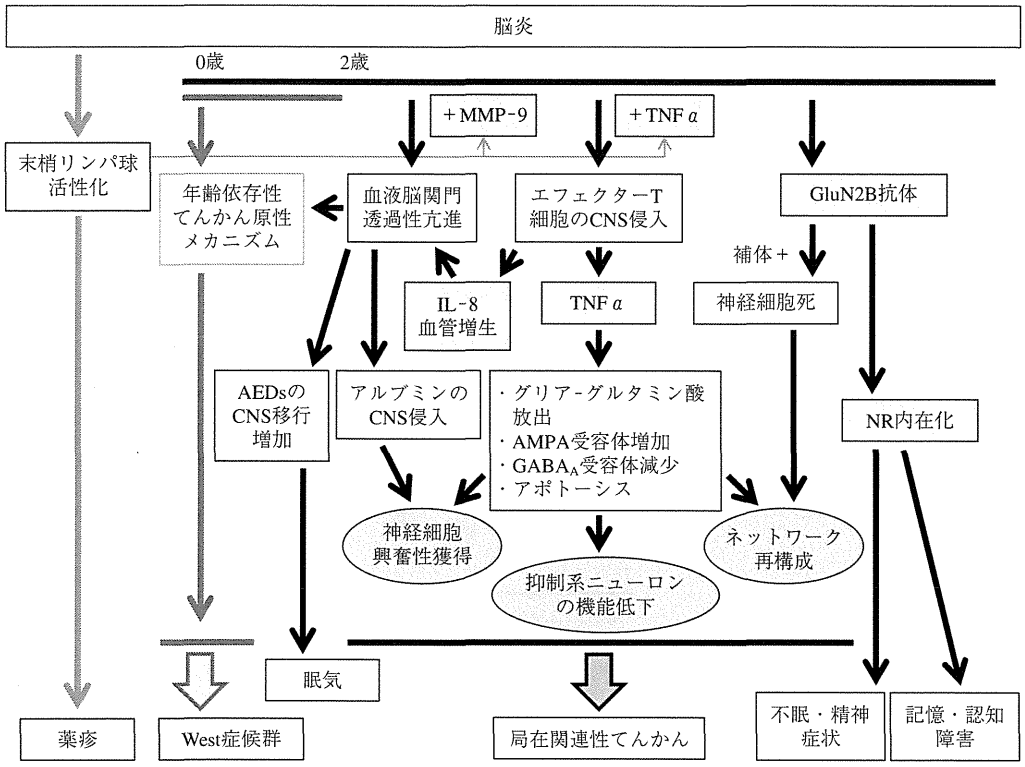

図7 脳炎後てんかんにおける免疫，生化学病態

MMP-9：matrix metalloploteinase 9，TNFα：tumor necrosis factor α，NR：N-methyl-D-aspartate（NMDA）type GluR，AMPA：alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid，GABA：γ-aminobutyric acid，CNS：central nervous system，AEDs：antiepileptic drugs.

脳炎後てんかんの血液脳関門障害は，MMP-9，TIMP-1のみならず，IL-8の幼弱血管増生作用も関与している可能性が大きい[13]．

脳炎後5年かけて血液脳関門障害が進行性に悪化することが，てんかん発作・知的障害の慢性期の悪化の一因となっていると推測している．血液脳関門障害により，髄液TNF αなどのサイトカインが増加し，神経細胞死が増え[14]，AMPA型GluR増加とGABA$_A$受容体を減少が起こり，神経興奮性を高めている可能性がある[15]．血液脳関門障害により髄液GluN2B抗体なども上昇し，LTP抑制が起こっている可能性がある．

脳炎後てんかん症例での抗てんかん薬治療では，38.8%と高頻度に眠気が出現するが，血液脳関門の障害で抗てんかん薬の中枢神経系への移行が強いためと推測している[13]．

6. 高頻度の薬疹

脳炎後てんかんでは薬疹が23.9%と高頻度に出現する[16]．薬疹症例では血清RANTESが高く，薬疹出現に関与している可能性がある．脳炎後てんかんの病態には免疫応答が関与しており，アレルギー反応を含め副作用が起こりやすい状態である可能性があると思われる．ただし，急性期に薬疹が出ても，DLSTなどを参考に再使用可能な場合がある．

ま と め

脳炎後てんかんでは，自己抗体やサイトカインなどの免疫因子，MMP-9やTIMP-1などの生化学因子が病態に関与して，難治なてんかん発作，併存症の問題が起こっている可能性がある．今後さらなる検討が必要である．

第55回日本小児神経学会総会において貴重な発表の機会をお与えいただきました，泉達郎教授，高橋孝雄教授，廣瀬伸一教授に深謝申し上げます．この研究は下記の研究費の支援を受けて行われた，科研費21591342，23591238，24591537；厚生科研障害者対策総合研究；難治性疾患等克服研究；てんかん治療振興財団；平成25年国立病院機構 政策医療ネットワーク共同研究．

著者の利益相反：本論文発表内容に関連して開示すべき事項なし．

文 献

1) Kwan P, Brodie MJ. Early identification of refractory epilepsy. *N Engl J Med* 2000;**342**:314-9.
2) Beghi E, Nicolosi A, Kurland LT, Mulder DW, Hauser WA, Shuster L. Encephalitis and aseptic meningitis, Olmsted County, Minnesota, 1950-1981:I. Epidemiology. *Ann Neurol* 1984;**16**:283-94.
3) Lee WT, Yu TW, Chang WC, Shau WY. Risk factors for postencephalitic epilepsy in children:a hospital-based study in Taiwan. *Eur J Paediatr Neurol* 2007;**11**:302-9.
4) 高橋幸利，山崎悦子，長尾雅悦，ら．急性脳炎の後遺症に関する調査．—ADL・てんかん発作・知的障害・精神障害・記憶障害・運動障害—Neuroinfection 2009;**14**:106-12.

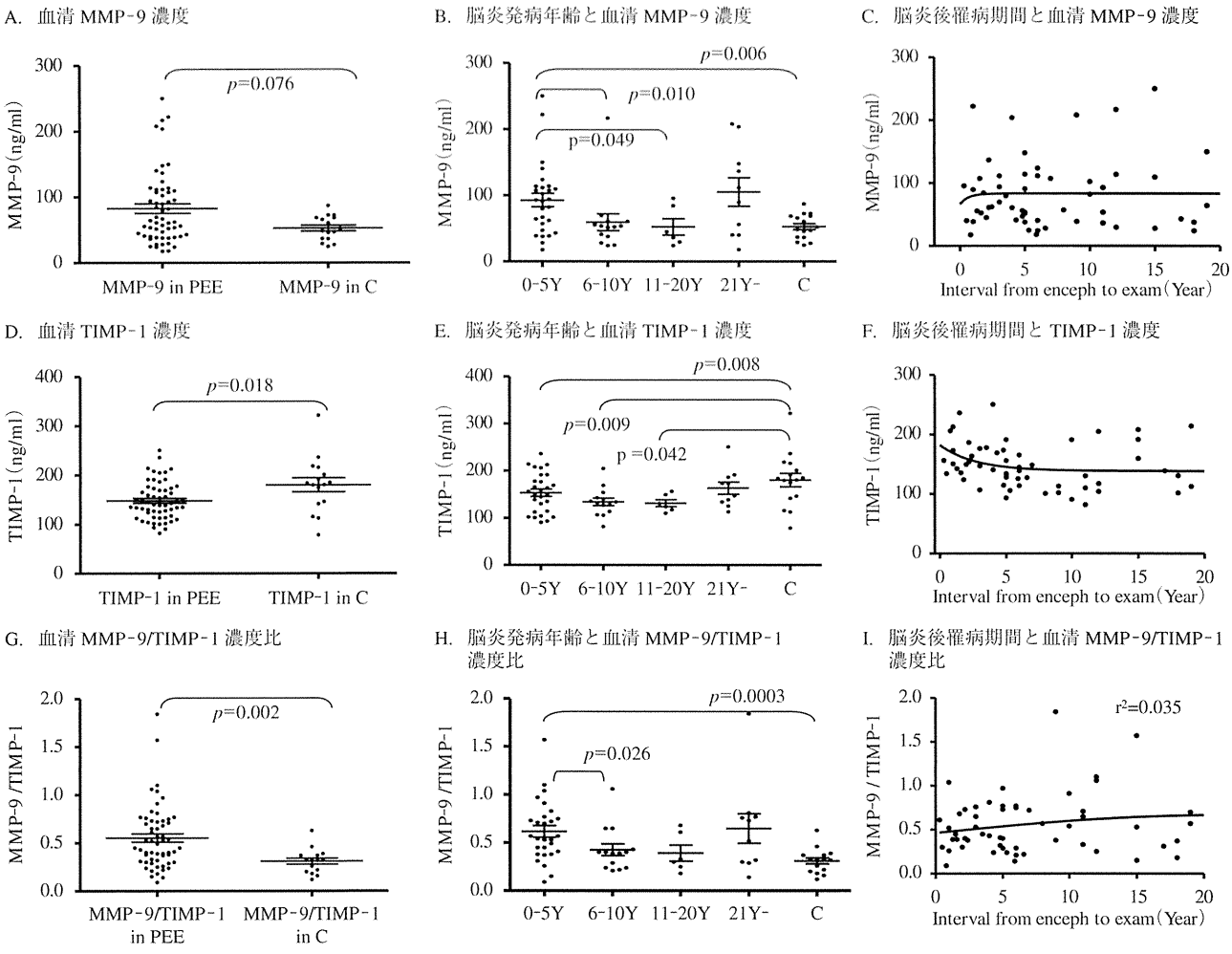

図 8 脳炎後てんかんにおける血液脳関門障害

PEE：脳炎後てんかん（postencephalitic epilepsy），C：対照（control subjects）．
MMP-9（matrix metalloploteinase-9）は activity assay kit（Amersham, Buckinghamshire, England）で測定．TIMP-1（tissue inhibitor of metalloproteinase-1）は sandwich type ELISA kit（Daiichi Fine Chemical Co., Ltd.）で測定．グラフ内の長い横棒は平均値，短い横棒は±standard error を示す．

5) Fujita K, Yuasa T, Takahashi Y, et al. Antibodies to N-methyl-D-aspartate glutamate receptors in Creutzfeldt-Jakob disease patients. *J Neuroimmunol* 2012;**251**:90-3.
6) 高橋幸利．グルタミン酸受容体抗体の意義．脳と発達 2013;**45**:99-105.
7) 高橋幸利，保立麻美子，植田佑樹，山口解冬，那須裕郷．Antibody Update グルタミン酸受容体自己抗体．*Brain Nerve* 2013;**65**:345-53.
8) 高橋幸利，西村成子，高尾恵美子，ら．GluRε2 抗体（NR2B 抗体）―神経疾患における意義．神経内科 2013;**79**:354-62.
9) DeGiorgio LA, Konstantinov KN, Lee SC, Hardin JA, Volpe BT, Diamond B. A subset of lupus anti-DNA antibodies cross-reacts with the NR2 glutamate receptor in systemic lupus erythematosus. *Nat Med* 2001;**7**:1189-93.
10) 高橋幸利，植田佑樹，保立麻美子．病因．辻 貞敏，編．新しい診断と治療の ABC74/神経 5 てんかん．大阪：最新医学社，**2012**:60-71.
11) Zhang Q, Tanaka K, Sun P, et al. Suppression of synaptic plasticity by cerebrospinal fluid from anti-NMDA receptor encephalitis patients. *Neurobiol Dis* 2012;**45**:610-5.
12) Suriadi MM, Takahashi Y, Nishimura S, et al. Dysfunction of blood-brain barrier in epileptic patients after acute encephalitis. *Epileptologia* 2012;**20**:51-61.
13) 最上友紀子，高橋幸利，福山哲広，ら．脳炎・脳症後てんかん症例における抗てんかん薬の副作用の検討―眠気について．脳と発達，2012;**44**:472-6.
14) Bernardino L, Xapelli S, Silva AP, et al. Modulator effects of interleukin-1beta and tumor necrosis factor-alpha on AMPA-induced excitotoxicity in mouse organotypic hippocampal slice cultures. *J Neurosci* 2005;**25**:6734-44.
15) Stellwagen D, Beattie EC, Seo JY, et al. Differential regulation of AMPA receptor and GABA receptor trafficking by tumor necrosis factor-alpha. *J Neurosci* 2005;**25**:3219-28.
16) Mogami Y, Takahashi Y, Takayama R, et al. Cutaneous adverse drug reaction in patients with epilepsy after acute encephalitis. *Brain Dev* 2012;**34**:496-503.

