 14 for 12 infants.

Longitudinal Aspects of EEG Findings

Six infants were excluded because EEG recordings were not performed during all 3 periods in the first month of life. Twenty-five infants had ASAs on days 1 to 4 followed by CSAs. Twenty-three of them had their worst grade of CSAs on days 5 to 14, whereas 2 infants had it on days 15 to 28. Fifteen infants had CSAs on days 1 to 4. Thirteen of them had their worst grade of CSAs on days 1 to 4, which resolved thereafter, whereas 2 had it on days 5 to 14. Five infants who had noncystic PVL had normal findings throughout the neonatal period (Table 3).

Relationships Among the Severity of ASAs, CSAs, and PVL

With the exclusion of 19 infants for whom CSAs were recognized on the first EEG recording, 36 infants were enrolled to investigate the relationship between the severity of ASAs and CSAs (Fig 7). If CSAs were observed several times in serial recordings, then the most-severe findings were used. Mild ASAs were followed by mild CSAs in 17% of cases, by moderate CSAs in 42%, and by severe CSAs in 25%. Moderate ASAs were followed by mild CSAs in 27% of cases, by moderate CSAs in 36%, and by severe CSAs in 36%. Severe ASAs were followed by severe CSAs in all cases. Statistically significant correlations were observed between the severity of ASAs and that of CSAs ($P = .003$), the severity of ASAs and that of PVL ($P = .034$), and the severity of CSAs and that of PVL ($P < .001$).

DISCUSSION

We revealed chronologic changes in neonatal EEG findings for infants with PVL. In general, the EEG activities were depressed immediately after birth to varying degrees, depending on the severity of the brain insult. This depressed EEG activity (ie, ASAs) recovered within a few days and was replaced by CSAs. The severity of CSAs was dependent on that of ASAs. CSAs were observed for longer peri-

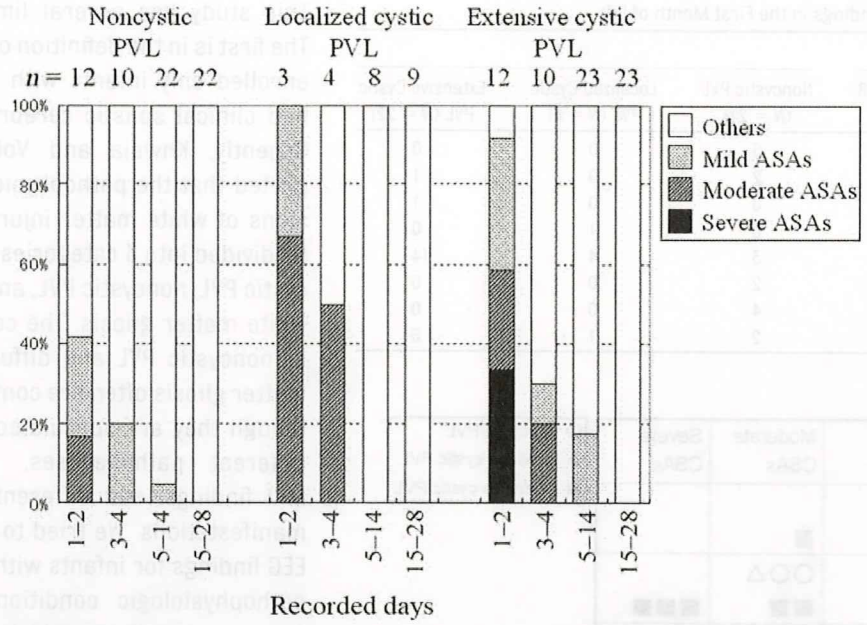

FIGURE 5
Chronologic changes in ASAs according to the severity of PVL. The first recordings on days 1 to 4 were divided into 2 periods, that is, days 1 to 2 and days 3 to 4.

