Table 4
EEG findings.

Patient	Acute stage		Remote stage	
	Age at EEG	EEG findings	Age at EEG	EEG findings
1	45 days (1)	Right frontal dominant slowing	12 months	Focal spikes on the right frontal area
2	7 days (2)	Right hemisphere dominant mild slowing Ictal discharges on the right fronto-centro-parietal area	48 months	Normal
3	ND	ND	ND	ND
4	59 days (1)	Mildly low voltage	ND	ND
5	45 days (1)	Widespread spikes	76 months	Multifocal spikes
6	2 days (1)	Left hemisphere dominant mild slowing Ictal discharges on the left frontal area	ND	ND

ND, not done.
The number in parentheses indicates days after the onset of encephalopathic manifestations.

and acts on the NEMO-mutated cells, inducing their apoptosis. Because the brain, like the skin, is of ectodermal origin, brain injury can result from the same pathogenesis. During the first weeks of life, several stimuli can induce an inflammatory response, including bacterial colonization of the skin and gastrointestinal tract, oxidative stress due to the transition from intrauterine to extrauterine life, and exposure to various environmental antigens. The occurrence of brain injury from the neonatal through the early infantile period lends some support to this hypothesis.

It is noteworthy that the seizures resolved within 5 days, although they were severe and mimicked acute encephalopathy with clusters or prolonged seizures that were relatively refractory to antiepileptic drugs, accompanied by reduced consciousness. Although additional seizures occurred in some patients as remote symptomatic epilepsy, none had a recurrence of the encephalopathic events. A recurrent encephalopathic event is likely uncommon, although recurrence of the CNS injury has rarely been reported [22,23]. These facts suggest that the encephalopathic events in infants with IP are self-limiting. This may also be explained by the hypothesis that the CNS injury is related to the increased sensitivity to the apoptosis of NEMO-mutated cells. After the NEMO-mutated cells are eliminated, a large majority of the surviving cells lack the mutation. The reduction in the number of cells with the mutation may be related to the paucity of the recurrence of the encephalopathic events.

The MRI findings in patients with IP include atrophic changes [13,15], hypoplasia of the corpus callosum [8,13,17,24], subcortical or deep white matter lesions [4–8,13–15], and hemorrhagic necrosis [15,17]. Pascual-Castroviejo et al. reported that the most severe lesions were located in the subcortical white matter [13]. Several authors have also reported CNS lesions in the subcortical or periventricular white matter in patients with IP [4–8,13–15]. MRI abnormalities were observed in the subcortical white matter in all of our patients. This indicates that the subcortical white matter is the most common site of CNS lesions in patients with IP. Diffusion-weighted image abnormalities during the acute phase were also impressive in our patients. Restricted water diffusion was seen in the corpus callosum, internal capsule, and basal ganglia in addition to the subcortical white matter. Some authors have reported that DWI showed reduced diffusion in the corpus callosum and subcortical white matter [5,11]. This is very similar to the images of our patients. These facts suggest that cytotoxic edema characterizes the CNS lesions of patients with IP and that DWI is useful for detecting the extent of the affected regions during encephalopathic events in patients with IP.

In conclusion, we report the clinical and neuroimaging features of encephalopathic manifestations in patients with IP during early infancy. The encephalopathic manifestations were characterized by clusters of seizures and reduced consciousness, although the duration of the episode was relatively short. MRI abnormalities were predominant in the subcortical areas in most patients. Further studies are necessary to determine the pathogenesis of the encephalopathic manifestations in patients with IP.

Acknowledgement

This work was supported by the grants from the Ministry of Education, Culture, Sports, Science and Technology (20591306 and 20249053).

References

[1] Smahi A, Courtois G, Vabres P, Yamaoka S, Heuertz S, Munnich A, et al. Genomic rearrangement in NEMO impairs NF-kB activation and is a cause of Incontinentia pigmenti: the international incontinentia pigmenti (IP) consortium. Nature 2000;405:466–72.
[2] Smahi A, Courtois G, Rabia SH, Döffinger R, Bodemar C, Munnich A, et al. The NF-kappaB signaling pathway in human

diseases: from incontinentia pigmenti to ectodermal dysplasias and immune-deficiency syndromes. Hum Mol Genet 2002;11:2371–5.
[3] Sebban H, Coutrois G. NFκB and inflammation in genetic disease. Biochem Pharmacol 2006;72:1153–60.
[4] Sasaki M, Hanaoka S, Suzuki H, Takashima S, Arima M. Cerebral white matter lesions in a case of incontinentia pigmenti with infantile spasms, mental retardation and left hemiparesis (in Japanese). No To Hattatsu 1991;23:178–83.
[5] Hennel SJ, Ekert PG, Volpe JJ, Inder TE. Insights into the pathogenesis of cerebral lesions in incontinentia pigmenti. Pediatr Neurol 2003;29:148–50.
[6] Pörksen G, Pfeiffer C, Hahn G, Poppe M, Friebel D, Kreuz F, et al. Neonatal seizures in two sisters with incontinentia pigmenti. Neuropediatrics 2004;35:139–42.
[7] Wolf NI, Krämer N, Harting I, Seitz A, Ebinger F, Pöschl J, et al. Diffuse cortical necrosis in a neonate with incontinentia pigmenti and an encephalitis-like presentation. Am J Neuroradiol 2005;26:1580–2.
[8] Lee JH, Im SA, Chun JS. Serial changes in white matter lesions in a neonate with incontinentia pigmenti. Childs Nerv Syst 2008;24:525–8.
[9] Kaczala GW, Messer MA, Poskitt KJ, Prendiville JS, Gardiner J, Senger C. Therapy resistant neonatal seizures, linear vesicular rash, and unusually early neuroradiological changes: incontinentia pigmenti. Eur J Pediatr 2008;167:979–83.
[10] Loh NR, Jadresic LR, Whitelaw A. A genetic cause for neonatal encephalopathy: incontinentia pigmenti with NEMO mutation. Acta Paediatr 2008;97:379–81.
[11] Hart AR, Edwards C, Mahajan J, Wood ML, Griffiths PD. Destructive encephalopathy in incontinentia pigmenti. Dev Med Child Neurol 2009;51:162–3.
[12] Shuper A, Bryan RN, Singer HS. Destructive encephalopathy in incontinentia pigmenti: a primary disorder? Pediatr Neurol 1990;6:137–40.
[13] Pascual-Castroviejo I, Roche MC, Martinez Fernández V, Perez-Romero M, Escudero RM, Garcia-Peñas JJ, et al. Incontinentia pigmenti: MR demonstration of brain changes. Am J Neuroradiol 1994;15:1521–7.
[14] Yoshikawa H, Uehara Y, Abe T, Oda Y. Disappearance of a white matter lesion in incontinentia pigmenti. Pediatr Neurol 2000;23:364–7.
[15] Lee AG, Goldberg MF, Gillard JH, Barker PB, Bryan RN. Intracranial assessment of incontinentia pigmenti using magnetic resonance imaging, angiography, and spectroscopic imaging. Arch Pediatr Adolesc Med 1995;149:573–80.
[16] O'Doherty NJ, Norman RM. Incontinentia pigmenti (Bloch–Sulzberger syndrome) with cerebral malformation. Dev Med Child Neurol 1968;10:168–74.
[17] Chatkupt S, Gozo AO, Wolansky LJ, Sun S. Characteristic MR findings in a neonate with incontinentia pigmenti. Am J Radiol 1993;160:372–4.
[18] Hauw JJ, Perie G, Bonnette J, Escourolle R. Les lesions cerebrales de l'incontinentia pigmenti. Acta Neuropathol (Berl) 1977;38:159–62.
[19] Siemes H, Schneider H, Dening D, Hanefeld F. Encephalitis in two members of a family with incontinentia pigmenti (Bloch–Sulzberger syndrome). Eur J Pediatr 1978;129:103–15.
[20] Pasparakis M, Courtois G, Hafner M, Schmidt-Supprian M, Nenci A, Toksoy A, et al. TNF-mediated inflammatory skin disease in mice with epidermis-specific deletion of IKK2. Nature 2002;417:861–6.
[21] Nenci A, Huth M, Funteh A, Schmidt-Supprian M, Bloch W, Metzger D, et al. Skin lesion development in a mouse model of incontinentia pigmenti is triggered by NEMO-deficiency in epidermal keratinocytes and requires TNF signaling. Hum Mol Genet 2006;15:531–42.
[22] Cartwright MS, White DL, Miller LM, Roach ES. Recurrent stroke in a child with incontinentia pigmenti. J Child Neurol 2009;24:603–5.
[23] Brunquell PJ. Recurrent encephalomyelitis associated with incontinentia pigmenti. Pediatr Neurol 1987;3:174–7.
[24] Aydingöz Ü, Midia M. Central nervous system involvement in Incontinentia pigmenti: cranial MRI of two siblings. Neuroradiology 1998;40:364–6.

ELSEVIER

Brain & Development 33 (2011) 77–82

BRAIN & DEVELOPMENT
Official Journal of the Japanese Society of Child Neurology

www.elsevier.com/locate/braindev

Case report

Amplitude-integrated electroencephalography in patients with acute encephalopathy with refractory, repetitive partial seizures

Akihisa Okumura [a,b,*], Mitsutaka Komatsu [b], Shinpei Abe [a], Tomohiro Kitamura [b], Kotoko Matsui [b], Mitsuru Ikeno [a], Toshiaki Shimizu [a]

[a] *Department of Pediatrics, Juntendo University School of Medicine, Japan*
[b] *Department of Pediatrics, Urayasu Ichikawa Municipal Hospital, Japan*

Received 28 August 2009; received in revised form 26 December 2009; accepted 27 December 2009

Abstract

We report amplitude-integrated EEG findings in two children with acute encephalopathy with refractory, repetitive partial seizures. Both patients had a febrile illness one week before the onset of seizure. They had reduction of consciousness and repetitive seizures refractory to first-line antiepileptic drugs. Seizure frequency rapidly increased and evolved into status epilepticus. Continuous seizure monitoring with amplitude-integrated EEG revealed frequent subclinical seizures which were missed by direct observation. In addition, the site of origin of seizures was multifocal, and seizure foci shifted from one hemisphere to the other. Their seizures were controlled after an administration of high-dose phenobarbital. Continuous seizure monitoring with amplitude-integrated EEG will contribute to correct estimation of seizure burden and efficacy of antiepileptic drugs in children with acute encephalopathy with refractory, repetitive partial seizures.

Keywords: Amplitude-integrated electroencephalography; Acute encephalopathy with refractory; Repetitive partial seizures; Seizure monitoring

1. Introduction

Acute encephalitis/encephalopathy with refractory, repetitive partial seizures (AERRPS) is a unique subtype of acute encephalopathy of children [1]. AERRPS is characterized by acute onset of frequent and refractory partial seizures in association with consciousness impairment. Although the duration of seizures is usually brief within 5 min, seizures evolve into status epilepticus within a week after the onset. Seizures in AERRPS are refractory to first-line antiepileptic drugs such as diazepam and phenytoin. High-dose barbiturate is often necessary for cessation of seizures. Seizure monitoring will be important in patients with AERRPS. We performed continuous seizure monitoring using amplitude-integrated electroencephalography (aEEG) in two patients with AERRPS. aEEG revealed frequent subclinical seizures in these patients. To our knowledge, this is the first reports on aEEG findings in patients with AERRPS.

2. Patients report

2.1. Patient 1

The patient was a seven-year-old girl. She was the second child of non-consanguineous healthy parents and was previously healthy except for a history of three simple febrile seizures. Her family history was unremarkable. Six days before admission, she had a febrile illness lasting for 3 days. She was admitted to a local

* Corresponding author. Address: Department of Pediatrics, Juntendo University School of Medicine, 2-1-1 Hongo, Bunkyo-ku, Tokyo 113-8421, Japan. Tel.: +81 3 3813 3111; fax: +81 3 5800 1580.
E-mail address: okumura@juntendo.ac.jp (A. Okumura).