FULL-LENGTH ORIGINAL RESEARCH

Posterior quadrant disconnection surgery for Sturge-Weber syndrome

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Summary

Objective: Some patients with Sturge-Weber syndrome (SWS) need epilepsy surgery for adequate seizure control and prevention of psychomotor deterioration. The majority of patients with SWS have leptomeningeal angioma located over the temporal, parietal, and occipital lobes. We applied posterior quadrant disconnection surgery for this type of SWS with intractable seizure. We evaluated the efficacy of this procedure in seizure control and psychomotor development.

Methods: Ten patients who were surgically treated using the posterior quadrantectomy (PQT) were enrolled in this study. Surgical outcome was analyzed as seizure-free or not at 2 years after surgery. Psychomotor development was evaluated by the scores of mental developmental index (MDI) and psychomotor developmental index (PDI) in the Bayley Scales of Infant Development II preoperatively, and at 6 and 12 months after the PQT.

Results: Eight of 10 patients were seizure-free. Patients without complete elimination of the angiomatous areas had residual seizures. Average MDI and PDI scores before the surgery were 64.8 and 71.6, respectively. Scores of MDI at 6 and 12 months after the PQT in seizure-free patients were 80.5 and 84.5, respectively ($p < 0.01$). PDI scores at these postoperative intervals were 87.3 and 86.4, respectively ($p < 0.05$). Patients with residual seizures did not improve in either MDI or PDI.

Significance: The PQT achieved good seizure control and improved psychomotor development in patients with SWS. The complete deafferentation of angiomatous areas is required for seizure-free results and psychomotor developmental improvement.

KEY WORDS: Sturge-Weber syndrome, Epilepsy surgery, Posterior quadrantectomy, Seizure outcome, Psychomotor development.

Historically, intractable multilobar epilepsy has been treated with resective surgery, performing the removal of large parts of the hemisphere. However, superficial hemosiderosis occurs as a severe complication after large resective procedures.[1,2] Therefore, to prevent this complication, disconnection surgeries such as functional hemispherectomy and hemispheric differentiation, hemispherotomy, and posterior quadrantectomy were developed for these cases. Understanding that interruption of the epileptic discharge propagation pathways has the same effect as removing the focus, resection surgeries were effectively modified into disconnective ones.[3–8] Therefore, currently, disconnective surgeries yield the same or better results with lower complication rates compared to resections. This is valid also for the current approach to surgical technique in Sturge-Weber syndrome (SWS).

Recently, surgical treatment by multilobular resection or disconnection in cases of posterior quadrant located foci has been increasingly used, although the frequency of these procedures account for <5% of all epilepsy surgeries.[3] In the

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majority of patients, the SWS leptomeningeal angioma involves the posterior quadrant, which justifies selective posterior quadrant disconnective surgery for this type of SWS. Similar to cases with intractable epilepsy due to complete unilateral hemispheric involvement, early surgery should be carried out for patients with epileptic foci in this area. In this study, we introduce the techniques and the details related to posterior quadrantectomy, and we evaluate its effectiveness for epilepsy control and psychomotor development.

Methods

We have followed 75 patients with SWS since 1986–2011 in Juntendo University, Tokyo, Japan. Clinical evaluation included clinical, electrophysiologic, neuroimaging, and neuropsychological examinations in all patients. The territory of leptomeningeal angioma was evaluated using magnetic resonance imaging (MRI) with contrast-enhanced fluid-attenuated inversion recovery (FLAIR) imaging.[9] We classified those patients into the following three groups according to the area involved by the leptomeningeal angioma: *bilateral*, *hemispheric*, and *partial*. We had six patients in the bilateral, 14 in the hemispheric, and 55 patients in the partial group. A hemispherotomy was indicated for all patients of the hemispheric group, and a corpus callosotomy was carried out for all of them in the bilateral group. Ten of 55 patients in the partial group were indicated for posterior quadrantectomy (PQT; Fig. 1).

We enrolled 10 patients with PQTs, six boys and four girls, in this study. The mean age at the time of surgery was 2 years and 4 months, and ranged from 8 months to 8 years. The postoperative follow-up period was from 24 to 47 months. In five patients the leptomeningeal angioma was in the left hemisphere, and in five it was in the right. Invasive EEG monitoring using subdural electrodes was indicated for one patient as a presurgical evaluation. That boy had continuous delay of psychomotor development; however, we did not confirm his clinical seizures on several occasions of video–scalp electroencephalography (EEG) monitoring. We speculated that he had several undetectable seizures that caused his developmental deterioration, and implanted subdural electrodes to confirm ictal activity. We obtained four subclinical seizures during 3 days of monitoring, and the seizure discharges came from within the posterior quadrant area. Postsurgical examinations were performed approximately every 6 months using clinical evaluation, assessment of seizure outcome, MRI, EEG, and neuropsychological batteries for all patients. We evaluated the seizure outcome, change of psychomotor development related to PQT in this study.

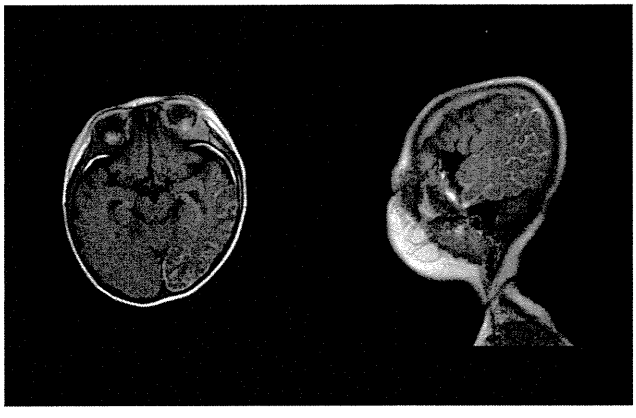

Figure 1.
Sturge-Weber syndrome with leptomeningeal angioma distributed in the posterior quadrant. The majority of our SWS patients (55/75) have the leptomeningeal angioma distributed in the temporal, parietal, and occipital lobes in our series. MRI with contrast-enhanced FLAIR imaging shows the accurate territory of leptomeningeal angioma. Ten of 55 patients were diagnosed with intractable epilepsy with continuous deterioration of psychomotor development and indicated for posterior quadrantectomy.

The posterior quadrantectomy surgical procedure

The patient's head was fixed on a horseshoe-shaped headrest 45 degrees rotation to the opposite side of the craniotomy. We used a neuronavigation system (Stealth station navigation system cranial application version 5; Medtronic, (Minneapolis, MN, U.S.A.) for this surgery. Before the skin incision, we simulated and decided on the disconnection line over the scalp using the neuronavigation system. Subsequently based on that we designed the craniotomy and the curvilinear scalp incision to expose adequate surgical field (Fig. 2).

After the craniotomy, we began with opening of the sylvian fissure. Because the temporal lobe is atrophic in almost all patients with SWS whose leptomeningeal angioma distributes in the posterior quadrant, the sylvian fissure is relatively easy to dissect. Widening the sylvian fissure provided adequate surgical field around the insular cortex and circular sulcus without brain retraction. The landmarks at this stage were the entire course of the circular sulcus, limen insulae, and M2 and M3 portions of the middle cerebral artery. Preservation of arteries and veins was preferable to reduce some not clearly predictable complications, such as postoperative temporal lobe swelling. The resection of cortex at the circular sulcus and white matter in the temporal stem was carried out and continued to the inferior horn of the lateral ventricle. Pes hippocampi and amygdala could be clearly observed at this stage. Subsequently, the amygdala was resected, and the uncinate fascicule was divided to disconnect anterior temporal lobe from frontal lobe. Disconnection of the temporal stem was continued to the posterior end of the circular sulcus, and the entire hippocampus from head to tail was exposed at this stage (Fig. 3).

Next, the direction of disconnection ascended to the parietal lobe. The line of disconnection of the parietal lobe was

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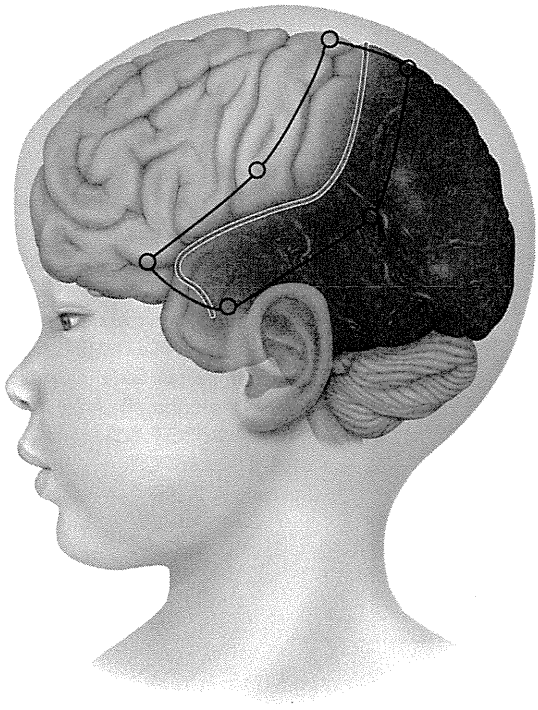

Figure 2.
Scalp incision. A curvilinear scalp incision is designed using the neuronavigation system as tracing over the supposed disconnection line. Craniotomy should be planned to obtain an adequate surgical field. Red line shows scalp incision, and black lines are margins of the free bone flap.
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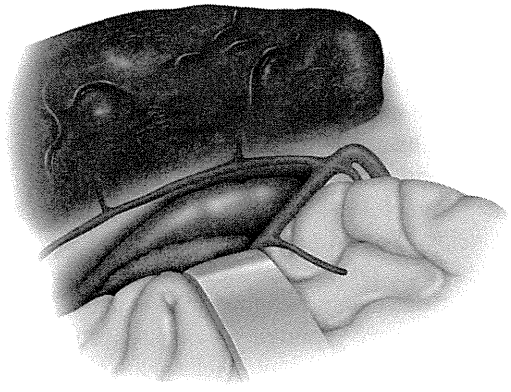

Figure 3.
Dissection of sylvian fissure. The key procedure of PQT is wide dissection of the sylvian fissure. Adequate surgical field can be obtained for exposure of limen insulae, circular sulcus, and branches of middle cerebral artery through the sylvian fissure. Temporal lobe disconnection can be accomplished from the circular sulcus to the inferior horn of lateral ventricle.
Epilepsia © ILAE

confirmed using neuronavigation. Central sulcus localization could be obtained by navigation and somatosensory evoked potentials. Disconnection at the distal end of circular sulcus was extended to operculum and convexity of the parietal lobe. Medial landmarks of this longitudinal disconnection were the choroid plexus and the falx. The splenium of corpus callosum was seen between the choroid plexus at trigonum and the falx. The commissural fibers through the splenium of corpus callosum should be divided at this stage. The vein of Galen and the velum interpositum under the divided splenium could be visualized through the arachnoid membrane just before completion of the posterior callosotomy. The distal fimbria was visible between the disconnected splenium and choroid plexus, and there they were divided to disconnect hippocampus. As a whole, the limbic network was deafferented by disconnecting fimbria and interfornicial commissure at this point, without hippocampectomy. Arachnoid membrane of the ambient cistern had to be completely exposed to guarantee the limbic disconnection. Surgical scheme and postsurgical MRI are presented in Figure 4.