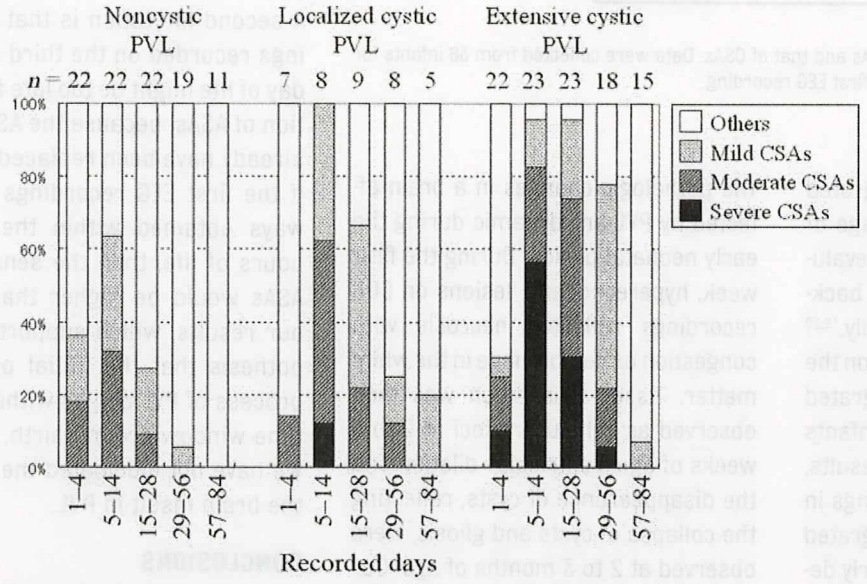

FIGURE 6
Chronologic changes in CSAs according to the severity of PVL.

ods with more-severe insults and disappeared at 1 to 2 months of age. Chronologic EEG changes after an insult were clarified by assessing 2 types of EEG abnormalities and their grades.

Many previous studies on EEG findings in PVL described the diagnostic and prognostic values of several sharp waves, especially PRSWs.[1–5] Baud et al[4] reported that the sensitivity and specificity of PRSWs at >1 per minute were 65% and 99.9%, respectively. Although many studies reported high sensitivity and specificity of PRSWs for the diagnosis of PVL, we detected PRSWs (markers of severe CSAs) only in infants with extensive cystic PVL during days 5 to 28 of life. Our study indicates that EEG findings in PVL differ markedly according to the severity and the timing of recording. Therefore, differences in the sensitivity and specificity of PRSWs can be explained on the basis of differences in the definitions of PRSWs, the study populations, and the timing of EEG recordings in various studies.

To detect PVL, it is important to know an appropriate time for recording. EEG abnormalities in infants with PVL, irrespective of its severity, were observed most often on days 5 to 14. Approximately 90% of infants had their worst grade of CSAs at that time. The worst grade of CSAs was strongly associated with the severity of PVL. In addition, we reported previously that the specificity of CSAs was 84% to 100%.[16,17] Therefore, EEG recording on days 5 to 14 is essential for accurate detection of PVL. It is also recommended that EEG findings be evaluated on days 1 to 4, if possible within the first 48 hours of life. ASAs are earlier EEG markers than are CSAs or PRSWs. ASAs themselves had a strong association with the severity of later outcomes.[15] The specificity of ASAs was 91% to 95%, which indicates their diagnostic value.

Serial EEG recordings are essential not only for predicting outcomes more accurately but also for determining the timing of brain injury in PVL.[18] For these reasons, we recommend that ≥2 serial EEG recordings be obtained for evaluation of the brain injury of PVL, 1 within 48 hours after birth, to detect ASAs, and 1 in the second week of life, to detect CSAs, because ASAs and CSAs were at their worst during these periods regardless of the severity of PVL.

Continuous EEG monitoring with amplitude-integrated EEG techniques has been used to evaluate brain func-

TABLE 3 Longitudinal Changes in EEG Findings in the First Month of Life

EEG Findings			*n*		
Days 1–4	Days 5–14	Days 15–28	Noncystic PVL ($N = 21$)	Localized Cystic PVL ($N = 6$)	Extensive Cystic PVL ($N = 22$)
Normal	Normal	Normal	5	0	0
Normal	CSAs ± ASAs	Normal	2	0	1
Normal	CSAs ± ASAs	CSAs	0	0	1
ASAs	CSAs ± ASAs	Normal	3	1	0
ASAs	CSAs ± ASAs	CSAs	3	4	14
CSAs	Normal	Normal	2	0	0
CSAs	CSAs	Normal	4	0	0
CSAs	CSAs	CSAs	2	1	6

