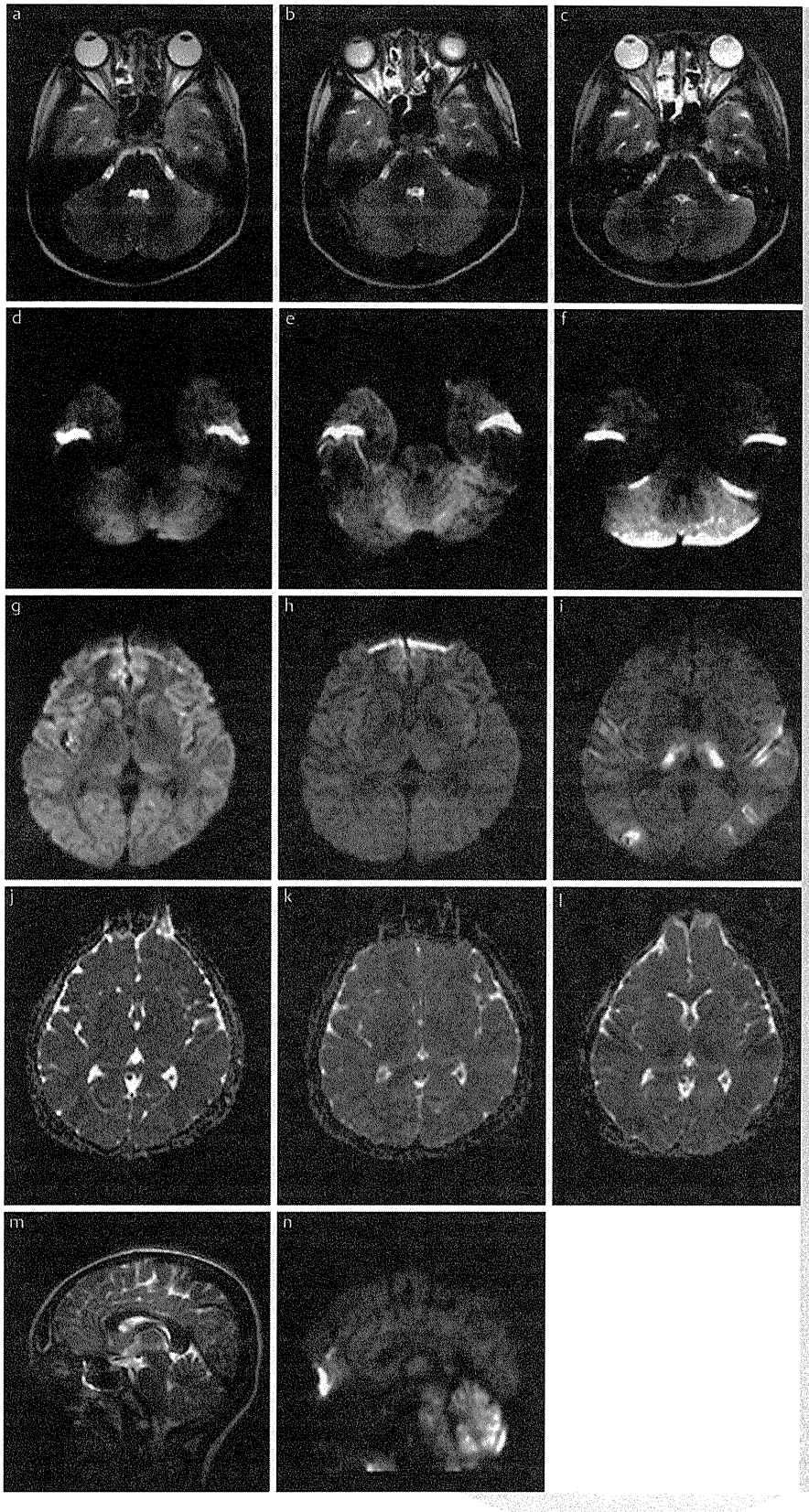

Fig. 1 Brain MRI: T_2-weighted images (**a–c**), diffusion-weighted images (**d–f**), diffusion-weighted images at basal ganglia levels (**g–i**), apparent diffusion coefficient maps (**j–l**), and sagittal images of T_2-weighted image and diffusion-weighted image. Images at 2 days (**a, d, g, j**), 3 days (**b, e, h, k, m, n**), and 5 days (**c, f, i, l**) of illness. Note that lesions in the diffusion-weighted images involve the thalami, cerebral cortex of parietal and occipital lobes symmetrically on day 5, with restricted apparent diffusion co-efficiency.