The free bone flap was fixed back using absorbable plates. We did not insert any drainage tubes in ventricular, epidural, or subcutaneous spaces for this surgery.

Seizure and psychomotor developmental evaluation

Assessments of seizure outcome, clinical neurologic condition, MRI, and EEG were undertaken every 6 months after surgery. Seizure outcome was evaluated as seizure-free or residual seizures 24 month after the PQT. All patients continued the antiepileptic drugs after surgery at presurgical prescription and dosage for the same period.

The neuropsychological evaluations were performed using the Bayley Scales of Infant Development II (BSID-II) in Japanese translation.[10,11] These evaluations were done every 6 months after surgery for all patients younger than 4 years of age. One patient operated at the age of 8 was excluded in the neuropsychological evaluation using the BSID-II. We compared the preoperative results of mental developmental index (MDI) and psychomotor developmental index (PDI) in BSID-II to those 6 and 12 months after the PQT, respectively.

The BSID-II data were analyzed using SPSS version 18 for Windows (IBM SPSS, IBM Japan, Chuo-ku, Tokyo, Japan). Repeated measures analysis of variance (ANOVA) was performed to investigate the changes after the PQT on MDI and PDI, respectively. On analysis for MDI, because these data were satisfying for sphericity, we analyzed them using Mauchly's test of sphericity. On analysis for PDI, because these data were violating sphericity, we applied Greenhouse-Geisser test and Huynh-Feldt test. A p-value < 0.05 was considered statistically significant.

Results

Seizure and neurologic outcome

Eight of 10 patients resulted seizure-free after surgery. Two patients were initially seizure-free; however, their sei-

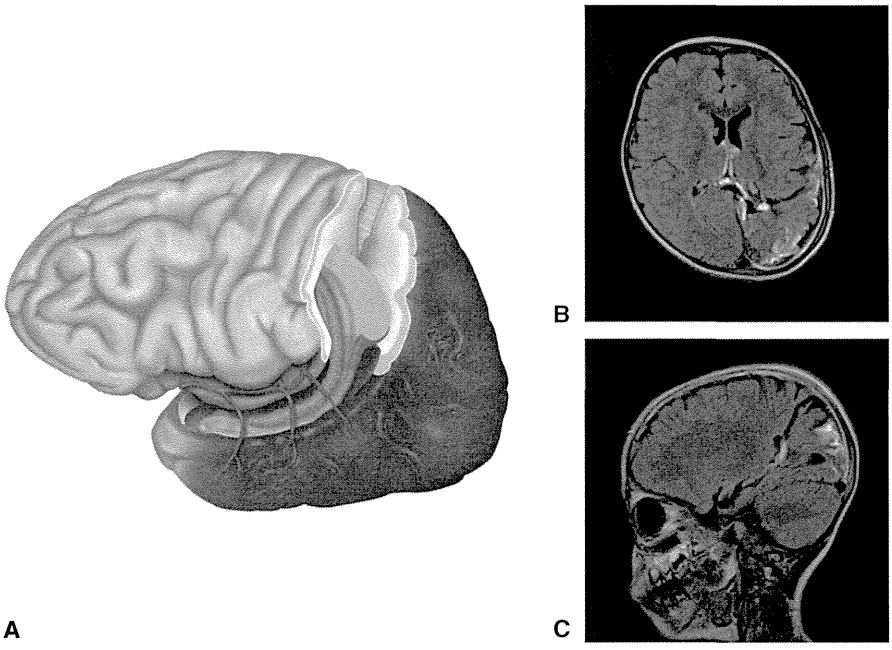

Figure 4.
Scheme of the PQT and postsurgical MRI. (**A**) The scheme presents the disconnection line of PQT. Pink zone represents the posterior callosotomy, and red area means disconnection of distal fimbria and hippocampal tail. See the detail in the Methods section. (**B**) Axial image of MRI in post-PQT. (**C**) Sagittal image of MRI in post-PQT.
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zures recurred 3–6 months after surgery. Seizure recurrence in one of these patients had the same semiology and frequency as those of presurgery, whereas in the other they changed from dyscognitive to focal facial motor type. We concluded that an incomplete disconnection was done in the first case, and revised the PQT again at a second surgery. An uncompletely disconnected region was high in the parietal lobe convexity. This patient became seizure-free after the second surgery. For the second patient, we found other epileptic foci with the leptomeningeal angioma in the left insular cortex and frontal operculum that we had not found out at the initial neuroimaging evaluation. We added cortical resection for those regions at the second surgery, although his seizures continued even after that.

Seven of the 10 patients had leptomeningeal angioma within the posterior quadrant. Three patients had the angioma extending also to the frontal lobe. One patient had the leptomeningeal angioma in the insular and frontal operculum, and two patients had it in the motor cortex. A patient who had the leptomeningeal angioma in the insular and frontal operculum was already presented earlier. Two patients who had angioma in the motor cortex underwent additional cortical resections to the PQT. Those patients had postoperative hemiparesis. Their seizures were completely controlled but they needed rehabilitation, and finally their motor weakness recovered completely. We did not have any patients with speech disturbance after PQT, even after left posterior quadrant involvement. Hydrocephalus or superficial hemosiderosis were not observed in this series.

Psychomotor development

Impairment of the MDI and PDI in the BISD-II were observed in the patients with intractable seizures before surgery. Average MDI and PDI before surgery were 64.8 and 71.6, respectively. Average MDIs at 6 and 12 months after PQT were 80.5 and 84.5, respectively. Average PDIs at the same points of time were 87.3 and 86.4, respectively. We confirmed statistically significant improvements of MDI and PDI after PQT in patients who became seizure-free after surgery (Fig. 5). Dramatic catch up of psychomotor development appeared within the first 6 months and gradually continued after that. We had two cases with residual seizures, and they did not improve their developmental scores (Fig. 5).

Discussion

Our surgical indications for PQT in SWS were the following: well-localized leptomeningeal angioma in the posterior quadrant, confirmation of seizures originating from the same area from video–scalp EEG monitoring, and developmental delay. Sometimes, we experienced patients with SWS, who had progressive developmental deterioration without any detectable seizures or interictal epileptic discharges.[12,13] As we reported previously, progressive psychomotor deterioration could be a sole clue for having subclinical seizures in patients with SWS.[14] We considered indicated invasive EEG monitoring for patients with progressive developmental delay but undetectable clinical seizures in this study, and found several subclinical seizures. Relative findings leading to surgical decision are progressive atrophy and transient increase of glucose metabolism in the affected cerebral cortex on fluorodeoxyglucose–positron emission tomography (FDG-PET) study. Transient hypermetabolism within the affected area in SWS is known as a finding in recent seizures.[15–17] Therefore, we accept the transient hypermetabolism on FDG-PET study as a relative indication for epilepsy surgery. As a rule, surgical indica-

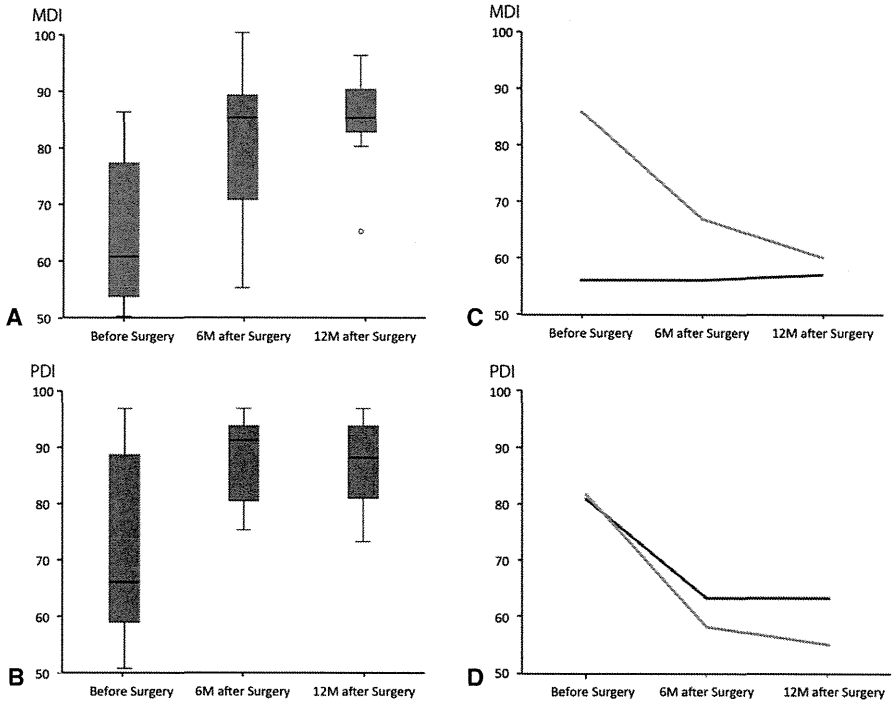

Figure 5.
Mental Developmental Index (MDI) and Psychomotor Developmental Index (PDI) in the Bayley Scales of Infant Development II (BSID-II). Average MDI and PDI before the surgery were 64.8 and 71.6, respectively. (**A**) MDIs at 6 and 12 months after the PQT in the seizure-free patients were 80.5 and 84.5, respectively ($p < 0.01$). (**B**) PDIs at those points were 87.3 and 86.4, respectively ($p < 0.05$). (**C**, **D**) Two patients with residual seizures continued deteriorating both in MDI and PDI even after the PQT.
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tions should be decided from the findings of a comprehensive set of tests and examinations.

Our PQT procedure has much in common with the technique described by Daniel et al.,[3] but differs in the use of neuronavigation system, smaller craniotomy, and wide opening of the sylvian fissure. Our PQT is suitable for the case having temporal lobe atrophy. In cases with atrophy, it is easier to dissect the sylvian fissure and preserve vessels. The surgeon needs sufficient surgical field only around the sylvian fissure and the disconnection line of the parietal lobe. Short distance disconnection of the temporal stem from the circular sulcus exposing the inferior ventricular horn gives us certain surgical orientation. In SWS there are poorly developed sylvian veins and atrophic temporal lobe; therefore, SWS is anatomically appropriate for our modified PQT. The relatively limited surgical field in our modified PQT technique reduces surgical invasiveness and shortens surgical time. Our modified PQT can be used also for cases without atrophy; however, sylvian fissure dissection may require a larger technical effort because of the narrow space. The standard PQT might be a better choice in some of these cases.

Surgical outcome following multilobar surgery is generally accepted as worse than that of a single lobar resection.[18] Koszewski et al.[19] reported on a cohort of 93 patients with multilobar resection, and obtained Engel class I classification in 53% of them. In the series of Daniel et al.,[3] where they focused on surgery of the posterior quadrant, Engel class I outcome was 92% without any mortality or significant morbidity. They emphasized that completeness of removal or disconnection was essential for good surgical outcome. Although in some cases, such as cortical dysplasia, it is difficult to demarcate the margin of epileptic areas, the epileptic zone of SWS is almost equal to the distribution of the leptomeningeal angioma. Therefore, the surgeon should completely disconnect or remove cortex under the leptomeningeal angioma in SWS to obtain good surgical outcome.[20,21] In our series, patients in whom we could disconnect and/or remove the regions under the angioma became seizure-free. Hence, the most important factor for successful surgery in SWS is to delineate the margin of the leptomeningeal angioma on MRI. Postsurgical evaluation using MRI is mandatory to confirm the completeness of the surgery. We had two cases with residual seizures in this series and found that their angiomatous areas were not completely disconnected or eliminated. Since their seizures recurred within 6 months after surgery, we should accept the incompleteness of the initial surgical management within this period.