0387-7604/$ - see front matter © 2010 The Japanese Society of Child Neurology. Published by Elsevier B.V. All rights reserved.
doi:10.1016/j.braindev.2009.12.009

hospital with repetitive seizures and reduced consciousness. Physical and neurological examination, and laboratory data were unremarkable, except for mild elevation of C-reactive protein (1.2 mg/dl). Cerebrospinal fluid examination was not performed. MRI including diffusion-weighted images was also unremarkable. Virological studies were not performed except for negative herpes simplex DNA in cerebrospinal fluid.

Her seizures were characterized by reduced consciousness, eye deviation, and oral automatism. The duration of seizures was 3–10 min. Although diazepam, carbamazepine, phenytoin and lidocaine were administered, her seizures increased and consciousness impairment was worsened. She was transferred to our hospital on the 3rd day of illness. EEG showed generalized slowing, and she was diagnosed as having AERRPS. Despite that she was treated with continuous midazoram and intravenous dexamethasone, but status epilepticus occurred on the 7th day of illness. Seizure monitoring with multi-channel aEEG was started. Although 0.5 mg/kg of intravenous diazepam was ineffective, her seizures were controlled after intravenous injection of 15 mg/kg of phenobarbital (Fig. 1). No clinical seizures were noted until the end of 24-h aEEG monitoring, although subclinical seizures appeared 3 h after the beginning of aEEG. Multifocal origin and a shift of seizure foci were observed on ictal conventional EEG. The first 3 seizures began in the right fronto-central area. Epileptiform discharges spread to adjacent areas, and then seizure focus shifted to the left fronto-central area. The fourth seizures began in the left centro-parietal area and end in the right fronto-central area. A total of 16 subclinical seizures were recorded. Eleven of them began in the left fronto-central areas and the remainders in the left fronto-central areas. A shift of seizure foci was not observed in any subclinical seizures. Her seizures were controlled by 10 mg/kg of phenobarbital and 0.3 mg/kg of clobazam 3 weeks after the onset.

She had subnormal mentality and mild conduct disorders with oppositional behavior. No motor impairment was observed. One month after the discharge, she had weekly seizures with loss of consciousness with or without head rotation or asymmetric posturing. Her seizures were almost controlled by a combination of lamotrigine, phenobarbital and clobazam.

2.2. Patient 2

The patient was a previously healthy eight-year-old girl. She was the third child of non-consanguineous healthy parents. Her mother and elder brothers had a history of simple febrile seizures. One week before admission, she had a febrile illness lasting for 4 days. She was admitted to a local hospital with clustering seizures and reduced consciousness. On admission, physical and neurological examination, and laboratory data were unremarkable. Cerebrospinal fluid revealed normal cell counts and protein level. MRI on admission revealed no abnormal findings, including diffusion-weighted images. Virological studies were not performed except for negative herpes simplex DNA in cerebrospinal fluid.

She had frequent seizures with desaturation with or without oral movement lasting for 3–5 min. She was diagnosed as having AERRPS and was treated with continuous infusion of midazoram, phenobarbital suppository, and intravenous dexamethasone. However, her seizures were refractory against these drugs. Conventional EEG on admission revealed general slowing and one ictal recording with a shift of seizure focus (Fig. 2). At the beginning of the seizure, spiky fast waves were observed on the right fronto-central area. Epileptiform discharges gradually spread to the adjacent areas and result in secondary generalization. Thereafter, ictal focus shifted to the left occipito-temporal area. Conventional EEG at 6th day of illness also showed generalized slowing and two ictal recordings. The seizure foci was located at the left central area in one seizure and at the right temporal area in the other. A shift of seizure focus was not observed.

Continuous seizure monitoring with single-channel aEEG was performed from the 6th day of illness. We chose Fp1–Fp2 derivation, because stable long-term electrode placement was easy. aEEG demonstrated marked clusters of seizures lasting for 3–5 min with short intervals (Fig. 2). This finding was continuously observed until the 11th day of illness. The number of seizures was more than 200 every day. However, approximately 20 seizures were noticed on the basis of nursing records every day. Large majority of seizures were not recognized by direct observation.

She was transferred to our hospital at the 11th day of illness. Seizure monitoring with multi-channel aEEG confirmed a cessation of seizures after the serum level of phenobarbital reached 67 μg/ml. One month later, she had sporadic seizures with loss of vision with preserved consciousness. Her seizures were controlled by valproate and clobazam. No cognitive or motor impairment was observed after 13 months of follow-up.

3. Discussion

We performed continuous seizure monitoring with aEEG in two children with AERRPS. aEEG unexpectedly revealed frequent subclinical seizures in both patients. In addition, ictal conventional EEG demonstrated not only that the site of origin of seizures was multifocal, but also that seizure foci shifted from one hemisphere to the other. These facts are very important to clarify the pathogenesis and optimal treatment in children with AERRPS.

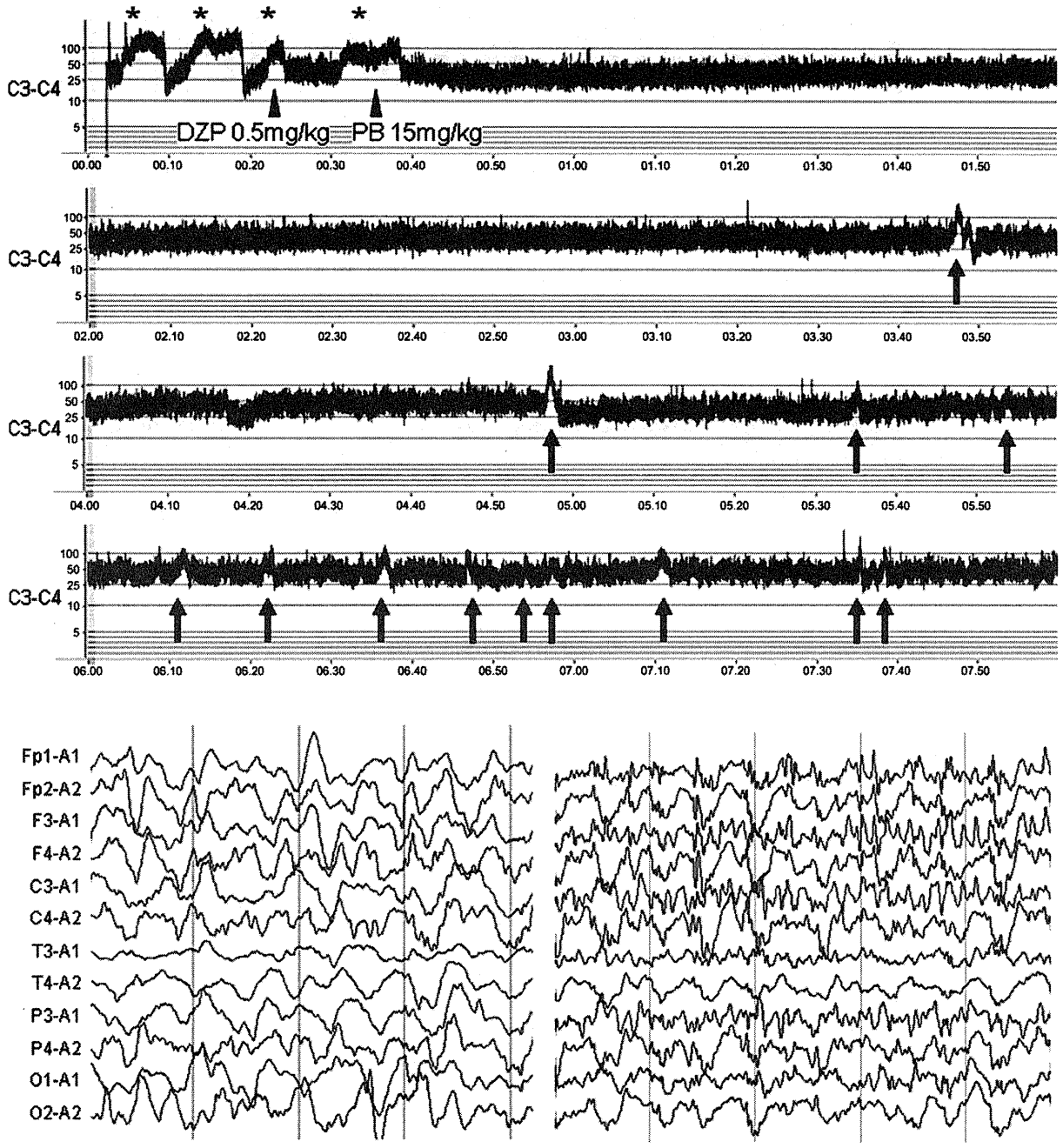

Fig. 1. Amplitude-integrated and raw EEG in Section 2.1. (Top) Amplitude-integrated EEG. The first 8 h is shown. Four clinical seizures were observed during the first 1 h. Seizures were transiently controlled after intravenous phenobarbital. However, subclinical seizures appeared after a 3-h of interval. The numbers below horizontal axes indicate time after the beginning of the recording. (Bottom) Raw EEG of the third seizure. At the beginning, rhythmic low-voltage fast wave bursts were seen in the right fronto-central area (left). Seizure focus shifted to the left hemisphere approximately 3 min after the beginning of the seizure (right). Asterisks indicate clinical seizure, and arrows indicate subclinical ones. DZP: diazepam, PB: phenobarbital.

Frequent subclinical seizures are an important problem in clinical settings. Although it is established that subclinical seizures are quite frequent in neonatal seizures [2,3], their occurrence has not been confirmed in older children with acute encephalitis/encephalopathy. There has been no previous description on subclinical seizures in patients with AERRPS. This may indicate that subclinical seizures have been left unnoticed and leads to under-estimation of seizure burden, over-estimation of efficacy of antiepileptic drugs, and insufficient treatment for seizures. In this aspect, continuous seizure monitoring using aEEG will be useful. At first, aEEG monitoring can show seizure burden quantitatively. Precise evaluation of seizure burden is difficult by direct