and central hypoventilation, which resolves spontaneously through months or even years [3]. However, this case manifested acutely developed seizures accompanied by irreversible neurological deficits, contrasting with the typical clinical course of anti-NMDAR encephalitis. Viral encephalitis is unlikely, as she showed negative PCR results in the CSF. An immune-mediated encephalopathy subsequent to the vaccination other than anti-NMDAR encephalitis is possible, however no evidence is presented.

It is noteworthy that a distribution of the abnormalities in DWI obtained in the early phase of illness closely resembled that of Nav1.1α in mice [6]. However, there are no reports on the vulnerability of neurons harboring SCN1A mutations. Furthermore, seizures were not observed after the episode of acute encepha-

lopathy with fewer medications. We speculate that the neuronal damage was extensive and the neurons loss reduced seizure susceptibility. In a retrospective study of 70 patients with Dravet syndrome, seizures following vaccinations were reported in 19 patients including one case with flu vaccination. The ages ranged from of 3 months to 4.5 years, relatively younger than our patient. They reported that status epilepticus occurred in 8 patients among those who manifested seizure, without mentioning the neurological outcome [9]. In our case, the flu vaccination may have triggered the acute encephalopathy. Furthermore, we presume that acute encephalopathy may partly contribute to the causes of deaths, which are thought to result from status epilepticus in Dravet syndrome. Further studies should reveal the relationship between vaccination, acute encephalopathy and Dravet syndrome.

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Brain & Development 33 (2011) 9

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

www.elsevier.com/locate/braindev

Editorial

Wide range of CNS manifestations of rotavirus infection ☆

Rotavirus is one of the most common pathogens of gastroenteritis in children, and sometimes causes a wide range of neurologic manifestations, from benign convulsions to lethal encephalitis/encephalopathy. Any virus (influenza virus, human herpes virus 6 [HHV-6], rotavirus, etc.) can cause an encephalopathy syndrome, such as acute necrotizing encephalopathy (ANE), acute encephalopathy with biphasic seizures and late reduced diffusion (AESD), and hemorrhagic shock and encephalopathy syndrome (HSES) [1,2]. Acute cerebellitis/cerebellopathy reported in this issue by Kubota et al. [3], however, seems to be specific to rotavirus infection, this condition being rarely reported in influenza or HHV-6 infection.

Thirteen patients with rotavirus cerebellitis recently reported (cases 2 and 3 in reference 3, and 11 patients in reference 4) exhibited nearly identical clinical and MRI features. They had disorders of consciousness with onset on days 2–4 of the gastroenteritis, followed by mutism. Other cerebellar symptoms included dysarthria following the mutism, hypotonia, ataxia, tremor, nystagmus and dysmetria. Transient involvement of the cerebellar white matter/nuclei may be associated with the characteristic clinical manifestation of mutism. A reversible splenial lesion was found in 7 of the 13 patients (3 isolated and 4 with concurrent cerebellar lesions). An isolated splenial lesion with homogenously reduced diffusion is a key finding for the diagnosis of clinically mild encephalitis/encephalopathy with a reversible splenial lesion [MERS] [1]. It is important to be aware that an isolated splenial lesion in patients with rotavirus gastroenteritis is not always a benign sign indicative of complete clinical and radiological recovery.

Two patients, who were excluded from a previous study on rotavirus cerebellitis [4], were diagnosed as having hypovolemic shock. MRI of the 2 patients revealed identical lesions in case 1 reported by Kubota et al. [3], i.e., symmetric lesions in the cerebral deep white matter and cerebellar cortex, suggesting border-zone infarctions due to hypovolemia/hypotension. During a mild to moderate reduction in perfusion, the brain's autoregulatory mechanisms preserve blood flow to the brainstem and basal ganglia. However, injury may occur in the intervascular boundary zones ("watershed zones") between the major vascular territories of the cerebrum and cerebellum (although the cerebellar lesions are less common). Reflecting this pathophysiology, MRI shows characteristic bilateral lesions in these areas. Alternatively, it is possible that rotavirus infection of the cerebellum may result in a higher metabolic rate than usual and, consequently, the cerebellum may suffer more than usual from even mild to moderate hypoperfusion. Further clinical, pathological and radiological studies are, of course, necessary to determine the exact mechanism of CNS manifestations associated with rotavirus infection.