We had two patients whose leptomeningeal angioma distributed to the motor cortex, beyond the margins of the distinct posterior quadrant. Reorganization of motor function after epilepsy surgery has been already reported.[22,23] Functional recovery after motor cortex injuries was studied mainly in experimental models in animals, and functional imaging studies in humans.[24–28] The primary motor cortex in younger subjects is usually recovered better than the non-primary motor area in adults.[27] Areas that can compensate for motor function are reported in the premotor cortex, supplementary motor area, and parietal lobe in the affected hemisphere, and the contralateral hemisphere.[25,28–31] In order to compensate the motor function, only cortex

removal and not beyond, particularly not interfering with the descending corticospinal tract, is essential.[22,32] From these findings, resection of only the primary motor cortex with preserving underlining corticospinal tract in a young child can compensate motor function even after initial weakness. Therefore, in cases with a leptomeningeal angioma distributed in and beyond the posterior quadrant to the primary motor cortex, the surgeon should consider the PQT complemented with additional motor cortex removal to improve the surgical and developmental outcomes.

Speech function should be a concern, especially in dominant hemisphere surgery. Surgery before the age of 5 is favorable for speech recovery.[33,34] We did not have morbidity related to speech function. Except for an 8-year-old girl with left side involvement, all of our patients underwent surgery before the age of 4 years, and that might have been the reason for not having speech deficit. Speech function of our patients might have been readapted through neural plasticity after surgery, or even before that, as this is a congenital lesion. Although we could not evaluate the language mapping in the 8-year-old patient because she did not cooperate with the test, her speech function did not deteriorate after the PQT. Some reports support reorganization of speech areas even after the age of 8.[35,36] In children with progressively deteriorating psychomotor development due to intractable seizures, surgery aiming at psychomotor recovery has to be considered even in those older than 5 years. Lippe et al.[37] reported that brain plasticity after parietooccipital epilepsy surgery in young children allows for an acceptable scholastic level of cognitive skills such as reading and arithmetic. They also indicated that recovery of visual perceptive cognition is limited compared to verbal functions. Our patients after PQT have never complained about problems with their contralateral visual field areas, and their routine daily performance was as without having visual field defect. Pediatric patients after occipital or posterior quadrant resection or disconnection can compensate their visual field defect by unintentional moving of their eyes and/or head position. Because uncontrollable seizures are the reason for their deteriorated cognition, early epilepsy surgery for pediatric patients with posterior quadrant epileptic involvement offers the possibility of optimizing cognitive outcomes even at the expense of visual field defect.

Our PQT modification can achieve complete disconnection of the affected posterior quadrant through a small craniotomy and reduce the surgical invasiveness for patients with atrophic temporal lobe such as in SWS. The use of a neuronavigation system is required for surgical planning and is helpful for confirmation of complete disconnection during surgery, even with adequate understanding of interlobar connective anatomy. With seizure control as the main objective, the results of use of our PQT method showed it to be an effective technique to achieve it. Complete seizure control after surgery improved psychomotor development. Therefore, we can recommend this procedure for epileptic children with partial type of SWS involving mainly the posterior quadrant.

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Disclosure

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

References

1. Rasmussen T. Postoperative superficial hemosiderosis of the brain, its diagnosis, treatment and prevention. *Trans Am Neurol Assoc* 1973;98:133–137.
2. Villemure JG. Anatomical to functional hemispherectomy from Krynauw to Rasmussen. *Epilepsy Res Suppl* 1992;5:209–215.
3. Daniel RT, Meagher-Villemure K, Farmer JP, et al. Posterior quadrantic epilepsy surgery: technical variants, surgical anatomy, and case series. *Epilepsia* 2007;48:1429–1437.
4. Delalande O, Bulteau C, Dellatolas G, et al. Vertical parasagittal hemispherotomy: surgical procedures and clinical long-term outcomes in a population of 83 children. *Neurosurgery* 2007;60:ONS19–ONS32; discussion ONS.
5. Schramm J, Behrens E, Entzian W. Hemispherical deafferentation: an alternative to functional hemispherectomy. *Neurosurgery* 1995;36:509–515; discussion 15–6.
6. Schramm J, Kral T, Clusmann H. Transsylvian keyhole functional hemispherectomy. *Neurosurgery* 2001;49:891–900; discussion -1.
7. Shimizu H, Maehara T. Modification of peri-insular hemispherotomy and surgical results. *Neurosurgery* 2000;47:367–372; discussion 72–3.
8. Villemure JG, Mascott CR. Peri-insular hemispherotomy: surgical principles and anatomy. *Neurosurgery* 1995;37:975–981.
9. Griffiths PD, Coley SC, Romanowski CA, et al. Contrast-enhanced fluid-attenuated inversion recovery imaging for leptomeningeal disease in children. *AJNR Am J Neuroradiol* 2003;24:719–723.
10. Berk RA. The discriminative efficiency of the Bayley Scales of infant development. *J Abnorm Child Psychol* 1979;7:113–119.
11. Lung FW, Shu BC, Chiang TL, et al. Predictive validity of Bayley scale in language development of children at 6–36 months. *Pediatr Int* 2009;51:666–669.
12. Arzimanoglou A, Aicardi J. The epilepsy of Sturge-Weber syndrome: clinical features and treatment in 23 patients. *Acta Neurol Scand Suppl* 1992;140:18–22.
13. Jansen FE, van Huffelen AC, Witkamp T, et al. Diazepam-enhanced beta activity in Sturge Weber syndrome: its diagnostic significance in comparison with MRI. *Clin Neurophysiol* 2002;113:1025–1029.
14. Sugano H, Nakanishi H, Nakajima M, et al. Seizures continue even after prompt anti-epileptic drug medication in Sturge-Weber syndrome–study from prolonged video electrocoticography, a case report. *Childs Nerv Syst* 2009;25:143–146.
15. Alkonyi B, Chugani HT, Juhasz C. Transient focal cortical increase of interictal glucose metabolism in Sturge-Weber syndrome: implications for epileptogenesis. *Epilepsia* 2011;52:1265–1272.
16. Alkonyi B, Miao Y, Wu J, et al. A perfusion-metabolic mismatch in Sturge-Weber syndrome: a multimodality imaging study. *Brain Dev* 2012;34:553–562.
17. Chugani HT, Mazziotta JC, Phelps ME. Sturge-Weber syndrome: a study of cerebral glucose utilization with positron emission tomography. *J Pediatr* 1989;114:244–253.

18. Leiphart JW, Peacock WJ, Mathern GW. Lobar and multilobar resections for medically intractable pediatric epilepsy. *Pediatr Neurosurg* 2001;34:311–318.
19. Koszewski W, Czarkwiani L, Bidzinski J. Multilobar resections in surgical treatment of medically intractable epilepsy. *Neurol Neurochir Pol* 1998;32(Suppl. 2):81–94.
20. Arzimanoglou AA, Andermann F, Aicardi J, et al. Sturge-Weber syndrome: indications and results of surgery in 20 patients. *Neurology* 2000;55:1472–1479.
21. Bourgeois M, Crimmins DW, de Oliveira RS, et al. Surgical treatment of epilepsy in Sturge-Weber syndrome in children. *J Neurosurg* 2007;106:20–28.
22. Barba C, Montanaro D, Frijia F, et al. Focal cortical dysplasia type IIb in the rolandic cortex: functional reorganization after early surgery documented by passive task functional MRI. *Epilepsia* 2012;53:e141–e145.
23. Benifla M, Sala F Jr, Jane J, et al. Neurosurgical management of intractable rolandic epilepsy in children: role of resection in eloquent cortex. Clinical article. *J Neurosurg Pediatr* 2009;4:199–216.
24. Baciu M, Le Bas JF, Segebarth C, et al. Presurgical fMRI evaluation of cerebral reorganization and motor deficit in patients with tumors and vascular malformations. *Eur J Radiol* 2003;46:139–146.
25. Calautti C, Leroy F, Guincestre JY, et al. Dynamics of motor network overactivation after striatocapsular stroke: a longitudinal PET study using a fixed-performance paradigm. *Stroke* 2001;32:2534–2542.
26. Carey JR, Kimberley TJ, Lewis SM, et al. Analysis of fMRI and finger tracking training in subjects with chronic stroke. *Brain* 2002;125:773–788.
27. Rouiller EM, Olivier E. Functional recovery after lesions of the primary motor cortex. *Prog Brain Res* 2004;143:467–475.
28. Yoshiura T, Hasuo K, Mihara F, et al. Increased activity of the ipsilateral motor cortex during a hand motor task in patients with brain tumor and paresis. *AJNR Am J Neuroradiol* 1997;18:865–869.
29. Alkadhi H, Kollias SS, Crelier GR, et al. Plasticity of the human motor cortex in patients with arteriovenous malformations: a functional MR imaging study. *AJNR Am J Neuroradiol* 2000;21:1423–1433.
30. Cao Y, D'Olhaberriague L, Vikingstad EM, et al. Pilot study of functional MRI to assess cerebral activation of motor function after poststroke hemiparesis. *Stroke* 1998;29:112–122.
31. Chollet F, DiPiero V, Wise RJ, et al. The functional anatomy of motor recovery after stroke in humans: a study with positron emission tomography. *Ann Neurol* 1991;29:63–71.
32. Chamoun RB, Mikati MA, Comair YG. Functional recovery following resection of an epileptogenic focus in the motor hand area. *Epilepsy Behav* 2007;11:384–388.
33. Devlin AM, Cross JH, Harkness W, et al. Clinical outcomes of hemispherectomy for epilepsy in childhood and adolescence. *Brain* 2003;126:556–566.
34. Muller RA, Chugani HT, Muzik O, et al. Language and motor functions activate calcified hemisphere in patients with Sturge-Weber syndrome: a positron emission tomography study. *J Child Neurol* 1997;12:431–437.
35. Pataraia E, Billingsley-Marshall RL, Castillo EM, et al. Organization of receptive language-specific cortex before and after left temporal lobectomy. *Neurology* 2005;64:481–487.
36. Vargha-Khadem F, Carr LJ, Isaacs E, et al. Onset of speech after left hemispherectomy in a nine-year-old boy. *Brain* 1997;120 (Pt 1):159–182.
37. Lippe S, Bulteau C, Dorfmuller G, et al. Cognitive outcome of parietooccipital resection in children with epilepsy. *Epilepsia* 2010;51:2047–2057.

Genotype–phenotype correlations in alternating hemiplegia of childhood

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ABSTRACT

Objective: Clinical severity of alternating hemiplegia of childhood (AHC) is extremely variable. To investigate genotype-phenotype correlations in AHC, we analyzed the clinical information and *ATP1A3* mutations in patients with AHC.

Methods: Thirty-five Japanese patients who were clinically diagnosed with AHC participated in this study. *ATP1A3* mutations were analyzed using Sanger sequencing. Detailed clinical information was collected from family members of patients with AHC and clinicians responsible for their care.

Results: Gene analysis revealed 33 patients with de novo heterozygous missense mutations of *ATP1A3*: Glu815Lys in 12 cases (36%), Asp801Asn in 10 cases (30%), and other missense mutations in 11 cases. Clinical information was compared among the Glu815Lys, Asp801Asn, and other mutation groups. Statistical analysis revealed significant differences in the history of neonatal onset, gross motor level, status epilepticus, and respiratory paralysis in the Glu815Lys group compared with the other groups. In addition, 8 patients who did not receive flunarizine had severe motor deteriorations.

Conclusions: The Glu815Lys genotype appears to be associated with the most severe AHC phenotype. Although AHC is not generally seen as a progressive disorder, it should be considered a disorder that deteriorates abruptly or in a stepwise fashion, particularly in patients with the Glu815Lys mutation. ***Neurology*® 2014;82:482–490**

GLOSSARY

AHC = alternating hemiplegia of childhood; **DYT12** = rapid-onset dystonia-parkinsonism.