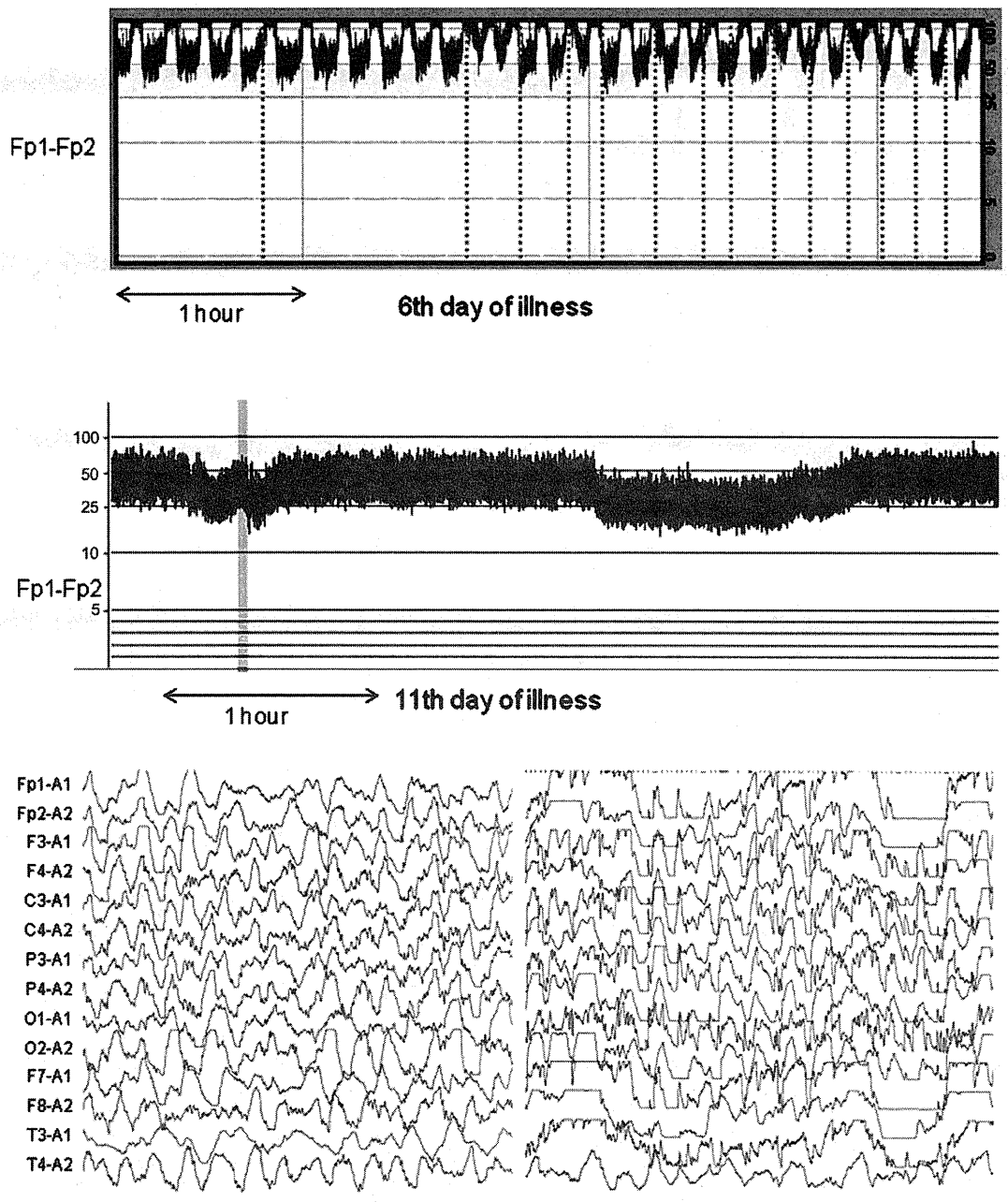

Fig. 2. Amplitude-integrated and conventional EEG in Section 2.2. (Top) Amplitude-integrated EEG on the 6th day of illness. Typical saw tooth pattern, characterized by continuous rise-and-falls of maximum and minimum boarders, was observed. This indicates continuous occurrence of short seizures. Broken lines indicate clinical seizures detected by the nursing stuff. A majority of seizures were missed. (Middle) Amplitude-integrated EEG on the 11th day of illness. No seizures were observed. (Bottom) Conventional EEG on the 6th day of illness. At the beginning, rhythmic low-voltage fast wave bursts appeared in the right fronto-central area (left). However, the seizure ended in the left occipito-parietal area (right).

observation, because the clinical symptoms of seizures in children with AERRPS are subtle. In fact, large majority of seizures were overlooked or subclinical in our patients. Secondly, aEEG monitoring clearly demonstrated the efficacy of antiepileptic treatment in our patients. Continuous infusion of midazoram was not effective, whereas intravenous phenobarbital was quite effective in our patients. aEEG will be quite useful to determine the optimal treatment in children with AERRPS.

A comparison between conventional EEG and aEEG is shown in Table 1 [4–6]. Application of the electrodes and data interpretation are easier in aEEG than in conventional EEG. aEEG recordings and their interpretation can be performed by untrained personnel after only a brief explanation. aEEG can be started anytime, whereas conventional EEG cannot be performed when experts are out of hospital. However, aEEG also possesses several limitations. The most significant problem is the limited number of electrodes, which may result

Table 1
The comparison between conventional EEG and amplitude-integrated EEG [4–6].

	Conventional EEG	Amplitude-integrated EEG
Application of electrodes	Sometimes complicated	Easy
Operation of recorder	Rather complex	Easy
Long-term recording	Difficult	Easy
Interpretation	Needs specialized skill	Usually easy
Sensitivity for seizure detection	Excellent	Less sensitive
Recognition of artifact	Usually easy	Sometimes difficult
Changes of waveforms	Detectable	Undetectable

in missing seizure discharges that occur far from the electrodes [7]. Therefore, conventional EEG is also necessary for the correct diagnosis of seizures. Secondly, aEEG is not useful for the detailed assessment of ictal EEG changes due to the limited number of channels and highly time-compressed output. It will be difficult to assess the relationship between aEEG findings and seizure semiology.

It is interesting that the site of seizure origin was multifocal in our patients, whereas seizure manifestation was almost uniform in each patient. There has been no description on multifocal seizure origins in children with AERRPS, although multifocal paroxysmal discharges have been reported. It is also remarkable that seizure foci sometimes shifted from one hemisphere to the other during a single seizure. A shift of seizure foci is quite frequent in seizures of neonates [8,9], and is sometimes observed in seizures during infancy [10]. Migrating seizure foci are characteristic in malignant migrating partial seizures in infancy, one of the most severe forms of early infantile epileptic encephalopathy [11]. However, a shift of seizure foci is very unusual in older children.

Several authors coincide with the efficacy of high-dose barbiturate inducing burst-suppression during the acute phase of AERRPS [12–15]. Lin et al. suggested efficacy of topiramate in combination with lidocaine and phenobarbital [14]. High-dose phenobarbital was markedly effective in our patients, although burst-suppression coma was not necessary. These facts strongly indicate that high-dose barbiturate should be the first choice of antiepileptic drugs, when we encounter the patients with probable AERRPS with severe clustering of focal seizures.

There can be a controversy on whether or not our patients should be included into AERPPS. The mode of onset and refractory, repetitive, partial seizures in our patients meet the proposed diagnostic criteria [1]. However, suppression-burst coma was not necessary in our patient. Moreover, short interval was present before the switchover to epilepsy as a sequel. These two items are not consistent with the diagnostic criteria. The core features of AERRPS will be the mode of onset and refractory, repetitive partial seizures, which were also seen in our patients. In addition, some of the patients with AERRPS reported by Lin et al. did not necessitate suppression-burst coma and had transient cessation of seizures [14]. Therefore, we considered that our patients can be included into less severe spectrum of AERRPS, because our patients fulfilled the core features and supportive findings.

In conclusion, continuous aEEG monitoring of seizures was performed in two children with AERRPS. Frequent subclinical seizures observed on aEEG highlighted the necessity of seizure monitoring in AERRPS. Continuous seizure monitoring with aEEG will contribute to correct estimation of seizure burden and efficacy of antiepileptic drugs. aEEG may help to improve antiepileptic treatment in children with AERRPS and their neurological outcome.

Acknowledgement

This work was supported by the grants from the Ministry of Education, Culture, Sports, Science and Technology (20249053 and 20591306).

References

[1] Sakuma H. Acute encephalitis with refractory, repetitive partial seizures. Brain Dev 2009;31:510–4.
[2] Murray DM, Boylan GB, Ali I, Ryan CA, Murphy BP, Connolly S. Defining the gap between electrographic seizure burden, clinical expression and staff recognition of neonatal seizures. Arch Dis Child Fetal Neonatal Ed 2008;93:F187–91.
[3] Malone A, Ryan CA, Fitzgerald A, Burgoyne L, Connolly S, Boylan GB. Interobserver agreement in neonatal seizure identification. Epilepsia 2009;50:2097–101.
[4] Hellström-Westas L, Rosén I. Continuous brain-function monitoring: state of the art in clinical practice. Semin Fetal Neonatal Med 2006;11:503–11.
[5] Shah DK, Mackay MT, Lavery S, Watson S, Harvey AS, Zempel J, et al. Accuracy of bedside electroencephalographic monitoring in comparison with simultaneous continuous conventional electroencephalography for seizure detection in term infants. Pediatrics 2008;121:1146–54.
[6] Toet MC, van der Meij W, de Vries LS, Uiterwaal CS, van Huffelen KC. Comparison between simultaneously recorded amplitude integrated electroencephalogram (cerebral function monitor) and standard electroencephalogram in neonates. Pediatrics 2002;109:772–9.
[7] Shellhaas RA, Clancy RR. Characterization of neonatal seizures by conventional EEG and single-channel EEG. Clin Neurophysiol 2007;118:2156–61.

[8] Okumura A, Hayakawa F, Kato T, Itomi K, Maruyama K, Kubota T, et al. Ictal electroencephalographic findings of neonatal seizures in preterm infants. Brain Dev 2008;30:261–8.
[9] Patrizi S, Holmes GL, Orzalesi M, Allemand F. Neonatal seizures: characteristics of EEG ictal activity in preterm and fullterm infants. Brain Dev 2003;25:427–37.
[10] Okumura A, Watanabe K, Negoro T, Hayakawa F, Kato T, Natsume J. Ictal EEG in benign partial epilepsy in infancy. Pediatr Neurol 2007;36:8–12.
[11] Coppola G, Plouin P, Chiron C, Robain O, Dulac O. Migrating partial seizures in infancy: a malignant disorder with developmental arrest. Epilepsia 1995;36:1017–24.
[12] Saito Y, Maegaki Y, Okamoto R, Ogura K, Togawa M, Nanba Y, et al. Acute encephalitis with refractory, repetitive partial seizures: case reports of this unusual post-encephalitic epilepsy. Brain Dev 2007;29:147–56.
[13] Ito H, Mori K, Toda Y, Sugimoto M, Takahashi Y, Kuroda Y. A case of acute encephalitis with refractory, repetitive partial seizures, presenting autoantibody to glutamate receptor Gluepsilon2. Brain Dev 2005;27:531–4.
[14] Lin JJ, Lin KL, Wang HS, Hsia SH, Wu CT. Effect of topiramate, in combination with lidocaine, and phenobarbital, in acute encephalitis with refractory repetitive partial seizures. Brain Dev 2009;31:605–11.
[15] Shyu CS, Lee HF, Chi CS, Chen CH. Acute encephalitis with refractory, repetitive partial seizures. Brain Dev 2008;30:356–61.

Is It Time to Study TLR3 or UNC-93B Pathway Deficiencies in Reactivated Herpes Simplex Encephalitis?

To The Editors:

I have read with keen interest the article by Gong et al titled "Herpes Simplex Virus Reactivation After Subtotal Hemispherectomy in a Pediatric Patient."[1] I would like to point out that in the last few years, 2 main primary immunodeficiencies have been identified related to herpes simplex infections: TLR3 and UNC-93B deficiencies. The authors do not mention whether these 2 deficiencies were ruled out.

TLR3 deficiency was reported in 2 children. They showed impaired responsiveness of their fibroblasts to poly(I:C) stimulation (mimicking viral dsRNA). These 2 patients had severe HSV-1 infection (encephalitis).[2]

To date only 2 children with UNC-93B deficiencies have been identified after isolated HSV-1 encephalitis. They lacked functional UNC-93B, an endoplasmic reticulum protein required for toll-like receptors signaling linked with viral defense (TLR3, TLR7, TLR8, and TLR9). In these 2 children upon HSV-1 stimulation, peripheral blood mononuclear cells produced almost absent levels of IFN-a and IFN-b.[3]

Although there have been only a few patients with these deficiencies, due to the uncommon presentation of this infection upon surgery, perhaps cases should lead us to rule out a deficiency in the host.

Luis I. Gonzalez-Granado, MD
Pediatrics and Immunodeficiencies
Hospital 12 octubre
Madrid, Spain
nachgonzalez@gmail.com

REFERENCES

1. Gong T, Bingaman W, Danziger-Isakov L, et al. Herpes simplex virus reactivation after subtotal hemispherectomy in a pediatric patient. *Pediatr Infect Dis J.* 2010;29:1148–1150.
2. Zhang SY, Jouanguy E, Ugolini S, et al. TLR3 deficiency in patients with herpes simplex encephalitis. *Science.* 2007;317:1522–1527.
3. Casrouge A, Zhang SY, Eidenschenk C, et al. Herpes simplex virus encephalitis in human UNC-93B deficiency. *Science.* 2006;314:308–311.