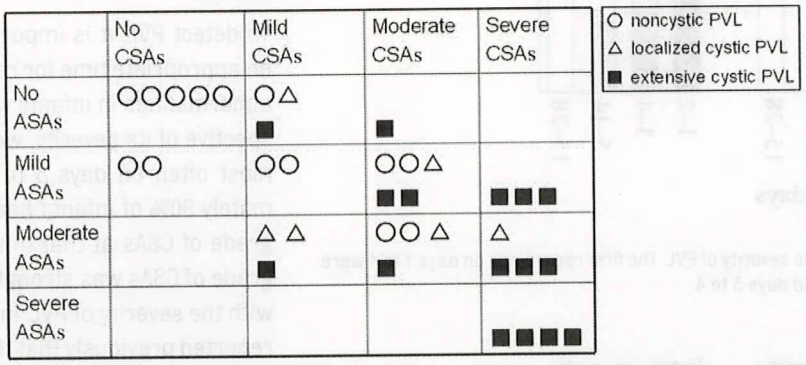

FIGURE 7
Relationship between the severity of ASAs and that of CSAs. Data were collected from 36 infants for whom CSAs were not recognized on the first EEG recording.

tion in neonates. Amplitude-integrated EEG monitoring has the advantage of allowing nonexpert clinicians to evaluate the degree of depression of background EEG activities more easily.[19,20] To date, however, sufficient data on the usefulness of amplitude-integrated EEG monitoring for preterm infants have not been gathered. Our results, based on conventional EEG findings in PVL, suggest that amplitude-integrated EEG recordings are useful for early detection of PVL in preterm infants if the recordings are started immediately after birth. However, they are not useful for detecting CSAs because the abnormal sharp or faster waves that are characteristic of CSAs cannot be detected with amplitude-integrated EEG findings alone. Therefore, additional raw EEG evaluation or another trend graph, such as the spectral edge frequency,[21] is necessary for detection of CSAs.

The pathologic changes in a brain affected by PVL are dynamic during the early neonatal period. During the first week, hyperechogenic lesions on CUS recordings reflected necrosis with congestion or hemorrhage in the white matter. Tissue dissolution was then observed as echolucent foci at 2 to 3 weeks of age. Ventricular dilation and the disappearance of cysts, reflecting the collapse of cysts and gliosis, were observed at 2 to 3 months of age. Our study showed that ASAs on EEG recordings were usually detected within a few days of life, which indicates that the pathologic changes had already begun. In contrast, CSAs were observed during the hyperechogenic stage on CUS scans. The ongoing damage and reconstruction of axons and glia in the deep white matter represented as hyperechogenicity on CUS scans may be associated with CSAs on EEG recordings.

This study has several limitations. The first is in the definition of PVL. We enrolled only infants with PVL who had clinical spastic cerebral palsy. Recently, Khwaja and Volpe[22] reported that the pathophysiologic lesions of white matter injury should be divided into 3 categories, namely, cystic PVL, noncystic PVL, and diffuse white matter gliosis. The conditions of noncystic PVL and diffuse white matter gliosis often are confused, although they are speculated to have different pathogeneses, different MRI findings, and different clinical manifestations. We tried to evaluate EEG findings for infants with a single pathophysiologic condition. Therefore, our results should be considered for infants with noncystic or cystic PVL and not for infants with diffuse white matter gliosis alone.

A second limitation is that EEG findings recorded on the third or fourth day of life might be too late for detection of ASAs, because the ASAs might already have been replaced by CSAs. If the first EEG recordings were always obtained within the first 48 hours of life, then the sensitivity of ASAs would be higher than that in our results, which supports the hypothesis that the initial pathologic process of PVL begins within a short time window around birth, although we have not elucidated the origin of the brain insult in PVL.

CONCLUSIONS

The EEG findings for infants with PVL differed markedly depending on the severity of PVL and the timing of recording. To evaluate brain injury in PVL, ≥2 EEG recordings are recommended, 1 within 48 hours of life, to detect ASAs, and 1 in the second week of life, to detect CSAs.

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Chronologic Changes in Neonatal EEG Findings in Periventricular Leukomalacia

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