Alternating hemiplegia of childhood (AHC) is a rare neurodevelopmental disorder characterized by recurrent flaccid or dystonic types of hemiplegic episodes lasting from several minutes to several days, abnormal ocular movements, involuntary movements, hypotonia, and seizures beginning in the infantile period (before 18 months of age).[1–4] Most patients have a sporadic form of the disorder, and routine laboratory and neuroimaging examinations do not show any specific abnormal findings.

ATP1A2 gene mutations have been reported as the cause of AHC in atypical familial cases.[5] However, these are rare. In 2012, 3 different research groups independently revealed that mutations of the sodium–potassium (Na^+/K^+)–ATPase α3 subunit gene (*ATP1A3*) cause AHC.[6–8]

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ATP1A3 mutations have also been reported in rapid-onset dystonia–parkinsonism (DYT12).[9,10] Although the onset and clinical courses of these disorders are different, AHC and DYT12 may constitute a continuum of disorder;[6–8,11] therefore, there should be a variety of phenotypes of *ATP1A3*-related movement disorders.

Even in AHC alone, there are remarkable clinical variations among individuals.[12–16] Onset time, motor development levels, and cognition deficit levels differ considerably among individuals. Investigations among large populations in Europe and the United States have provided evidence of a nonprogressive course of AHC.[3,14,15] However, some degree of motor or intellectual deterioration has been observed in some patients with AHC.[13,16,17] Patients with early onset tend to have a severe clinical course.[16] We are unaware of the reason behind this clinical diversity in AHC. The position of the point mutations in *ATP1A3* and treatment methods used could be key factors.

METHODS Patients. ***Standard protocol approvals, registrations, and patient consents.*** Patients with AHC were recruited through the Japanese AHC Family Association. Thirty-four patients (8 female and 26 male) who were clinically diagnosed with AHC according to clinical diagnostic criteria[1–4] participated in the study with ages ranging from 1 year 4 months to 43 years. Another male patient who did not fulfill the criteria (onset at 2 years of age) was also enrolled in the study. All patients had sporadic AHC. Most of the parents participated in the study.

Ethics statement. This study was approved by the Ethics Review Committee of Fukuoka University. The parents of the patients provided informed consent before the start of the study.

We collected detailed clinical information regarding the onset time of the initial symptoms, frequency and type (flaccid or dystonic) of recurrent hemiplegic attacks, frequency of seizures, experience of status epilepticus and respiratory paralysis, involuntary movements, developmental history, level of gross motor development, and cognitive function in the intermittent period between recurrent hemiplegic attacks and flunarizine usage (particularly age at initiation, dose, continuation, and age at which drug was stopped if appropriate) from the parents of patients with AHC and clinicians (primarily pediatric neurologists) responsible for their care through an intake form. All participants except one boy (onset at 2 years of age) were confirmed to fulfill the AHC criteria and were subsequently screened for *ATP1A3* mutations.

Mutation analysis. Sanger sequencing was performed to analyze genomes of the patients and their parents. Genomic DNA was prepared from EDTA-Na_2-containing blood samples using a QIAamp DNA Blood Maxi Kit (Qiagen, Hilden, Germany) according to the protocol provided by the manufacturer. All of the exons and intron–exon boundaries of *ATP1A3* were amplified by PCR using the designed PCR primers. The primer sequences and PCR conditions are available upon request. PCR products were purified in ExoSAP-IT for PCR Product Clean-Up (Affymetrix, Santa Clara, CA) with 1 cycle of 15 minutes at 37°C and another of 15 minutes at 80°C. The purified PCR products were sequenced using the ABI PRISM BigDye 3.1 terminator method (Applied Biosystems, Foster City, CA) and an ABI PRISM® 3100 Genetic Analyzer (Applied Biosystems). We also recruited 96 unrelated healthy Japanese volunteers who were free of seizures or without any history of epilepsy as a control group.

Before the present study, we attempted to identify the genes responsible for AHC by whole-exome sequencing analysis (using a new generation sequencer) of 8 Japanese patients with AHC who were clinically diagnosed with typical AHC. This previous study revealed heterozygous missense mutations in *ATP1A3* in all of the 8 patients studied.[8] Subsequently, we continued our *ATP1A3* analyses using Sanger sequencing of 35 Japanese patients with AHC (including the 8 patients).

Evaluation of clinical information and statistical analysis. We compared the relationship between the point mutations in *ATP1A3* and clinical information. All the data analyses were performed using the SAS software package (version 9.2; SAS Institute Inc., Cary, NC). Frequency distributions of the phenotypes were evaluated using Fisher exact test.

Table 1 *ATP1A3* mutations and protein modifications in patients with alternating hemiplegia of childhood

Exon	Nucleotide change	Amino acid change	Number (%) of probands
5	410 C>A	Ser137Tyr (S137Y)	1
9	1072 G>T	Gly358Cys (G358C)	1
16	2263 G>T	Gly755Cys (G755C)	1
16	2263 G>A	Gly755Ser (G755S)	1
16	2264 G>C	Gly755Ala (G755A)	1
17	2312 C>A	Thr771Asn (T771N)	1
17	2401 G>A	Asp801Asn (D801N)	10 (30)
18	2443 G>A	Glu815Lys (E815K)	12 (36)
20	2767 G>A	Asp923Asn (D923N)	1
20	2780 G> T	Cys927Phe (C927F)	2
21	2839 G>C	Gly947Arg (G947R)	1
22	2974 G>T	Asp992Tyr (D992Y)	1
Total			33

RESULTS Gene mutations. A heterozygous missense mutation in *ATP1A3* was confirmed in 33 of the 35 patients by Sanger sequencing. Thirty-three (7 female and 26 male) of the 35 patients were observed to have a heterozygous missense mutation. The rate of genetic mutation was as high as 94%. None of the parents showed any *ATP1A3* mutations. All mutations were thus confirmed as de novo mutations. Of the 33 patients with *ATP1A3* mutations, 12 (36%) had a c.2443 G>A, p.Glu815Lys (E815K) mutation; 10 patients (30%) had a c.2401 G>A, p.Asp801Asn (D801N) mutation; 2 patients (7%) had a c.2780 G>T, Cys927Phe (C927F) mutation; and the remaining 9 patients had other mutations. There were 3 Gly755 mutations: c.2263 G>T, p.Gly755Cys (G755C); c.2263 G>A, p.Gly755Ser (G755S); and c.2264 G>C, p.Gly755Ala (G755A) (table 1).

The patient who experienced disease onset at age 2 had an Asp923Asn (D923N) mutation.

Clinical features. We divided the patients into 3 groups based on the *ATP1A3* mutations. Group 1 included patients with an E815K mutation (12 cases), group 2 those with a D801N mutation (10 cases), and group 3 those with other mutations (11 cases). The clinical information from all of the patients (table 2 and table 3) was compared among these groups. Distinct differences in several of the items were observed in group 1 compared with the other groups (table 4).

In group 1 (E815K mutation), the onset time of abnormal ocular movements or seizures was during

Table 2 First symptoms of onset and development in each patient

Case number	Age, y	Sex	*ATP1A3* mutation	Onset times and symptoms	First hemiplegic attack	Head control	Sitting	Stand with support	Unassisted walk	Run
G-1-01	33	F	E815K	2 d; abnormal eye movements	1 y, 0 mo	2 y, 0 mo	2 y, 6 mo	3 y, 0 mo	Impossible	
G-1-02	16	M	E815K	0 d; convulsion	1 y, 3 mo	1 y, 0 mo	1 y, 9 mo	Impossible		
G-1-03	14	M	E815K	1 mo; abnormal eye movements, convulsion	5 mo	7 mo	1 y, 0 mo	1 y, 6 mo	Impossible	
G-1-04	14	M	E815K	17 d: abnormal eye movements, convulsion	10 mo	7 mo	9 mo	2 y, 2 mo	Impossible	
G-1-05	14	M	E815K	1 d; abnormal eye movements	5 mo	1 y, 6 mo	1 y, 10 mo	2 y, 6 mo	Impossible	
G-1-06	12	M	E815K	1 d; abnormal eye movements	3 mo	8 mo	1 y, 0 mo	Impossible		
G-1-07	9	M	E815K	1 d; abnormal eye movements, convulsion	10 mo	2 y	3 y, 6 mo	4 y, 6 mo	Impossible	
G-1-08	9	M	E815K	2 d; abnormal eye movements	8 mo	2 y, 6 mo	3 y, 3 mo	8 y	Impossible	
G-1-09	7	M	E815K	0 d; abnormal eye movements, convulsion	4 mo	Impossible				
G-1-10	4	M	E815K	0 d; abnormal eye movements	6 mo	1 y, 0 mo	1 y, 6 mo	1 y, 10 mo	Impossible	
G-1-11	1 y, 6 mo	M	E815K	1 d; convulsion	7 mo	Impossible				
G-1-12	1 y, 4 mo	M	E815K	0 d; abnormal eye movements	9 mo	Impossible				
G-2-01	43	F	D801N	10 mo; dystonic hemiplegia	10 mo	5 mo	1 y, 0 mo	No record	3 y	5 y
G-2-02	33	F	D801N	3 mo; flaccid paralysis	3 mo	4 mo	7 mo	No record	5 y, 5 mo	Impossible
G-2-03	25	M	D801N	1 mo; abnormal eye movements	9 mo	4 mo	7 mo	11 mo	5 y	Impossible
G-2-04	20	M	D801N	1 d; convulsion	4 mo	5 mo	9 mo	1 y, 0 mo	2 y, 3 mo	3 y, 6 mo
G-2-05	19	M	D801N	2 mo; convulsion	2 mo	5 mo	10 mo	12 mo	Impossible	
G-2-06	18	F	D801N	4 mo; abnormal eye movements	4 mo	6 mo	No record	2 y	3 y, 6 mo	Impossible
G-2-07	13	M	D801N	0 d; abnormal eye movements	9 mo	6 mo	11 mo	3 y, 10 mo	Impossible	
G-2-08	12	M	D801N	4 mo; hemidystonia	9 mo	5 mo	7 mo	1 y, 10 mo	4 y, 6 mo	6 y
G-2-09	12	M	D801N	6 mo; hemidystonia	6 mo	3 mo	9 mo	10 mo	3 y, 3 mo	Impossible
G-2-10	3	M	D801N	5 mo; hemidystonia	5 mo	3 mo	1 y, 2 mo	1 y, 3 mo	Impossible	
G-3-01	30	F	S137Y	1 mo; seizure	6 mo	5 mo	2 y, 0 mo	4 y, 1 mo	Impossible	
G-3-02	25	M	G755A	2 mo; abnormal ocular movements	6 mo	1 y, 0 mo	2 y, 0 mo	3 y, 0 mo	Impossible	
G-3-03	24	M	T771N	5 mo; abnormal ocular movements, seizure	1 y, 0 mo	5 mo	9 mo	11 mo	2 y, 0 mo	3 y
G-3-04	23	M	D992Y	8 mo; abnormal ocular movements	8 mo	No record	No record	1 y, 5 mo	2 y, 10 mo	4 y
G-3-05	18	M	G755C	2 mo; abnormal ocular movements	10 mo	6 mo	1 y	1 y, 6 mo	3 y	5 y
G-3-06	17	F	C927F	2 mo; abnormal ocular movements	1 y, 0 mo	4 mo	7 mo	10 mo	2 y, 2 mo	4 y
G-3-07	13	M	G755S	3 mo; abnormal ocular movements	4 mo	4 mo	7 mo	1 y, 2 mo	Impossible	
G-3-08	12	F	C927F	2 mo; abnormal ocular movements	3 y	3 mo	5 mo	No record	1 y, 10 mo	3 y
G-3-09	11	M	D923N	2 y; left hemiplegia	2 y	3 mo	6 mo	No record	1 y, 2 mo	1 y, 8 mo
G-3-10	8	M	G358C	1 d; seizure	1 mo	7 mo	Impossible			
G-3-11	2 y, 8 mo	M	G947R	2 d; seizure	8 mo	4 mo	No record	8 mo	2 y, 8 mo	Impossible