Pandemic A (H1N1) Influenza in Hospitalized Children in Warsaw, Poland

To the Editors:

The report by Kumar et al[1] on hospitalized children with pandemic influenza prompts us to present our data on pandemic variant A (H1N1) influenza, confirmed with reverse transcription polymerase chain reaction in 100 children (51 boys and 49 girls) with a median age of 5 years and 2 months. Most of them (85%) were diagnosed between November 15 and December 30, 2009; no case was diagnosed after January 2010. All children were admitted to Warsaw hospitals for diagnosis and therapy. Of the 100 children, 48 (48%) children had underlying medical conditions recognized as risk factors for serious influenza infection (Table 1).

Because pandemic influenza vaccines were not purchased and registered in Poland, none of our patients had been vaccinated against A (H1N1) influenza. (The Polish Ministry of Health did not decide for central purchase of any of the "pandemic" vaccines, because the experts regarded investigations on safety as insufficient and requested that producers to take responsibility for possible adverse effects. After prolonged negotiations, producers have refused this request.)

Ninety-six patients had clinically apparent influenza infection. The leading symptoms were as follows: fever in 89.6%, cough in 70.8%, coryza in 53.1%, sore throat in 34.4%, digestive tract disorders (vomiting, diarrhea, abdominal pain) in 25.0%, malaise (muscle and/or bone pains) in 19.8%, headache in 13.5%, dyspnea in 10.4%, and conjunctivitis in 7.3%.

In 20 of the 96 (20.3%) cases, influenza was complicated by pneumonia. Of these, 11 (55%) children had risk factors; 4 of the latter required intensive care and mechanical ventilation for respiratory distress and heart failure. Three children died: 2 with acute lymphoblastic leukemia and 1 with bronchopulmonary dysplasia and congenital heart defect complicated by pulmonary hypertension.

In 62 of 100 (62%) children, oseltamivir was administered. In 4 of 100 children with hematologic malignancy, prophylactic oseltamivir treatment was given, and despite the fact that A (H1N1) infection was confirmed by reverse transcription polymerase chain reaction, symptomatic influenza did not develop in these children. In the remaining 58 of 100 (58%) children, oseltamivir was used for treatment and in 25 of 58 (43%) children, antibiotic therapy was also given. In most of these children, 57 of 62 (91%), oseltamivir was well tolerated.

The clinical course of A (H1N1) influenza infection was similar to seasonal influenza, as has been reported from the United States and Canada.[2–4]

TABLE 1. Leading Risk Factors

Risk Factors	Children (Number)
Age <2 yr	23/100
Chronic diseases and defects	
Hematologic malignancy	11/100
Asthma and chronic lung disease	8/100
Inflammatory bowel diseases	5/100
Cardiac defects and heart failure	4/100
Other	11/100

Andrzej Radzikowski, MD, PhD
Łukasz Dembiński, MD
Department of Paediatric Gastroenterology and Nutrition
Medical University of Warsaw
Public Paediatric Teaching Hospital

Ewa Talarek, MD, PhD
Department of Children's Infectious Diseases
Medical University of Warsaw
Hospital of Infectious Diseases

Katarzyna Smalisz-Skrzypczyk, MD
Department of Paediatrics, Haematology and Oncology
Medical University of Warsaw
Public Paediatric Teaching Hospital
Warsaw, Poland

Teresa Jackowska, MD, PhD
Clinical Department of Paediatrics
Medical Centre for Postgraduate Education
Warsaw, Poland

Magdalena Marczyńska, MD, PhD
Department of Children's Infectious Diseases
Medical University of Warsaw
Hospital of Infectious Diseases
Warsaw, Poland

REFERENCES

1. Kumar S, Havens PL, Chusid MJ, et al. Clinical and epidemiologic characteristics of children hospitalized with 2009 pandemic H1N1 influenza A infection. *Pediatr Infect Dis J.* 2010;29:591–594.
2. O'Riordan S, Barton M, Yau Y, et al. Risk factors and outcomes among children admitted to hospital with pandemic H1N1 influenza. *CMAJ.* 2010;182:39–44.
3. Centers for Disease Control and Prevention. 2009 pandemic influenza A(H1N1) virus infection—Chicago, Illinois, April–July 2009. *MMWR Morb Mortal Wkly Rep.* 2009;58:913–918.
4. Miroballi Y, Baird JS, Zackai S, et al. Novel influenza A(H1N1) in a pediatric health care facility in New York City during the first wave of the 2009 pandemic. *Arch Pediatr Adolesc Med.* 2010;164:24–30.

Amoebic Abscess of the Spleen and Fatal Colonic Perforation

To the Editors:

Each year about 50 million patients develop amoebic dysentery from *Entamoeba histolytica* infections; 40,000 to 110,000 die of the disease annually.[1] Complications are liver, lung, or brain abscesses, and severe colitis, leading to colonic perforation and toxic shock with a case-fatality rate of more than 50%, especially in young children.[1–4] Occasionally involvement of the spleen has been reported.[5–7]

We present 2 young Tanzanian children who suffered from an abscess of the spleen and colonic perforation, respectively, and were treated at Haydom Lutheran Hospital, a rural health institution in northern Tanzania. The 400-bed hospital serves a population of more than 500,000 people and consists of surgical, internal medicine, gynecologic/obstetric, pediatric, and tuberculosis wards. The laboratory and radiology facilities are quite basic, but medical and surgical treatment is of good quality compared to other health facilities in the country.

Case 1. A 7-year-old boy was admitted with a history of high temperature, chest and abdominal pain, cough, and dyspnea for several days. Vomiting, diarrhea, or dysentery were not reported. Malaria, anemia (hemoglobin, 5.6 g/dL), and bacterial pneumonia were diagnosed and treated with intravenous quinine (30 mg/kg/d t.i.d.), and ampicillin (100 mg/kg/d t.i.d.) for 7 days. A blood transfusion was not indicated. After having improved for some days, the patient again complained of severe abdominal pain. At that time, a protrusion of the left upper abdominal quadrant was visible. An abdominal ultrasound showed a cystic lesion at the position of the spleen (7 × 7 × 8 cm), splenic tissue itself was not clearly visible. The liver was unremarkable. A chest radiograph was normal. No other imaging techniques were available. The white blood cell count was 9800/μL and the erythrocyte sedimentation rate 130 mm in the first hour. More investigations like cultures were not possible. Because an abscess was suspected, an exploratory laparotomy was performed. At the time of operation, a cystic lesion was found within small remnants of splenic tissue. The cyst was cleaned and drained for 5 days. On examination of the whitish, thickened fluid, trophozoites of *E. histolytica* were found microscopically. The patient was treated with intravenous metronidazole (50 mg/kg/d t.i.d.) for 10 days and recovered well. An oral luminal amoebicide for eradication of amoeba was not available. A control ultrasound 2 weeks after operation showed a normal spleen. The patient was discharged in good condition, but then lost to follow-up.

Case 2. An 11-day-old male neonate (home delivery) was admitted with signs and symptoms of neonatal sepsis, including fever at 39°C, difficulty in breathing, distended abdomen, severe jaundice (bilirubin measurement not possible), and anemia (7.2 g/dL). Further investigation revealed that, after an uneventful pregnancy and delivery at home, the neonate developed fever on the third day of life and was treated with chloroquine (total 25 mg/kg in 4 doses) because of suspected congenital malaria by the local nonphysician health care provider. The following days, the neonate was breast-feeding, but only with reduced effort, and developed constipation. Bloody diarrhea was not reported. Shortly afterward the condition deteriorated, according to the parents, and the infant was brought to hospital. Further diagnostic work-up with plain abdominal radiograph and ultrasound revealed intestinal paralysis without clear signs of perforation or free fluid. After the infant had been stabilized for 1 day with intravenous fluids, antibiotics (ampicillin [200 mg/kg/d t.i.d.], gentamicin [5 mg/kg/d o.d.], and metronidazole [50 mg/kg/d t.i.d.]), and a blood transfusion, a laparotomy was performed on the second day. Multiple perforation sites were found at the cecum and transverse and descending colon, accompanied by a small bowel obstruction and fecal peritonitis. Large parts of the transverse and descending colon had to be resected, a colostomy was necessary. Trophozoites of *E. histolytica* were identified in the stool in the abdominal cavity. After operation, the condition deteriorated further due to the scarcity of medical and intensive care options (besides fluids and antibiotics only ventilation by hand possible), and the neonate died on the first postoperative day in septic shock. After his death, the parents admitted that they had given him nonsterile rainwater during the first week of life, a common traditional remedy for constipation in neonates in their tribe. No further inquiries were possible as the parents left shortly after their child's death and never returned to the hospital.

Amoebic abscess of the spleen has been reported only a few times so far.[5–7] Typically, adults were affected. Because of suspected bacterial abscess, laparotomy was frequently performed.[6,7] Because a diagnosis of amoebic abscess of the spleen is extremely rare, even in endemic countries, most likely in all cases an exploratory operation is indicated. The risk of spreading amoebic infection to the peritoneal cavity appears to be low; it has not yet been reported. Medical treatment with intravenous metronidazole (or tinidazole) was added after diagnosis. The overall prognosis seems to be excellent as all patients recovered.[5–7] An oral luminal amoebicide like paromomycin should be added after treatment to eliminate amoebic parasites in the colon,[1] but this was not available at our hospital. The pathogenesis of amoebic splenic abscesses remains unclear. Possibly, some organisms invade via the vena lienalis or directly into the spleen from adjacent intestines.[1]

A symptomatic amoebic infection in neonates is extremely rare, even in endemic regions like rural Africa, and usually presents as septicemia.[2,8,9] Vertical transmission has been documented, but more often the neonates get infected by nonsterile feeding techniques, either with milk, water, or nonsterile utensils. Often these fluids are given due to cultural or traditional reasons.[10] If infection occurs, severe colitis seems to be the most common clinical manifestation although amoebic liver abscess has been reported as well.[2,8,9] The prognosis in neonates is guarded especially with the development of toxic colitis and colonic perforation.[9] In developing countries, where most of these cases would occur, the prognosis is especially poor. Besides the neonate's immature immune system and often delayed presentation by the parents to the health institution, lack of appropriate diagnostic and therapeutic tools contributes to the high mortality. High-level intensive care medicine is rarely available. Whether an operation is justifiable under these circumstances, must be decided upon each single case. Traditional customs have to be considered as in our second case, and should be discouraged in a culturally sensitive approach.[10]

Carsten Krüger, MD, MIH, Dr Med
Department of Paediatrics,
St.-Franziskus-Hospital
Ahlen, Germany

Isaack Malleyeck, AMO
Naftali Naman, AMO
Haydom Lutheran Hospital
Mbulu, Tanzania

REFERENCES

1. Stanley SL Jr. Amoebiasis. *Lancet.* 2003;361: 1025–1034.
2. Chan M. Perinatal infections. In: Stan-

field P, Brueton M, Chan M, et al, eds. *Diseases of Children in the Subtropics and Tropics*. 4th ed. London: Edward Arnold; 1991: 180–185.

3. Roy Choudhury S, Sen AK. Necrotizing amebic colitis in a child. *Pediatr Surg Int*. 2002;18: 498–500.
4. Lami JL, Moore TC. Colectomy for necrotizing amebic pancolitis in early childhood with survival. *J Pediatr Surg*. 1989;24:1174–1176.
5. Lawford R, Sorrell TC. Amebic abscess of the spleen complicated by metronidazole-induced neurotoxicity: case report. *Clin Infect Dis*. 1994;19:346–348.
6. Mujahid S, Ahmed A, Siddiqui MN. Amoebic splenic abscess. *Trop Doct*. 1993;23:136–138.
7. Misra SC, Kar P, Kulpati DD. Amoebic liver and splenic abscesses. *Indian J Gastroenterol*. 1989;8:204.
8. Nazir Z, Qazi SH. Amebic liver abscesses among neonates can mimic bacterial sepsis. *Pediatr Infect Dis J*. 2005;24:464–466.
9. Rennert W, Ray C. Fulminant amebic colitis in a ten-day-old infant. *Pediatr Infect Dis J*. 2000; 19:1111–1112.
10. Thairu L, Pelto G. Newborn care practices in Pemba Island (Tanzania) and their implications for newborn health and survival. *Matern Child Nutr*. 2008;4:194–208.

Acute Encephalopathy in a Child With Secondary Carnitine Deficiency due to Pivalate-conjugated Antibiotics

To the Editors:

Secondary carnitine[1] deficiency caused by chronic administration of pivalate-conjugated antibiotics has been reported to cause hypoketotic hypoglycemia and acute encephalopathy.[1,2] We also report a case of a boy with acute encephalopathy associated with carnitine deficiency due to pivalate-conjugated antibiotics.

A 3-year-11-month-old boy was admitted to our hospital because of reduced consciousness and pyrexia. He had a lumbar meningocele treated with ventriculoperitoneal shunt. For the prophylaxis of urinary tract infection, 100 mg of cefteram pivoxil had been administered daily for 12 months. Two weeks before admission, he had transiently reduced consciousness with hypoketotic hypoglycemia (blood glucose of 12 mg/dL).

On admission, he was comatose. Physical and neurologic examinations were unremarkable. Laboratory examinations revealed blood glucose of 16 mg/dL with negative urinary ketone. Blood gas analysis, liver and renal function, and serum ammonia tests were normal. Although blood glucose returned to normal range after intravenous glucose infusion, he remained comatose and had repetitive seizures in the right arm.

MRI on the third day of illness revealed increased signal intensities in the left frontal and parietal regions on diffusion-weighted images (Fig., Supplemental Digital Content 1, http://links.lww.com/INF/A633). He was treated with methylprednisolone pulse therapy and midazolam infusion. He regained consciousness on the 11th day of illness. Fluid-attenuated inversion-recovery images on the 20th day of illness revealed gliotic changes (Fig., Supplemental Digital Content 1, http://links.lww.com/INF/A633). He was discharged from our hospital 26 days after admission.

He had additional episodes of hypoglycemia after discharge. Urinary metabolic screening revealed nonketotic dicarbonic aciduria suggesting carnitine deficiency. Secondary carnitine deficiency due to cefteram pivoxil was proven by decreased serum free carnitine value of 0.37 μmol/L (reference, 41.3 ± 15.5 μmol/L) and elevated C5-acylcarnitine attributable to pivalate on tandem mass spectrometry. After cefteram pivoxil was changed to cefaclor with oral L-carnitine supplementation, no episodes of hypoglycemia occurred. His carnitine serum concentration was 58.65 μmol/L at 3 months after the cessation of cefteram pivoxil.

We consider that acute encephalopathy of our patient is not totally attributable to hypoglycemia alone. Hypoglycemia in our patient was mild and transient and MRI findings were different from those of hypoglycemic encephalopathy demonstrating bilateral lesions in deep gray matter, cerebral cortex and white matter, and/or hippocampi.[3,4] Our patient had unilateral lesion similar to acute encephalopathy caused by influenza or other viral infections.[5]

Makino et al[2] reported a boy with reduced consciousness, repetitive seizures, and hypoketotic hypoglycemia similar to our patient. Their patient had been taking cefditoren pivoxil for 6 months. His serum free carnitine level was 6.2 μmol/L. They concluded that carnitine deficiency was the direct cause of acute encephalopathy. Another possible explanation is that carnitine deficiency may be a predisposition to acute encephalopathy with a febrile illness. As stated above, neuroimaging findings were different from those of hypoglycemic encephalopathy, and cardiac or skeletal muscle involvement, that is typical for primary carnitine deficiency, was not observed. Long-term use of pivalate-conjugated antibiotics should be avoided for prevention of secondary carnitine deficiency.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.pidj.com).

ACKNOWLEDGMENTS

The authors thank Prof. Seiji Yamaguchi and Dr. Mitsuru Endo (Department of Pediatrics, Shimane University, Faculty of Medicine) for gas chromatography mass spectrometry and tandem mass spectrometry.

Akihisa Okumura, MD, PhD
Department of Pediatrics
Juntendo University School of Medicine

Masao Morita, MD, PhD
Department of Pediatrics
Futawa Hospital
Funabashi, Japan

Mitsuru Ikeno, MD, PhD
Shinpei Abe, MD, PhD
Toshiaki Shimizu, MD, PhD
Department of Pediatrics
Juntendo University School of Medicine
Tokyo, Japan

REFERENCES

1. Stanley CA. Carnitine deficiency disorders in children. *Ann N Y Acad Sci*. 2004;1033:42–51.
2. Makino Y, Sugiura T, Ito T, et al. Carnitine-associated encephalopathy caused by long-term treatment with an antibiotic containing pivalic acid. *Pediatrics*. 2007;120:e739–e741.
3. Lo L, Tan AC, Umapathi T, et al. Diffusion-weighted MR imaging in early diagnosis and prognosis of hypoglycemia. *Am J Neuroradiol*. 2006;27:1222–1224.
4. Aoki T, Sato T, Hasegawa K, et al. Reversible hyperintensity lesion on diffusion-weighted MRI in hypoglycemic coma. *Neurology*. 2004;63:392–393.
5. Nagasawa T, Kimura I, Abe Y, et al. HHV-6 encephalopathy with cluster of convulsions during eruptive stage. *Pediatr Neurol*. 2007;36: 61–63.

ELSEVIER

Brain & Development 33 (2011) 21–27

BRAIN & DEVELOPMENT
Official Journal of the Japanese Society of Child Neurology

www.elsevier.com/locate/braindev

Original article

Chronological diffusion-weighted imaging changes and mutism in the course of rotavirus-associated acute cerebellitis/cerebellopathy concurrent with encephalitis/encephalopathy

Tetsuo Kubota [a,*], Toshihiko Suzuki [a], Yuma Kitase [a], Hiroyuki Kidokoro [a], Yuji Miyajima [a], Akimasa Ogawa [a], Jun Natsume [b], Akihisa Okumura [c]

[a] *Department of Pediatrics, Anjo Kosei Hospital, Aichi, Japan*
[b] *Department of Pediatrics, Nagoya University Graduate School of Medicine, Nagoya, Japan*
[c] *Department of Pediatrics, Juntendo University School of Medicine, Tokyo, Japan*

Received 29 October 2009; received in revised form 25 February 2010; accepted 28 April 2010

Abstract

Rotavirus is one of the most common causes of gastroenteritis in children and is known to accompany some neurological disorders such as encephalitis/encephalopathy and seizures. Although cerebellar disorders sometime occur as a complication of rotavirus gastroenteritis in Japan, few reports have addressed these issues. Here, we report three cases of insulted cerebellums in addition to encephalitis/encephalopathy associated with rotavirus. Similar to posterior fossa syndrome after surgery, mutism was a notable symptom that lasted about 1 month. Brain diffusion-weighted imaging (DWI) revealed chronological changes, i.e., marked hyperintensity in the bilateral dentate nucleus followed by the vermis and cerebellar hemisphere. The bilateral dentate nucleus is known to be a key lesion site for mutism, and these clinical and radiological findings may be tightly connected in rotavirus-associated cerebellitis/cerebellopathy.

Keywords: Rotavirus; Cerebellitis/cerebellopathy; Mutism; Diffusion-weighted imaging; Encephalitis/encephalopathy

1. Introduction

Rotavirus is the primary cause of severe gastroenteritis in children. Infection is basically localized in the intestine, but rare cases with morbidity result from extra-intestinal involvement. Several reports have discussed patients with rotavirus gastroenteritis coexisting with encephalitis/encephalopathy [1]. Patients with rotavirus diarrhea, benign or severe convulsions, or encephalitis have evidence of rotavirus in the cerebrospinal fluid (CSF) [2,3]. Although rotavirus antigenemia is frequently observed in a patient's serum during the acute phase [4], the CSF is not always positive for rotavirus antigen or PCR product [5]. The pathophysiological mechanism is still unclear. Although cerebellar disorders sometimes occur as a complication of rotavirus gastroenteritis in Japan, few reports about these issues have appeared [6,7]. Here, we report three cases of rotavirus-associated acute cerebellitis/cerebellopathy with concurrent encephalitis/encephalopathy, focusing on chronological diffusion-weighted imaging changes and cerebellar mutism.

* Corresponding author. Address: Department of Pediatrics, Anjo Kosei Hospital, 28 Higashihirokute, Anjo-cho, Anjo, Aichi 446-8602, Japan. Tel.: +81 566 75 2111; fax: +81 566 76 4335.
E-mail address: t-kubota@kosei.anjo.aichi.jp (T. Kubota).

0387-7604/$ - see front matter © 2010 The Japanese Society of Child Neurology. Published by Elsevier B.V. All rights reserved.
doi:10.1016/j.braindev.2010.04.007

2. Case reports

2.1. Case 1

An 18-month-old boy was referred to our hospital because of frequent diarrhea and vomiting for 2 days. Although he had started to walk independently at 14 months of age, he had been unable to speak any meaningful words and could not follow verbal instructions. On admission (day 0), his heart rate was 162 beats/min, respiratory rate 48 breaths/min, and body temperature was 38.2 °C. He had cyanotic lips and peripheral coldness. Additionally, he occasionally had episodes of loss of consciousness for several seconds with upward eye deviation and apnea. He presented with drowsiness (Glasgow coma scale; E2 V1 M4). He had hypotonus of the trunk and extremities but no focal neurological signs. His hematological and biochemical studies were normal except for increased sodium (150 mmol/l), increased BUN and creatinine (94 and 2.23 mg/dl, respectively), and increased blood ketone (3222 μmol/l). A CSF analysis revealed a normal cell count (4 cells/mm^3 mononuclear), protein (20 mg/dl), and glucose level (81 mg/dl). A brain CT was normal. Rotavirus antigen was detected in a stool specimen using an immunochromatographical method. Rotavirus PCR was not performed in the stool specimen, and PCR and antigen were also not performed in both serum and CSF. On day 1, following fluid loading and an electrolyte correction, his mother said that his consciousness was normal. On day 2, although he showed no high fever and no disturbance of consciousness, his sleep electroencephalogram (EEG) showed bilateral frontal dominant (slight left predominance) delta activity with no paroxysms. On day 3, brain diffusion-weighted imaging (DWI) showed marked hyperintensity in the left hemisphere, dominant bilateral front-parietal white matter, and bilateral dentate nucleus. On day 9, sleep and wake EEGs were almost normal except for a slightly slow basic rhythm. On day 10, an MRI showed no new abnormal lesions and a decrease in size of the abnormal lesion. He was discharged on day 14. The brain MRI 15 months after this event revealed slightly widened cerebellar sulci, diffuse cerebellar atrophy, and hyperintensity in the left frontoparietal white matter on fluid-attenuated inversion-recovery (FLAIR) imaging. Clinically, he had a moderate mental delay and was diagnosed with autism but normal motor function (see Fig. 1).