Table 3 **Details of clinical symptoms in each patient**

Case number	Flunarizine	Motor deterioration; trigger	Cognitive deficit	Convulsion (status epilepticus)	Frequency of hemiplegia/mo	Respiratory paralysis	Respirator care	Tube feeding
G-1-01	Not used	+ At 6 y: stand→bedridden; fever	Profound	+	Flaccid, continuous	+	RC, T	TC
G-1-02	Discontinued at 5 y	+ At 6 y: stand→bedridden; fever	Sentence	+	Flaccid 25	+		
G-1-03	15 mg	No	Words	+	Flaccid 10	+		
G-1-04	Discontinued at 6 y	+ At 7 y: stand→bedridden; status epilepticus	Words	+	Flaccid 15, dystonic 1	+	RB	TB
G-1-05	Discontinued at 3 y	+ At 4 y: stand→bedridden	Profound	+	Flaccid, continuous	+	RB, T	TC
G-1-06	Not used	+ At 3 y: sit→bedridden; status epilepticus	Profound	+	Flaccid 2	+	RB	TC
G-1-07	5 mg	No	Words	+	Flaccid 10, dystonic 30	+		
G-1-08	12.5 mg	+ At 8 y: stand→sit; unknown	Sentence	+	Flaccid 10	+		
G-1-09	5 mg	No	Severe	+	Flaccid 30	+	RB	
G-1-10	Not used	No	Words	+	Flaccid 4	+		
G-1-11	Not used	No	Severe	+	Flaccid 30	+		
G-1-12	7.5 mg	No	Severe	+	Flaccid 15	+		TC
G-2-01	Discontinued at 16 y	No at 16 y: long-lasting left hemidystonia	Sentence	−	Flaccid 1, dystonic 2	−		
G-2-02	5 mg	No	Sentence	−	Flaccid 6, dystonic 2	−		
G-2-03	10 mg	No	Sentence	−	Flaccid 12, dystonic 8	−		
G-2-04	Discontinued at 9 y	No	Sentence	−	Flaccid 10	−		
G-2-05	Discontinued at 5 y	No	Sentence	+	Flaccid 3	−		
G-2-06	30 mg	No	Sentence	−	Flaccid 15	−		
G-2-07	5 mg	No	Words	+	Flaccid, dystonic 4	+		
G-2-08	10 mg	No at 3 y: long-lasting left hemidystonia	Sentence	−	Flaccid 8, dystonic continuous	+		
G-2-09	Discontinued at 3 y	No	Sentence	−	Flaccid 25	−		
G-2-10	5 mg	No at 11 mo: long-lasting left hemidystonia	Words	−	Flaccid 2, dystonic 4	+		TB
G-3-01	Discontinued at 16 y	+ At 17 y: stand→bedridden; status epilepticus	Profound	+	Flaccid, continuous	+	RB	TC
G-3-02	Discontinued at 15 y	+ At 16 y: stand→bedridden; status epilepticus	Words	+	Flaccid 1	+		
G-3-03	Discontinued at 12 y	+ At 13 y: run→walk; unknown	Sentence	−	Flaccid 5, dystonic 2	−		
G-3-04	5 mg	No	Sentence	−	Flaccid 2, dystonic 10	−		
G-3-05	5 mg	No	Sentence	+	Flaccid 2	+		
G-3-06	Discontinued at 3 y	No	Sentence	−	Flaccid 15	−		
G-3-07	Discontinued at 5 y	+ At 12 y: stand→bedridden; status epilepticus	Profound	+	Flaccid, continuous	+	RC, T	TC
G-3-08	5 mg	No	Sentence	−	Flaccid 1, dystonic 2	−		
G-3-09	5 mg	No	Sentence	−	Dystonic 10	−		
G-3-10	5 mg	No	Profound	+	Flaccid 5	+	RB	
G-3-11	5 mg	No	Words	−	Flaccid 2, dystonic 2	−		

Abbreviations: B = before; C = continue; R = respirator; T = tracheostomy.

Table 4 Comparison between group 1 vs group 2, group 3, and groups 2 + 3

	Group 1 (n = 12), n (%)	Group 2 (n = 10), n (%)	p Value (group 1 vs 2)	Group 3 (n = 11), n (%)	p Value (group 1 vs 3)	Groups 2 + 3 (n = 21), n (%)	p Value (group 1 vs 2 + 3)
Neonatal onset	11 (91.7)	2 (20)	0.0015[a]	2 (18.2)	0.0006[a]	4 (19.0)	0.0001[a]
Unassisted walking	0 (0.0)	7 (70)	0.0007[a]	7 (63.6)	0.0013[a]	14 (66.7)	0.0002[a]
Prolonged severe motor deterioration	5 (41.7)	0 (0)	0.040[b]	3 (27.3)	0.67	3 (14.2)	0.11
Cognitive deficit, severe or profound	8 (66.7)	0 (0)	0.0017[a]	3 (27.3)	0.10	3 (14.2)	0.0055[a]
Status epilepticus	12 (100)	2 (20)	0.0001[a]	5 (45.5)	0.0046[a]	7 (33.3)	0.0002[a]
Respiratory paralysis	12 (100)	3 (30)	0.0007[a]	5 (45.5)	0.0046[a]	8 (38.0)	0.0005[a]
Respirator care	5 (41.7)	0 (0)	0.040[b]	3 (27.3)	0.67	3 (14.2)	0.11
Tube feeding	5 (41.7)	1 (10)	0.16	2 (18.2)	0.37	3 (14.2)	0.11

Group 1: E815K mutation; group 2: D801N mutation; group 3: other mutations.
[a] Statistically significant ($p < 0.01$) (Fisher exact test).
[b] Statistically significant ($p < 0.05$) (Fisher exact test).

the neonatal period (less than 7 days after birth) in 11 of the 12 patients. The first symptom was observed in the last patient at 1 month of age. All patients showed very slow early development. None of the patients was able to control head movements before 6 months of age. Three patients did not develop head control at all, although they could all roll over during the interictal period.

The peak motor development was identified as "standing with support" in 7 patients. None of the patients in group 1 could walk independently, even in the interictal period between recurrent hemiplegic attacks (figure, A). All 12 patients experienced both status epilepticus and respiratory paralysis, and most had visited emergency rooms of hospitals. Five patients experienced a permanent severe motor deterioration from sitting or standing with support to becoming bedridden in childhood. All 5 patients experienced this severe deterioration: the condition of 3 patients deteriorated because of status epilepticus and that of the remaining 2 patients deteriorated because of recurrent fever. Four of these patients were immediately treated by the emergency hospitals using mechanical respiratory care. Thereafter, 2 patients were placed under all-day respiratory care. In these 5 patients, only mild brain atrophy or mild cerebellar atrophy was revealed by brain MRI. Tube feeding was required in 4 patients. Out of the 5 patients in whom severe deterioration was observed, 4 had discontinued flunarizine before the severe deterioration occurred and the remaining patient was not administered flunarizine.

In group 2 (D801N mutation), the onset time was during the neonatal period in only 2 of the 10 patients. Patients in this group were characterized by slower than normal early development, but all patients were able to control their head movements by 6 months of age. Seven patients could walk independently in the interictal period between hemiplegic attacks (figure, B). Three patients experienced several episodes of hemidystonia lasting for several weeks to a few months. None of the patients showed severe motor deterioration. All 10 patients were treated with flunarizine. Four patients had discontinued flunarizine more than 10 years previously, but they showed no severe motor deterioration.

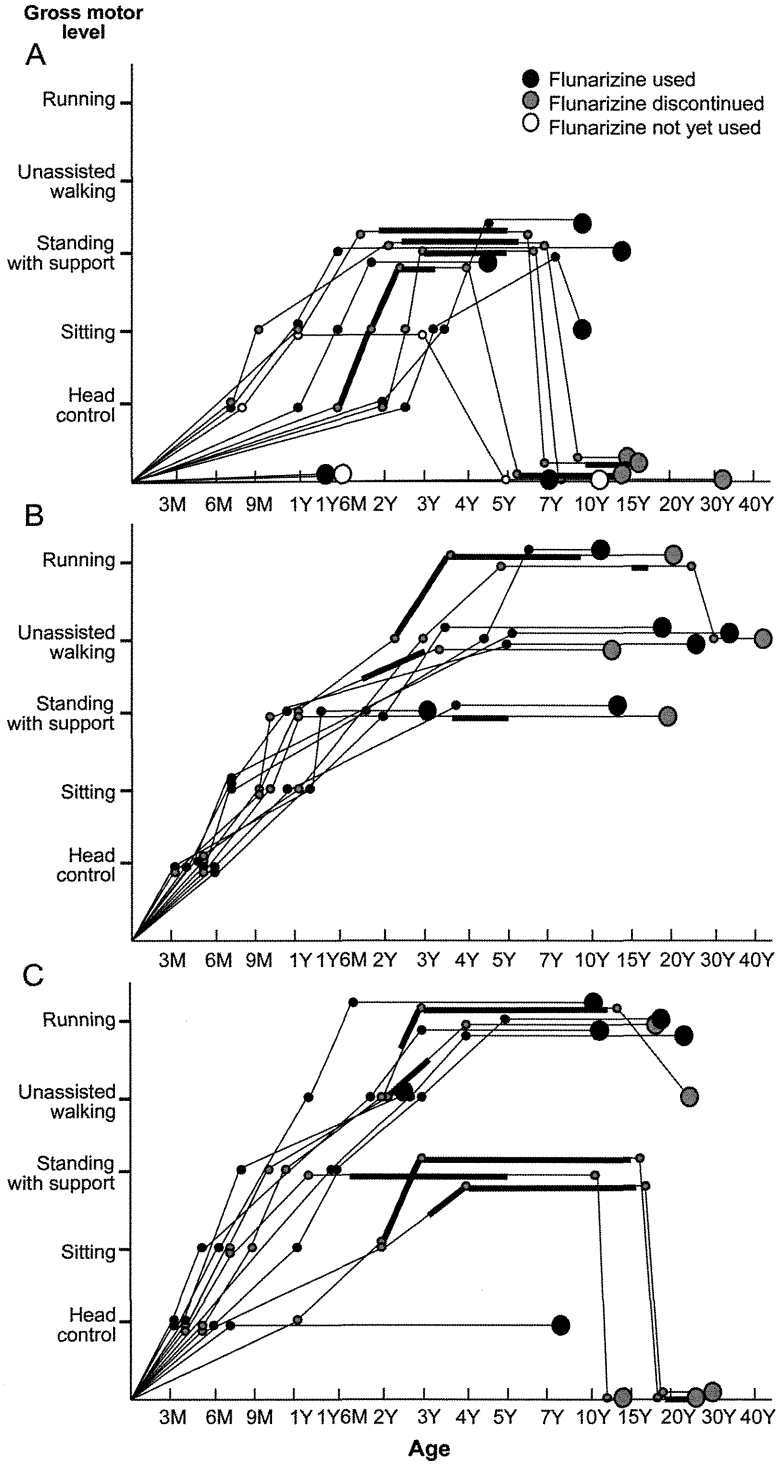
In group 3 (other mutations), the onset time was during the neonatal period in only 2 of the 11 patients. Most patients in this group showed slight delays in early development, and 7 of the 11 patients were able to walk unassisted in the interictal period between recurrent hemiplegic attacks. Six of these 7 patients had no obvious signs of motor deterioration. However, 3 patients who could stand with support abruptly experienced a severe motor deterioration in their teens (figure, C). All 11 patients were treated with flunarizine, and 3 of the 5 patients who discontinued flunarizine treatment showed permanent severe deterioration after status epilepticus; these 3 patients had the following *ATP1A3* mutations: S137Y, G755A, and G755S.