2.2. Case 2

A 38-month-old boy was referred to our emergency room at night because of pyrexia, diarrhea, and vomiting for the past 3 days. He was healthy and had no neurological abnormalities. On admission (day 0), his heart rate was 128 beats/min, respiratory rate 28 breaths/min, and body temperature was 39.2 °C. He presented with drowsiness (Glasgow coma scale; E3 V1 M5) and repeatedly flapped his arms and legs with apneic episodes. He had hypotonus of the trunk and extremities but no focal neurological signs. His hematological and biochemical studies were normal except for decreased sodium (126 mmol/l) and increased blood ketone (5084 μmol/l). A CSF examination showed a slightly increased cell count (53 cells/mm^3, polymorphonuclear/mononuclear = 40/13) and protein (180 mg/dl) and a normal glucose level (61 mg/dl). A brain CT was normal. Rotavirus antigen was detected in a stool specimen, but the rotavirus PCR and antigen were negative in serum and CSF. On day 1, he showed no fever, but his consciousness was disturbed. A brain DWI showed marked hyperintensity in the bilateral dentate nucleus without cerebral lesions. His sleep EEG showed normal background activity with no paroxysms. Methylprednisolone pulse therapy was started on day 1 (30 mg/kg/day for 3 days, one course) due to the persistent consciousness disturbance, and two courses were administered at 2-week intervals. After one course, his general condition and consciousness improved, and he could gradually follow simple verbal instructions (looking at the television, raising his arms), but he could not speak for about 1 month, reflecting mutism, and revealed abnormal cerebellar symptoms such as intentional hand tremors and generalized ataxia. A brain DWI revealed chronological changes, i.e., marked hyperintensity in the bilateral dentate nucleus followed by hyperintensity in the vermis (on day 3) and cerebellar hemisphere (on day 9). On day 15, he was able to control his head position. On day 22, he could sit slightly unsteadily. On day 44, he could stand with support, and he was walking with ataxia on a wide base on day 50. Hypophonic and scanned speech with a few words appeared on day 34, and his expressive language gradually recovered, but more slowly than the improvement in motor symptoms. Five months after onset, though his gross motor function was good and equal to that before the disease, his fine motor function was still dysmetric, and slurred and explosive speech persisted. A brain MRI indicated marked diffuse cerebellar atrophy (see Fig. 2).

2.3. Case 3

A 28-month-old girl was healthy and well until she developed vomiting, diarrhea, and pyrexia. She was referred to our emergency room at night because of a seizure cluster. On admission (day 0), her heart rate was 157 beats/min, respiratory rate 30 breaths/min, and body temperature was 38.9 °C. She was almost alert (Glasgow coma scale; E4 V5 M6). Her hematological and biochemical studies were normal except for increased blood ketone (5982 μmol/l). A CSF analysis

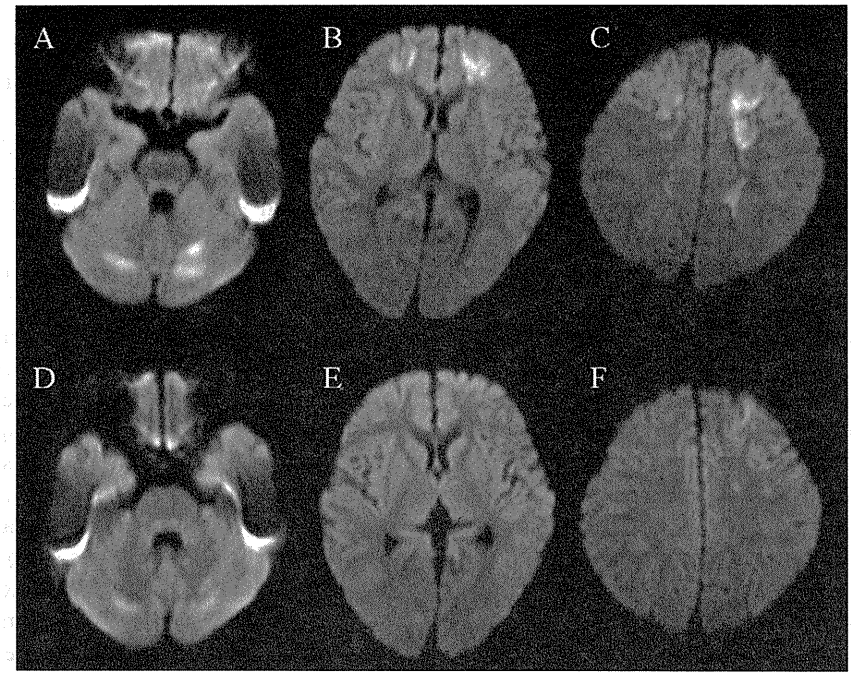

Fig. 1. MRI findings in case 1. (A–C) Axial DWI on day 3 showed marked hyperintensity in the left hemisphere, dominant bilateral front-parietal white matter, and bilateral dentate nucleus. (D–F) Axial DWI on day 10 showed no new abnormal lesions and a decrease in size of the abnormal lesion.

revealed a normal cell count (1 cell/mm^3 mononuclear), protein (8 mg/dl), and glucose level (73 mg/dl). A brain CT was normal. Rotavirus antigen was detected in a stool specimen. We could not perform rotavirus PCR or antigen in either the serum or CSF. On day 1, she presented with drowsiness (Glasgow coma scale; E3 V2 M6) and had clusters of generalized tonic–clonic seizures with apnea. We administered carbamazepine and phenobarbital because we tentatively diagnosed this as benign convulsions with mild gastroenteritis. A brain DWI showed hyperintensity in the splenium of the corpus callosum and small spotty lesions near the dentate nucleus. Her interictal EEG showed bilateral frontal dominant monotonous delta activity with no paroxysms. High-dose immunoglobulin therapy (1 g/kg/day, 1 day) and methylprednisolone pulse therapy were started on that day due to persistent disturbances of consciousness. After one course of this therapy, her consciousness improved, and her abnormal cerebellar symptoms (intentional tremor, trunk ataxia) were gradually revealed. She could obey simple verbal instructions, but could not speak any words, reflecting mutism. A brain DWI (day 3) showed marked hyperintensity in the bilateral dentate nucleus and a disappearance of the high intensity signal in the splenium of the corpus callosum. On day 17, after finishing a second course of methylprednisolone pulse therapy, she could finally speak just one very slurred word. A brain DWI revealed chronological changes such as those seen in case 2, i.e., marked hyperintensity in the bilateral dentate nucleus followed by hyperintensity in the vermis (on day 3) and cerebellar hemisphere (on day 5), and decreased intensity (on day 9 and day 18), which finally disappeared on day 25. On day 5, she was able to roll over and sit slightly unsteadily, but she was crawling on day 10. She could stand with support on day 17 and was walking alone with ataxia and a wide base on day 26. The mutism lasted until day 17, when the second course of methylprednisolone pulse therapy was finished; however, the dysarthria continued. Hypophonic, scanned, and slurred speech with few words appeared on day 20. Three months after onset, although her fine motor movements were almost normal, the slurred and explosive speech persisted. A brain MRI at 6 months after onset indicated slight atrophy in both cerebellar hemispheres and the vermis (see Figs. 3 and 4).

3. Discussion

The most striking findings in this report are the chronological DWI changes. Our patients mainly experienced an insulted cerebellum in addition to the encephalitis/encephalopathy associated with rotavirus. Patients presented with similar symptoms, i.e., apnea in the acute phase, mutism in the subacute phase, and DWI abnormalities characterized by marked hyperintensity in the bilateral dentate nucleus, followed by hyperintensity in the vermis and cerebellar hemispheres. Acute cerebellitis is defined as an inflammatory syndrome that reflects an infectious, postinfectious, or postvaccination disorder

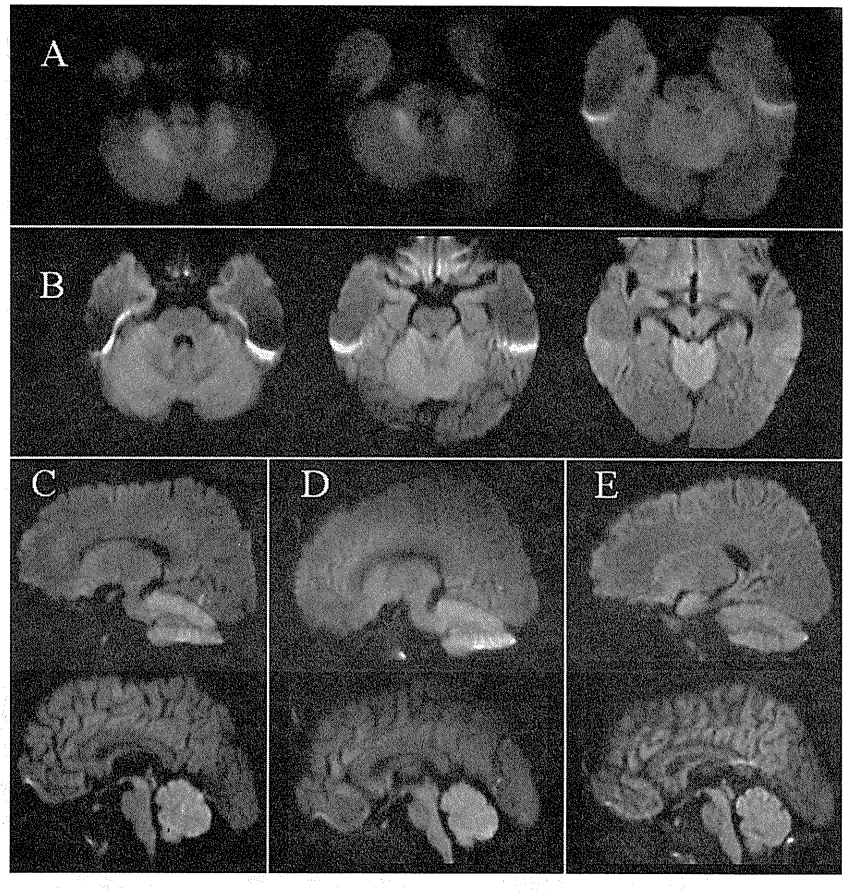

Fig. 2. MRI findings in case 2. (A) Axial DWI on day 1 showed marked hyperintensity in the bilateral dentate nucleus without cerebral lesions. (B) Axial DWI on day 3 showed marked hyperintensity in the bilateral dentate nucleus followed by hyperintensity in the vermis and cerebellar hemisphere. (C) Sagittal DWI on day 9 showed marked hyperintensity in cerebellar hemisphere. (D) Sagittal DWI on day 15 showed marked hyperintensity in cerebellar hemisphere, especially in lower part of cerebellar hemisphere. (E) Sagittal DWI on day 23 showed decreased hyperintensity in cerebellar hemisphere.

[8]. As we could not conclusively distinguish whether cerebellar symptoms were due to cerebellitis or cerebellopathy, we used the term "cerebellitis/cerebellopathy". Rotavirus gastroenteritis is one of the causes of acute encephalitis/encephalopathy and cerebellitis/cerebellopathy [6,7]. However, neither the pathophysiology nor the chronological clinical and diffusion-weighted imaging changes are fully characterized. Recent clinical studies of infectious encephalitis/encephalopathy have revealed several new syndromes, such as acute encephalopathy with biphasic seizures and late reduced diffusion (AESD) [9,10], clinically mild encephalitis/encephalopathy with reversible splenial lesion (MERS) [11], and acute encephalopathy predominantly affecting the frontal lobes (AIEF) [12]. We thought that rotavirus cereberitis/cerebellopathy might represent one of the specific clinical and radiological manifestations of infectious central nervous system disorders.

We performed serial MRI examinations and demonstrated chronological diffusion-weighted imaging changes due to rotavirus-associated acute cerebellitis/cerebellopathy concurrent with encephalitis/encephalopathy. Cerebellar involvement in rotavirus gastroenteritis has been reported in few patients [8,9]. Only one report, using MRI in patients with rotavirus cereberitis/cerebellopathy, did not describe chronological changes in MRI findings. Almost all other previous reports of acute cerebellitis/cerebellopathy associated with unknown etiology described bilateral cerebellar cortex swelling, followed by mild diffuse cerebellar atrophy [6,7,13–18]. The chronological DWI abnormalities described here, which presented as marked hyperintensity in the bilateral dentate nucleus followed by hyperintensity in the vermis and cerebellar hemispheres, were consistent with those reported in other studies of acute cerebellitis/cerebellopathy. We could not confirm these chronological DWI changes were specific character in rotavirus-associated acute cerebellitis/cerebellopathy.

In addition to the MRI findings, these cases have a number of unique clinical features. The clinical courses of cases 2 and 3 were very similar. Acute neurological dysfunction such as seizures and conscious disturbances were followed by acute cerebellar motor dysfunction,

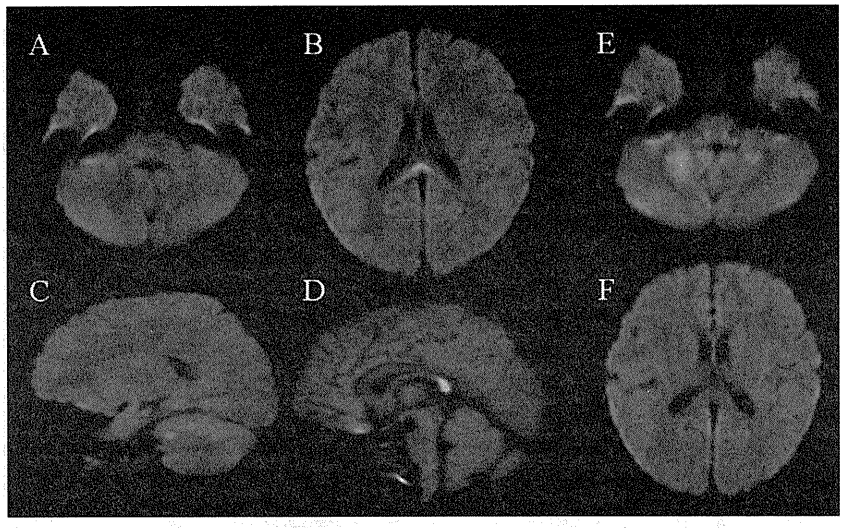

Fig. 3. MRI findings in case 3. (A–D) Axial and sagittal DWI on day 1 showed hyperintensity in the splenium of the corpus callosum and small spotty lesions near the dentate nucleus. (E and F) Axial DWI on day 3 showed marked hyperintensity in the bilateral dentate nucleus and a disappearance of the high intensity signal in the splenium of the corpus callosum.

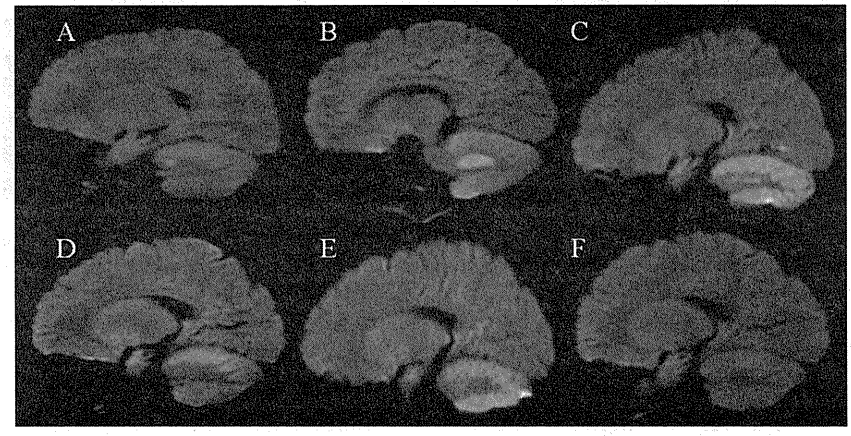

Fig. 4. Chronological cerebellar DWI findings in case 3. (A) Sagittal DWI on day 1 showed small spotty hyperintensity lesions near the dentate nucleus. (B) Sagittal DWI on day 3 showed marked hyperintensity in the bilateral dentate nucleus and the vermis. (C) Sagittal DWI on day 5 showed decreased hyperintensity in the vermis and increased intensity in cerebellar hemisphere. (D) Sagittal DWI on day 9 showed ceased hyperintensity in the vermis and increased intensity in cerebellar hemisphere. (E) Sagittal DWI on day 18 showed almost the same findings as those on day 9. The hyperintensity in lower part of cerebellar hemisphere was greater. (F) Sagittal DWI on day 25 showed decreased hyperintensity in cerebellar hemisphere.

i.e., trunk hypotonia, ataxia, and intentional tremor. Of the above motor symptoms, mutism was the most interesting clinical finding in the acute and subacute phases of these cases. In both cases, mutism and dysarthria continued for about 1 month, and the recovery from mutism was delayed compared to that of the cerebellar motor dysfunction. Disturbed higher cortical function due to encephalitis/encephalopathy is also the likely cause of altered consciousness and transient loss of speech. It is difficult to rule out their mutism as one symptom of total cortical function. In case 2, although we did not observe abnormal early EEG findings in sleep and cerebral MRI findings, cortical involvement was undeniable. Abnormal EEG and MRI findings (as MERS) were present in case 3, and thus we considered cerebral dysfunction as a possible cause. However, given the clinical course of consciousness recovery and other physiological findings, i.e., wakefulness and normal sleep pattern, we believe that the mutism observed in the subacute phase was caused mainly by cerebellar dysfunction.

Cerebellar mutism is a well-known complication of posterior fossa tumor resection. Various mechanisms have been proposed such as impaired vascular supply possibly secondary to vasospasm, bilateral edema within the brachium pontis, splitting of the vermis, involvement of the dentatothalamic tract, trauma to the left cerebellar hemisphere, and development of hydrocephalus

[19–25]. Operations on the cerebellum to remove tumors can be followed by mutism, often after an interval of a few days, which may last for several months, only to be followed by dysarthria [26–28]. In these reports, mutism, for which the accepted cause may be vasospasm, appeared to be due to involvement of the dentate nucleus and its outflow dentatorubrothalamic tracts to the brain stem and cortex in the superior cerebellar peduncle. In all three cases, an early brain DWI showed marked hyperintensity in the bilateral dentate nucleus. Considering previously reported surgical cases [26–28] and our three presented cases, hyperintensity in the bilateral dentate nucleus might be a significant DWI finding and a valuable predictor of cerebellar mutism. In all cases, the patients had apneic episodes with or without convulsions. In particular, the patient in case 2 had apnea accompanied by flapping of his arms and legs that did not seem to be a convulsion. Because we could not examine the ictal EEG, we could not preciously determine whether this episode was an epileptic seizure. Considering that the cerebellar dentate nucleus contacts the thalamus and red nucleus via the superior cerebellar peduncle, these apneic episodes might have occurred due to dysfunction of the brain stem reticular formation.

Cerebral DWI abnormalities were seen in two cases. In case 3, the brain DWI showed hyperintensity in the splenium of the corpus callosum in addition to bilateral dentate nucleus. This corpus callosum finding is well described for MERS. The most common neurological symptom in MERS is delirious behavior, followed by disturbances in consciousness and seizures. Though transient mutism has been reported in adults undergoing callosotomy for drug-resistant epilepsy [29], considering the patient's general and neurological condition, this DWI finding was thought to be MERS and unrelated to mutism or callosotomy. In case 1, the brain DWI showed marked hyperintensity in the dominant bilateral frontoparietal white matter of the left hemisphere as well as the bilateral dentate nucleus. In this case, we were unable to observe clear sequential DWI changes in cerebellar lesions. It was thought that the main lesion might be acute encephalitis/encephalopathy like AIEF and that the cerebellitis/cerebellopathy might be an additional lesion. We could not evaluate clinical cerebellar function in detail because of this patient's predominant developmental delay before this event. Clinically, he was moderately mentally delayed and was diagnosed with autism and normal motor function. We could not reject the possibility that this event might have influenced his autism, although he was already delayed.

In all three cases, later brain MRIs revealed atrophy in both cerebellar hemispheres and the vermis. Clinically, all cases showed abnormal cerebellar symptoms to varying degrees, especially a speech disorder. Some reports have indicated that rotavirus antigen and/or PCR in the CSF was not always positive in cases of encephalitis/encephalopathy associated with rotavirus gastroenteritis [5]. The rotavirus PCR and antigen were negative in serum and CSF in case 2. Though the effectiveness of steroid pulse therapy and high-dose immunoglobulin therapy remains controversial for treatment of encephalitis/encephalopathy, considering our clinical experience that the patients' condition improved dramatically following steroid pulse therapy, immunomodulatory treatment might be effective for treating rotavirus-associated cerebellitis/cerebellopathy. Further research is needed to clarify the pathophysiology and to identify the optimal therapy for rotavirus-associated cerebellitis/cerebellopathy.

Acknowledgements

We appreciate helpful, advice by Kenji Yokochi, MD, Seirei-Mikatabara General Hospital; Takeshi Tsuji and Fumio Hayakawa, Okazaki City Hospital; and all members of Tokai Pediatric Neurology Group.

References

[1] Lynch M, Lee B, Azimi P, Gentsch J, Glaser C, Gilliam S, et al. Rotavirus and central nervous system symptoms: cause or contaminant? Case reports and review. Clin Infect Dis 2001;33:932–8.
[2] Keidan I, Shif I, Keren G, Passwell JH. Rotavirus encephalopathy: evidence of central nervous system involvement during rotavirus infection. Pediatr Infect Dis J 1992;11:773–5.
[3] Ushijima H, Bosu K, Abe T, Shinozaki T. Suspected rotavirus encephalitis. Arch Dis Child 1986;61:692–4.
[4] Sugata K, Taniguchi K, Yui A, Miyake F, Suga S, Asano Y, et al. Analysis of rotavirus antigenemia and extraintestinal manifestations in children with rotavirus gastroenteritis. Pediatrics 2008;122:392–7.
[5] Nakagomi T, Nakagomi O. Rotavirus antigenemia in children with encephalopathy accompanied by rotavirus gastroenteritis. Arch Virol 2005;150:1927–31.
[6] Shiihara T, Watanabe M, Honma A, Kato M, Morita Y, Ichiyama T, et al. Rotavirus associated acute encephalitis/encephalopathy and concurrent cerebellitis: report of two cases. Brain Dev 2007;29:670–3.
[7] Nigrovic LE, Lumeng C, Landrigan C, Chiang VW. Rotavirus cerebellitis? Clin Infect Dis 2002;34:130.
[8] Bakshi R, Bates VE, Kinkel PR, Mechtler LL, Kinkel WR. Magnetic resonance imaging findings in acute cerebellitis. Clin Imaging 1998;22:79–85.
[9] Mizuguchi M, Yamanouchi H, Ichiyama T, Shiomi M. Acute encephalopathy associated with influenza and other viral infections. Acta Neurol Scand 2007;115:45–56.
[10] Takanashi J, Oba H, Barkovich AJ, Tada H, Tanabe Y, Yamanouchi H, et al. Diffusion MRI abnormalities after prolonged febrile seizures with encephalopathy. Neurology 2006;66:1304–9.
[11] Tada H, Takanashi J, Barkovich AJ, Oba H, Maeda M, Tsukahara H, et al. Clinically mild encephalitis/encephalopathy with a reversible splenial lesion. Neurology 2004;63:1854–8.
[12] Yamanouchi H, Mizuguchi M. Acute infantile encephalopathy predominantly affecting the frontal lobes (AIEF): a novel clinical