Severe motor deterioration after status epilepticus or fever during childhood was observed in 5 of the 12 patients with an E815K mutation and 3 of the 11 patients with other mutations.

Regarding flunarizine usage, 31 of the 33 patients with *ATP1A3* mutations were administered flunarizine, and this was discontinued in 13 patients. Seven of the 13 patients who discontinued flunarizine experienced either an abrupt or stepwise severe motor deterioration. In addition, 8 patients with severe motor deterioration had not been administered flunarizine during the period of deterioration. No patient who continued flunarizine showed severe motor deterioration.

The patient with the D923N mutation showed normal motor development.

Figure **History of gross motor development during the intermittent period for each patient**



(A) E815K mutation group (group 1), (B) D801N mutation group (group 2), (C) other mutations group (group 3). Small circles: Age at which gross motor development was attained or lost. Large circles: Age of each patient during the study. Thin lines: Gross motor level ignoring short-term fluctuations. Thick lines: Period of flunarizine administration among patients for whom flunarizine treatment was discontinued.

Statistical analysis. Statistical analyses revealed significant differences between group 1 and the other groups in terms of neonatal onset, unassisted walking, severe cognitive deficit, and history of status epilepticus and respiratory paralysis (table 4). Group 1 was shown to have a more severe phenotype than the other groups.

DISCUSSION Similar to patients in Europe and the United States, *ATP1A3* genetic analysis revealed that E815K (36%) and D801N (30%) mutations are common in Japanese patients with AHC. Reasons for male/female ratio deviation in this study were unclear. Because a male bias is not typical of AHC, it is possible that some female patients may have not yet been diagnosed in Japan.

We observed that the E815K mutation group had more severe symptoms than the other mutation groups with respect to 1) onset time of the first symptoms, 2) unassisted walking, 3) cognitive deficit, 4) status epilepticus, and 5) respiratory paralysis. Although the number of participants was relatively small, this study demonstrated that the E815K mutation was associated with the most severe AHC phenotype. The D801N mutation possibly results in a moderate to mild form of AHC. Some other mutations, such as G755A, G755S, and S137Y, may also result in a severe phenotype, but the rest of "other mutations" identified in this study could result in a relatively mild phenotype. The reason why the early-onset group tended to show a more severe clinical course[16] could be partly explained by the findings of this study.

Previous studies have not been able to establish any genotype–phenotype correlations in patients with AHC.[6,7] However, one study of 24 patients reported a tendency for AHC patients with an E815K mutation to have a more severe subtype than those with a D801N mutation because 1) only 2 of the 7 patients with an E815K mutation had a peak motor function of "walking unassisted" compared with 8 of the 9 patients with a D801N mutation, 2) progression of nonparoxysmal features was seen in 4 of the 7 patients with an E815K mutation but only in 1 of the 9 patients with a D801N mutation, and 3) muscular hypotonia was seen in all 7 patients with an E815K mutation but only in 5 of the 9 patients with a D801N mutation.[7] These findings support our observation that the E815K mutation results in a more severe AHC phenotype. However, a larger study of 82 patients demonstrated no genotype–phenotype correlations in AHC.[6] Our positive findings may thus be because of our relatively small sample size.

Severe deterioration or sudden death have long been associated with AHC.[14,16,17] Permanent loss of function has sometimes been reported after a severe episode, which is a major concern for many families.[17] However, it has been suggested that AHC is probably not an intrinsically progressive disease, but one that can show stepwise deterioration with severe episodes in some patients.[17] Several studies have reported that some children with AHC may require intensive care for breathing problems associated with whole-body

attacks and severe seizures, which are the main life-threatening symptoms associated with AHC.[17] A report from a large European study also mentioned 7 deaths due to severe plegic attacks or epileptic seizures.[14] These reports confirm that some patients with AHC have a severe clinical course. In our study, 8 of the 33 patients with AHC experienced stepwise or abrupt permanent severe motor deterioration, and none of these 8 patients showed any sign of recovery. Fever or status epilepticus could be a factor in this severe deterioration.

We investigated the severe motor deterioration in patients with AHC. We suspect that a genetic factor could be related to severe deterioration. Although severe motor deterioration was not observed among patients with the D801N mutation, it was observed in 5 of the 12 patients with an E815K mutation and 3 of the 11 patients with other specific mutations. We should be aware of the possibility of severe motor deterioration in patients, particularly among those with E815K and G755A/S mutations.

Previous studies have shown that patients with early-onset AHC fared the poorest in terms of development.[15,16] One reason for the correlation with early-onset and poor development could be that the E815K mutation is associated with a severe phenotype of AHC.

Patients with AHC who experience severe deterioration do not recover, which is similar to the outcome for patients with DYT12 who experience fixed dystonic symptoms. The difference in clinical symptoms between patients with AHC and DYT12 is probably because of differences in the position of the *ATP1A3* mutations or amino acid sequence changes, which could influence the structure, function, and protein expression of the Na^+/K^+-ATPase transporting pump. Mutations in *ATP1A3* can be clearly differentiated for AHC and DYT12,[6–10] but they could be viewed as an allelic disorder or as different aspects on a continuum of a single disease.[11] It is not yet clear why these 2 disorders are clinically different. AHC may be a severe manifestation, whereas DYT12 may be a milder type. Differences in *ATP1A3* mutations influence the function of Na^+/K^+-ATPase, and an intermediate phenotype must exist. The D923N mutation, which has already been reported as causing DYT12,[18,19] could be a mild form of AHC. In our study, the G-3-09 patient who had a D923N mutation showed later onset, normal cognitive function, frequent dystonia, and dysarthria. This patient could have an intermediate form of the disorder between AHC and DYT12.[20,21]

Most causative *ATP1A3* mutations lie within conserved domains or in the transmembrane region of the Na^+/K^+-ATPase enzyme protein.[6–8] The amount of the enzyme remains stable, but enzyme activity is reduced with both E815K and D801N mutations.[6] At a molecular level, the reason for the E815K mutation causing more severe symptoms is unclear.[22–25] E815K and G755A/S mutations could be responsible for the more severe subtypes of AHC because both E815 and G755 are predicted to be located in the cytoplasmic domains adjacent to the membrane.[6] The reason for the G755A/S mutations resulting in a more severe phenotype than the G755C mutation may be explained by the same molecular mechanism responsible for the relationship between D801Y in DYT12 and D801N in AHC. Further investigations of the function of Na^+/K^+-ATPase harboring *ATP1A3* mutations causing AHC or DYT12 should be performed to elucidate the mechanism of these disorders and develop proper treatments.

In patients with AHC, flunarizine administration is recommended,[26] because it has been reported to be effective in reducing the frequency and intensity of plegic attacks.[26,27] However, it is not known whether flunarizine protects patients with AHC from manifestations of permanent severe motor deterioration. In this study, flunarizine may have had a protective effect on severe motor deterioration. The genotype could also affect the decline in motor function on flunarizine discontinuation. Although the mechanism of flunarizine efficacy is not fully understood, it blocks calcium and sodium currents in cultured rat cortical neurons.[28] Flunarizine had been discontinued in some patients because 1) it had not been shown to reduce the frequency or duration of recurrent flaccid types of hemiplegic attacks, or 2) approval for flunarizine was withdrawn in Japan by the Ministry of Health and Welfare in 1999.[29] Since then, it has not been possible to prescribe flunarizine in Japan. Therefore, families of patients with AHC have to import flunarizine from foreign countries. None of the patients with severe deteriorations recovered even when flunarizine was readministered after their collapse. It is uncertain whether these patients would have experienced severe deterioration if they had continued flunarizine therapy.

Although there is no gold standard treatment for patients with AHC, extensive care, e.g., administration of flunarizine, anticonvulsants, immediate treatments for status epilepticus or apnea attacks, is essential. This is even more important for patients with substantial severe motor deterioration who have E815K and other mutations and have discontinued flunarizine therapy. We recommend that all patients with AHC, regardless of genotype, should not discontinue flunarizine administration even if this does not show any obvious short-term effectiveness against recurrent hemiplegic attacks. Because the number of patients with AHC in this study was small, a global prospective study with a larger population is necessary to confirm the protective effect of flunarizine.

In this study, we observed that the E815K genotype appears to be associated with the most severe

AHC phenotype. Although AHC is not generally seen as a progressive disorder, it should be considered a disorder that can be associated with abrupt or stepwise severe deterioration, particularly among patients with an E815K mutation. Genotype–phenotype correlations in AHC should be further explored in a global study.

AUTHOR CONTRIBUTIONS

M. Sasaki, A.I., Y.S., S. Tsuji, and S. Hirose designed the study, wrote the report, performed the literature search, and created the figures. A.I., N.M., K.I., and S. Hirose performed the Sanger sequencing and data analyses for the de novo single-nucleotide polymorphisms. M. Sasaki, A.I., and B.Z. performed the statistical analyses. M. Sasaki, Y.S., S. Takada, A.A., Y.T., H.A., S.Y., T.O., Y. Oda, H. I., S. Hirabayashi, A.Y., H.K., S.K., M. Shimono, S.N., M. Suzuki, T.Y., Y. Oyazato, S. Tsuneishi, S.O., K.Y., S.D., T.A., N.K., R.K., T.I., and H.O. obtained samples from patients and clinical data.

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DISCLOSURE

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REFERENCES

1. Anderman F, Aicaridi J, Vigevano F, eds. Alternating Hemiplegia of Childhood. New York: Raven Press; 1995.
2. Bourgeois M, Aicardi J, Goutières F. Alternating hemiplegia of childhood. J Pediatr 1993;122:673–679.
3. Sweney MT, Silver K, Gerard-Blanluet M, et al. Alternating hemiplegia of childhood: early characteristics and evolution of a neurodevelopmental syndrome. Pediatrics 2009;123:e5345–e5341.
4. Tenney JR, Schapiro MB. Child neurology: alternating hemiplegia of childhood. Neurology 2010;74:e57–e59.
5. Swoboda KJ, Kanavakis E, Xaidara A, et al. Alternating hemiplegia of childhood or familial hemiplegic migraine? A novel ATP1A2 mutation. Ann Neurol 2004;55:884–887.
6. Heinzen EL, Swoboda KJ, Hitomi Y, et al. De novo mutations in *ATP1A3* cause alternating hemiplegia of childhood. Nat Genet 2012;44:1030–1034.
7. Rosewich H, Thiele H, Ohlenbusch A, et al. Heterozygous de-novo mutations in *ATP1A3* in patients with alternating hemiplegia of childhood: a whole-exome sequencing gene-identification study. Lancet Neurol 2012;11:764–773.
8. Ishii A, Saito Y, Mitsui J, et al. Identification of *ATP1A3* mutations by exome sequencing as the cause of alternating hemiplegia of childhood in Japanese patients. PLoS One 2013;8:e56120.
9. de Carvalho Aguiar P, Sweadner KJ, Penniston JT, et al. Mutations in the Na^+/K^+-ATPase α3 gene *ATP1A3* are associated with rapid-onset dystonia parkinsonism. Neuron 2004;43:169–175.
10. Brashear A, Dobyns WB, de Carvalho Aguiar P, et al. The phenotypic spectrum of rapid-onset dystonia-parkinsonism (RDP) and mutations in the *ATP1A3* gene. Brain 2007; 130:828–835.
11. Ozelius LJ. Clinical spectrum of disease associated with *ATP1A3* mutations. Lancet Neurol 2012;11:741–743.
12. Sakuragawa N. Alternating hemiplegia in childhood: 23 cases in Japan. Brain Dev 1992;14:283–288.
13. NevŠimalová S, Dittrich J, Havlová M, et al. Alternating hemiplegia in childhood; a cross-sectional study. Brain Dev 1994;16:189–194.
14. Panagiotakaki E, Gobbi G, Neville B, et al. Evidence of a non-progressive course of alternating hemiplegia of childhood: study of a large cohort of children and adults. Brain 2010;133:3598–3610.
15. Mikati MA, Kramer U, Zupanc ML, Shanahan RJ. Alternating hemiplegia of childhood: clinical manifestations and long-term outcome. Pediatr Neurol 2000;23:134–141.
16. Saito Y, Inui T, Sakakibara T, Sugai K, Sakuma H, Sasaki M. Evolution of hemiplegic attacks and epileptic seizures in alternating hemiplegia of childhood. Epilepsy Res 2010;90:248–258.
17. Neville BG, Ninan M. The treatment and management of alternating hemiplegia of childhood. Dev Med Child Neurol 2007;49:777–780.
18. Roubergue A, Roze E, Vuillaumier-Barrot S, et al. The multiple faces of the *ATP1A3*-related dystonic movement disorder. Mov Disord 2013;28:1457–1459.
19. Anselm IA, Sweadner KJ, Gollamudi S, Ozelius LJ, Darras BT. Rapid-onset dystonia-parkinsonism in a child with a novel *ATP1A3* gene mutation. Neurology 2009;73:400–401.
20. Brashear A, Mink JW, Hill DF, et al. *APT1A3* mutation in infants: a new rapid-onset dystonia-Parkinsonism phenotype characterized by motor delay and ataxia. Dev Med Child Neurol 2012;54:1065–1067.
21. Sasaki M, Ishii A, Saito Y, Hirose S. Intermediate form between alternating hemiplegia of childhood and rapid-onset dystonia–parkinsonism. Mov Disord Epub 2013 Sep 30.
22. Morth JP, Pedersen BP, Toustrup-Jensen MS, et al. Crystal structure of the sodium-potassium pump. Nature 2007; 450:1043–1049.