category and its tentative diagnostic criteria. Epilepsy Res 2006;70(Suppl. 1):S263–8.
[13] Riva D. The cerebellar contribution to language and sequential functions: evidence from a child with cerebellitis. Cortex 1998;34:279–87.
[14] Papavasiliou AS, Kotsalis C, Trakadas S. Transient cerebellar mutism in the course of acute cerebellitis. Pediatr Neurol 2004;30:71–4.
[15] Mewasingh LD, Kadhim H, Christophe C, Christiaens FJ, Dan B. Nonsurgical cerebellar mutism (anarthria) in two children. Pediatr Neurol 2003;28:59–63.
[16] Drost G, Verrips A, Thijssen HO, Gabreels. Cerebellar involvement as a rare complication of pneumococcal meningitis. Neuropediatrics 2000;31:97–9.
[17] Dimova PS, Bojinova VS, Milanov IG. Transient mutism and pathologic laughter in the course of cerebellitis. Pediatr Neurol 2009;41:49–52.
[18] Sawaishi Y, Takada G. Acute cerebellitis. Cerebellum 2002;1:223–8.
[19] Dietze Jr DD, Mickle JP. Cerebellar mutism after posterior fossa surgery. Pediatr Neurosurg 1990;16:25–31.
[20] Nagatani K, Waga S, Nakagawa Y. Mutism after removal of a vermian medulloblastoma: cerebellar mutism. Surg Neurol 1991;36:307–9.
[21] Koh S, Turkel SB, Baram TZ. Cerebellar mutism in children: report of six cases and potential mechanisms. Pediatr Neurol 1997;16:218–9.
[22] van Dongen HR, Catsman-Berrevoets CE, van Mourik M. The syndrome of 'cerebellar' mutism and subsequent dysarthria. Neurology 1994;44:2040–6.
[23] Pollack IF. Posterior fossa syndrome. Int Rev Neurobiol 1997;41:411–32.
[24] Gordon N. Mutism: elective or selective, and acquired. Brain Dev 2001;23:83–7.
[25] Aguiar PH, Plese JP, Ciquini O, Marino R. Transient mutism following a posterior fossa approach to cerebellar tumors in children: a critical review of the literature. Childs Nerv Syst 1995;11:306–10.
[26] Ersahin Y, Mutluer S, Saydam S, Barcin E. Cerebellar mutism: report of two unusual cases and review of the literature. Clin Neurol Neurosurg 1997;99:130–4.
[27] Fraioli B, Guidetti. Effects of stereotactic lesions of the dentate nucleus of the cerebellum in man. Appl Neurophysiol 1975;38:81–90.
[28] Kusano Y, Tanaka Y, Takasuna H, Wada N, Tada T, Kakizawa Y, et al. Transient cerebellar mutism caused by bilateral damage to the dentate nuclei after the second posterior fossa surgery. Case report. J Neurosurg 2006;104:329–31.
[29] Quattrini A, Del Pesce M, Provinciali L, Cesarano R, Ortenzi A, Paggi A, et al. Mutism in 36 patients who underwent callosotomy for drug-resistant epilepsy. J Neurosurg Sci 1997;41:93–6.

Acute Encephalopathy in a Patient with Dravet Syndrome

Authors M. Tsuji[1], E. Mazaki[2], I. Ogiwara[2], T. Wada[1], M. Iai[1], A. Okumura[3], S. Yamashita[1], K. Yamakawa[2], H. Osaka[1]

Affiliations
[1] Division of Neurology, Kanagawa Children's Medical Center, Yokohama, Japan
[2] Laboratory for Neurogenetics, RIKEN Brain Science Institute, Wako, Saitama, Japan
[3] Department of Pediatrics, Juntendo University, Tokyo, Japan

Key words
- Dravet syndrome
- acute encephalopathy
- SCN1A
- voltage-dependent sodium channel
- vaccination

received 05.12.2010
accepted 05.05.2011

Bibliography
DOI http://dx.doi.org/10.1055/s-0031-1279725
Published online: June 6, 2011
Neuropediatrics 2011; 42: 78–81

ISSN 0174-304X

Correspondence
Hitoshi Osaka
Division of Neurology
Kanagawa Children's Medical Center
2-138-4 Mutsukawa
Minami-ku
Yokohama
Kanagawa 232-8555
Japan
Tel.: +81/45/711 2351
Fax: +81/45/721 3324
hosaka@kcmc.jp

Abstract

Dravet syndrome (severe myoclonic epilepsy in infancy) is an epileptic syndrome with various types of seizures that begin in the first year of life and may result in intellectual impairment. Mutations of the SCN1A gene are the most prevalent genetic cause of Dravet syndrome. In this study, we report a 12-year-old girl with Dravet syndrome carrying an SCN1A mutation, c.2785Cdel (L929del fsX934). She had an episode of status epilepticus and persistent lethargy after 48 h of acute febrile illness that was preceded by an annual flu vaccination. Low voltage activities detected by electroencephalogram and elevated neuron-specific enolase/interleukin-6 concentrations in the cerebrospinal fluid suggested acute encephalopathy. MRI showed abnormalities in the bilateral thalami, cerebellum and brainstem. These abnormalities were protracted over a month. The biochemical and MRI characteristics of this case are different from any known type of encephalopathy, and may suggest a vulnerability of neurons expressing mutant SCN1A in the brain.

Abbreviations

AEIMSE	acute encephalopathy with inflammation-mediated status epilepticus
ANE	acute necrotizing encephalopathy
CSF	cerebrospinal fluid
DWI	diffusion-weighted imaging
FIRES	febrile infection-related epilepsy syndrome
GCS	Glasgow coma scale
IHHE	idiopathic hemiconvulsion-hemiplegia syndrome
NMDAR	*N*-methyl-D-aspartate receptor
NORSE	new-onset refractory status epilepticus
NSE	neuron-specific enolase
PCR	polymerase chain reaction

Introduction

Acute encephalopathy associated with Dravet syndrome (severe myoclonic epilepsy in infancy) is not recognized commonly and has been described rarely in the literature. Dravet syndrome is an epileptic syndrome that begins in the first year of life, and is characterized by generalized tonic, clonic or tonic-clonic seizures that are easily evoked by fever or a hot bath. Seizures are intractable and are followed by mental decline [2]. More than 60% of patients with Dravet syndrome show mutations in SCN1A, which encodes the voltage-dependent sodium channel (Nav1.1) α subunit, and most of the mutations are de novo.

In this study, we report a patient with Dravet syndrome who developed an acute encephalopathy after a flu vaccination. The patient presented unique MRI abnormalities and severe neurological sequelae.

Case Report

The patient was a Japanese female born at full term with a normal delivery. She manifested a generalized myoclonic seizure during a hot water bath at 3 months of age, and showed repeated status epilepticus in febrile conditions since 6 months of age. At 12 years of age, she was administered valproate, sodium bromide, clonazepam, clobazam and lamotrigine, and showed daily absence seizures and weekly brief generalized tonic seizures. She was able to speak two-word sentences that contained grammatical errors and

had an ataxic gait. From the typical clinical course of Dravet syndrome, the SCN1A gene was analyzed, and showed a c.2785Cdel (L929del fsX934) mutation.

The patient had an annual flu vaccination at 3 days before the onset of febrile illness. The patient had a single generalized tonic-clonic seizure soon after the acute febrile illness with prompt recovery of consciousness. A second seizure occurred as a status epilepticus at 8 h after the first seizure. The seizure lasted 65 min and requiring thiopental to stop. She did not become alert after the second seizure and had a score of 6 on the Glasgow coma scale (GCS). On the second day she had no spontaneous movement and progressed to coma with a score of 3 on the GCS accompanied by a fever of 40 °C at 3 days after the onset of illness. Routine laboratory tests were normal on admission with a successive elevation of creatine kinase on the third day (2536 IU/L; normal 83±60). Cerebrospinal fluid (CSF) analysis revealed pleocytosis (58 cells/μL) with increases in protein (74.2 mg/dL), and interleukin-6 (9140 pg/mL; normal 28±20), and a remarkable increase in neuron-specific enolase (NSE) (990 ng/mL; normal 6.0±1.9). Myelin basic protein in the CSF was only slightly increased at 110 pg/mL (normal <102 pg/mL). A second lumber puncture at day 5 revealed a decrease of cell count (25 cells/μL), protein concentration (38 mg/dL) and NSE (330.1 ng/mL) in the CSF. Oligoclonal bands were examined on day 5 with a negative result, and the IgG index was not evaluated. No microbial infection was detected. Gamma-globulin, cyclosporine and steroid pulse therapy were introduced under mild hypothermia for a suspected acute encephalopathy of unknown etiology. After the specific therapies for encephalopathy, limb myoclonus developed and was difficult to control. The patient regressed to spastic quadriplegia with lack of visual contact or verbalization. Nasogastric tube feeding was begun due to oral dyskinesia. The seizures disappeared for a while although the previous antiepileptic medications were tapered. At 14 years of age, she showed severe mental retardation and quadriplegia. Seizures appeared within a year despite polytherapy with valproate, clonazepam and potassium bromides. She has monthly generalized tonic-clonic seizures at fever and weekly complex partial seizures.

Results

Radiological findings

Neuroimaging was performed at days 2, 3 and 5 of illness (**Fig. 1**). The MR images at day 2 were unremarkable, but those performed at day 3 showed minimal swelling of the cerebellar hemisphere with high signal intensities in diffusion-weighted imaging (DWI) with restricted apparent diffusion co-efficiency. At day 5, the abnormalities in DWI advanced to the bilateral thalami, brain stem and posterotemporal cortex. The high signals on DWI persisted with growing areas including the diffuse cerebral cortex, bilateral caudate nuclei, putamina, dentate nuclei and splenium of the corpus callosum. Follow-up MRI at day 8 showed T_2 elongation in the bilateral thalami, and subsequently T_2 elongation of the bilateral putamina and the caudate nuclei developed at day 22. These findings disappeared at day 50, with mild atrophy of the cerebral cortex and the basal ganglia. No obvious gross brain edema in the supratentorial areas was observed in the course of the disease. MR spectroscopy performed in the basal ganglia and semioval center showed no lactate elevations at any course of the disease.

Discussion

There have been few reports of acute encephalopathy associated with Dravet syndrome. In one Japanese series, 12 of 85 patients with Dravet syndrome died during follow-up periods from 1 to 28 years, and convulsive status was the leading cause of death. They mentioned 2 children with residual severe neurological deficits after prolonged status epilepticus triggered by acute febrile illness [7]. Only one case of hemiconvulsion-hemiplegia syndrome has been reported in a child who subsequently developed a characteristic feature of Dravet syndrome [8]. Chipaux et al. reported an unusual pattern in 3 patients with Dravet syndrome who had refractory status epilepticus followed by severe cognitive and motor deterioration, and whose neuroimages showed anoxic-ischemic like lesions [1]. They suggested a role of the aggravating effects of barbiturates and its combination use of drugs, which reduce barbiturate clearance, since high doses of barbiturates reduce cerebral blood flow in both animals and humans. Follow-up MRI of our patient in a chronic stage revealed mild atrophy of the basal ganglia, which is similar to the results of Chipaux et al., except for the age group. Our patient had been taking anticonvulsants including lamotrigine, and intravenous infusion of thiopental was used during the prolonged seizure. There is a possibility that lamotrigine, an anticonvulsant that acts on sodium channels, may have had a negative effect on her condition [4].

Van Baalen et al. reported a retrospective study on 22 previously healthy children with prolonged seizures after fever onset that involved mesial temporal structures and resulted in pharmacoresistant epilepsy and major cognitive deterioration [10]. They proposed the term "febrile infection-related epilepsy syndrome" (FIRES) for those patients that lack evidence for specific encephalitis. Nabbout et al. reviewed acute encephalopathy with inflammation-mediated status epilepticus (AEIMSE) including idiopathic hemiconvulsion-hemiplegia syndrome (IHHE), FIRES and new-onset refractory status epilepticus (NORSE) according to ages at onset. They suggest that brain maturation stage affects the difference in the clinical manifestations [5]. Although our patient showed some clinical similarities with these syndromes, she was different in that the seizure activity diminished after status epilepticus.

The encephalopathic episode was accompanied by neuron dominant damage demonstrated by a considerable increase in NSE compared to myelin basic protein, and by MR images that were clinically distinct from acute disseminated encephalomyelitis. Neuroimaging findings in our case revealed bilateral thalamic involvement, which is often seen in acute necrotizing encephalopathy (ANE). However, our patient's clinical course was not similar to the typical features of ANE for several reasons. First, although ANE is likely to be accompanied by gross brain edema and multiple organ failure with significantly fluctuating parameters of inflammation in the serum such as interleukin-6, our patient showed none of these features. Second, there was no evidence of necrotizing lesions in MR spectroscopy without lactate elevation. Thus, we presume that a pathophysiology different from that of typical ANE occurred in this patient. As the encephalopathic episode occurred after a vaccination, we considered other forms of immune-mediated encephalitis such as anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis, encephalitis induced directly by influenza, or encephalitis induced by vaccination. Anti-NMDAR encephalitis starts commonly with psychiatric symptoms followed by abnormal movement, seizure