23. Ogawa H, Shinoda T, Cornelius F, Toyoshima C. Crystal structure of the sodium-potassium pump (Na^+/K^+ ATPase) with bound potassium and ouabain. Proc Natl Acad Sci USA 2009;106:13742–13747.
24. Shinoda T, Ogawa H, Cornelius F, Toyoshima C. Crystal structure of the sodium-potassium pump at 2.4 Å resolution. Nature 2009;459:446–450.
25. Poulsen H, Khandelia H, Morth JP, et al. Neurological disease mutations compromise a C-terminal ion pathway in the Na^+/K^+ ATPase. Nature 2010;467:99–102.
26. Casear P, Azou M. Flunarizine in alternating hemiplegia in childhood. Lancet 1984;2:579.
27. Silver K, Andermann F. Alternating hemiplegia of childhood: a study of 10 patients and results of flunarizine treatment. Neurology 1993;43:36–41.
28. Ye Q, Yan L, Xue L, et al. Flunarizine blocks voltage-gated Na^+ and Ca^{2+} currents in cultured rat cortical neurons: a possible locus of action in the prevention of migraine. Neurosci Lett 2011;487:394–399.
29. Sasaki M, Sakuragawa N, Osawa M. Long-term effect of flunarizine on patients with alternating hemiplegia of childhood in Japan. Brain Dev 2001;23:303–305.

Earlier tachycardia onset in right than left mesial temporal lobe seizures

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ABSTRACT

Objective: To clarify whether the presence and timing of peri-ictal heart rate (HR) change is a seizure lateralizing sign in patients with mesial temporal lobe epilepsy (mTLE).

Methods: Long-term video EEGs were retrospectively reviewed in 21 patients, 7 men and 14 women aged 13 to 67 years, diagnosed as mTLE with MRI lesions in the mesial temporal structures (hippocampal sclerosis in 20 cases, amygdala hypertrophy in 1 case). Seventy-seven partial seizures without secondary generalization were extracted. Peri-ictal HR change was compared between 29 right seizures (9 patients) and 48 left seizures (12 patients).

Results: HR abruptly increased in all 29 right seizures and 42 of 48 left seizures. Onset time of HR increase in relation to ictal EEG onset was significantly earlier in right seizures than in left seizures (mean ± SD, −11.5 ± 14.8 vs 9.2 ± 21.7 seconds; $p < 0.0001$). Time of maximum HR was also significantly earlier in right seizures than in left seizures (36.0 ± 18.1 vs 58.0 ± 28.7 seconds; $p < 0.0001$). Maximum HR changes from baseline showed no significant difference between right and left seizures (47.5 ± 19.1 vs 40.8 ± 20.0/min).

Conclusions: Significantly earlier tachycardia in right than left mTLE seizures supports previous hypotheses that the right cerebral hemisphere is dominant in the sympathetic network. No HR change, or delayed tachycardia possibly due to seizure propagation to the right hemisphere, may be a useful lateralizing sign of left mTLE seizures. ***Neurology*® 2014;83:1332–1336**

GLOSSARY

CI = confidence interval; **HR** = heart rate; **mTLE** = mesial temporal lobe epilepsy.

Tachycardia is known to frequently precede ictal EEG changes in patients with mesial temporal lobe epilepsy (mTLE).[1–3] The mesial temporal structures have an important role in the central autonomic network.[4] However, conflicting reports have shown that hemispheric seizures on the right cause tachycardia more frequently than on the left[3,5,6]; that hemispheric seizures on the left are occasionally but more often accompanied by bradycardia[7]; and that no clear differences are found between right and left seizures.[1,8–11] These controversial results might reflect variation in the seizure types, location of epileptic foci, or etiologies among the subjects of these studies.[8–11] We hypothesized that ictal heart rate (HR) changes show significant differences between right and left seizures. The present study evaluated patients with mTLE specifically with MRI evidence of unilateral mesial temporal lesion to investigate whether the presence, timing, and degree of ictal HR change are different between right and left seizures.

METHODS

Patients and seizures. A total of 271 patients were recruited from the database of Tohoku University Hospital Epilepsy Monitoring Unit, Sendai, Japan, who underwent long-term video EEG monitoring for 4 or 5 days and brain MRI between September 2010 and December 2012. Inclusion criteria for this study were (1) partial seizures without secondary generalization, (2) scalp EEG seizures arising from the unilateral anterior temporal region, (3) ictal ECG recording with identifiable QRS complex, (4) MRI lesion in the mesial temporal structures ipsilateral to the ictal EEG onset, (5) no disease other than epilepsy, (6) no neurologic deficit, and (7) no ECG abnormality during the interictal period. Twenty-one of the 271 patients, 7 men and 14 women aged 13 to 67 years, fulfilled these criteria. All patients were right-handed. A total of 77 seizures, consisting of 29 right and 48 left temporal seizures, were reviewed (table 1). MRI showed hippocampal sclerosis in 20 patients and amygdalar hypertrophy in 1 patient.

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Table 1 Summary of the patients

Patient no.-side of epilepsy	Age, y/sex	Epilepsy duration, y	Seizure frequency	No. of R/L onset seizures
1-R	45/M	10	Monthly	11/0
2-R	29/F	12	Daily	1/0
3-R	24/F	13	Weekly	4/0
4-R[a]	67/F	15	Weekly	4/0
5-R	17/M	16	Monthly	1/0
6-R	38/F	22	Weekly	2/0
7-R	44/F	26	Daily	1/0
8-R	33/M	30	Monthly	1/0
9-R	51/M	41	Monthly	4/0
10-L	21/F	2	Monthly	0/6
11-L	13/F	7	Weekly	0/5
12-L	17/F	9	Weekly	0/8
13-L	53/M	11	Monthly	0/2
14-L	15/F	14	Weekly	0/1
15-L	29/F	17	Monthly	0/5
16-L	26/F	19	Monthly	0/6
17-L	32/F	22	Monthly	0/3
18-L	50/M	28	Daily	0/1
19-L	60/F	36	Monthly	0/8
20-L	44/M	38	Monthly	0/5
21-L	47/F	44	Weekly	0/2

[a] Amygdalar hypertrophy.

Standard protocol approvals, registrations, and patient consents. We received approval from the ethical standards committee on human experimentation of the institutional review boards of Tohoku University School of Medicine. The clinical trial number is 2012-1-568. Written informed consent was obtained from all patients (or guardians of patients) participating in the study.

EEG and ECG recording. Scalp EEG was performed using the 10-20 system with additional anterior temporal electrodes, simultaneous with ECG from lead I, CM5 lead, or NASA lead. The data were recorded by the Nihon Kohden video EEG system (Nihon Kohden, Tokyo, Japan) with a sampling rate of 500 Hz. A board-certified clinical neurophysiologist (K.J.), unaware of the RR interval change, reviewed the ictal video EEG recordings and determined the time of EEG seizure onset.

Peri-ictal HR changes. Peri-ictal time-series of ECG RR intervals were extracted by MemCalc/Win (PC software developed by Suwa-Trast, Tokyo, Japan). HR was calculated from the 5-second moving mean of RR. The time of EEG seizure onset was defined as zero, and the time-series of HR (/min) were examined from −100 to +300 seconds. Detection of the "onset time of HR increase" adopted a similar method to that described by van Elmpt et al.[12] The median HRs within a time window (20-second length) and an adjacent analysis time window (10-second length) were compared to determine whether the 2 medians differed by more than 5/min. "Time of maximum HR" was defined as the time of the largest value in the time-series of HR from 0 to 300 seconds. All video recordings of seizures were reviewed to check for the presence of any behavioral manifestations before the onset time of HR increase.

MRI. All patients underwent 3-tesla MRI with either a Magnetom Trio scanner (Siemens AG, Erlangen, Germany) or an Intera Achieva scanner (Philips Healthcare, Best, the Netherlands). The protocol consisted of axial T1-weighted, T2-weighted, and fluid-attenuated inversion recovery imaging (slice thickness, 7 mm), and coronal T2-weighted and fluid-attenuated inversion recovery imaging (slice thickness, 3.8 mm). Axial 3-dimensional T1-weighted imaging was also performed (slice thickness, 1 mm).

Statistical analysis. Onset time of HR increase, time of maximum HR, and maximum HR changes from the baseline (mean HR from −60 to 0 seconds) were compared between right and left temporal seizures. Statistical assessments were performed with the F test, Welch t test, and Student t test using JMP pro 10 software (SAS Institute, Cary, NC).

RESULTS Figure 1 shows typical examples of HR change associated with right and left mTLE seizures. All 29 right seizures were accompanied by abrupt HR increase, which started before ictal EEG onset in 22 of the 29 seizures (75.9%). In contrast, 42 of 48 left seizures were accompanied by abrupt HR increase, which started after ictal EEG onset in 31 of 42 seizures (73.8%), and 6 were accompanied by no obvious HR change. Before the tachycardia onset, none of these patients had made body or limb movements extensive enough to trigger HR increase. Sixteen seizures (7 right and 9 left) showed aura and/or mild distal automatism before the tachycardia onset, but were too small to cause tachycardia. Twenty-three seizures (10 right and 13 left) were accompanied by extensive body and limb movements, but exclusively after the tachycardia onset.

Figure 2 shows the cumulative distribution of "onset time of HR increase" and "time of maximum HR." The distribution of time of maximum HR in left seizures was significantly different from the normal distribution according to the Shapiro–Wilk W test ($p < 0.0001$). Then, we rejected one outlier value (267 seconds) to reduce the difference ($p = 0.0976$). The other distributions were not significantly different from the normal distribution without outlier rejection (onset time in right seizures, $p = 0.0907$; onset time in left seizures, $p = 0.6256$; time of maximum HR in right seizures, $p = 0.1338$). Variance equality of onset time of HR increase between right and left temporal seizures was rejected by the F test ($F_{41,28} = 2.1723$, $p = 0.0338$). Variance equality of time of maximum HR between right and left temporal seizures was also rejected ($F_{40,28} = 2.5258$, $p = 0.0121$). Therefore, we used the Welch t test to compare the group means. Onset time of HR increase in right seizures was significantly earlier than that in left seizures ($p < 0.0001$). Time of maximum HR in right seizures was also significantly earlier than that in left seizures ($p < 0.0001$).