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Jun-ichi Takanashi *
Department of Pediatrics, Kameda Medical Center, Kamogawa, Japan
E-mail address: jtaka@kameda.jp

☆ Editorial to: "Chronological diffusion-weighted imaging changes and mutism in the course of rotavirus-associated acute cerebellitis/cerebellopathy concurrent with encephalitis/encephalopathy" in this issue.

* Address: Department of Pediatrics, Kameda Medical Center, 929 Higashi-cho, Kamogawa-shi, Chiba 296-8602, Japan. Tel.: +81 470 92 2211; fax: +81 470 99 1198.

0387-7604/$ - see front matter
doi:10.1016/j.braindev.2010.10.012

Journal of the Neurological Sciences xxx (2011) xxx–xxx

Contents lists available at SciVerse ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Short communication

Kawasaki disease complicated by mild encephalopathy with a reversible splenial lesion (MERS)

Jun-ichi Takanashi [a,e,*], Kentaro Shirai [b], Yuji Sugawara [b], Yoko Okamoto [c], Toshimasa Obonai [d], Hitoshi Terada [e]

[a] Department of Pediatrics, Kameda Medical Center, Kamogawa, Japan
[b] Department of Pediatrics, Tokyo Medical and Dental University, Tokyo, Japan
[c] Department of Pediatrics, Saitama Citizen's Medical Center, Saitama, Japan
[d] Department of Pediatrics, Tama-Hokubu Medical Center, Higashi-murayama, Japan
[e] Department of Radiology, Toho University Sakura Medical Center, Sakura, Japan

ARTICLE INFO

Article history:
Received 20 August 2011
Received in revised form 6 November 2011
Accepted 8 November 2011
Available online xxxx

Keywords:
Clinically mild encephalitis/encephalopathy with a reversible splenial lesion (MERS)
Kawasaki disease
Corpus callosum
Diffusion-weighted image
Delirium
Cardiac aneurysm

ABSTRACT

We reported four patients (2 to 10 years) with Kawasaki disease complicated by clinically mild encephalitis/encephalopathy with a reversible splenial lesion (MERS). All were treated with γ-globulin (2 to 6 g/kg) after the diagnosis of Kawasaki disease, the fever being alleviated between day 6 and 25. One of two patients exhibiting a poor response to γ-globulin had a cardiac aneurysm as a sequela. Their neurological manifestations (delirious behavior and drowsiness), laboratorial hyponatremia, and radiological abnormalities completely disappeared. It is important for pediatricians to acknowledge that MERS can be observed in patients with Kawasaki disease, especially in older children, and that they might be at high risk for cardiac abnormalities.

1. Introduction

Kawasaki disease (KD) is an acute febrile, systemic vasculitis of unknown pathogenesis, most often affecting young children under 5 years old. The most important complication of KD is coronary arterial aneurysms (in 15-25% of untreated children), which may cause ischemic heart disease and sudden death [1,2]. Irritability, lethargy, transient unilateral facial nerve palsy are sometimes observed, and pleocytosis in the cerebrospinal fluid (CSF) is found in around 40% [1–4], however, febrile convulsions and acute encephalopathy are extremely rare [5–7].

Magnetic resonance imaging (MRI) finding of a reversible lesion with transiently reduced diffusion in the splenium of the corpus callosum has been reported in patients with clinically mild encephalitis/encephalopathy, leading to a new clinical-radiological syndrome, clinically mild encephalitis/encephalopathy with a reversible splenial lesion (MERS) [8,9]. We present here four patients with KD complicated by MERS, which suggest that MERS is a more common neurological complication than previously considered.

2. Methods

Information on patients with KD who developed MERS was collected retrospectively after approval by the institutional review board of the Kameda Medical Center. The diagnosis of KD and MERS were established according to diagnostic criteria [1,2,8], respectively. We reviewed the clinical charts of the patients in order to accrue information on symptoms, medication, treatment, outcome, and results of CSF analysis, MRI, and electroencephalography (EEG).

3. Results

Four previously healthy Japanese patients (1 male and 3 females, aged from 2 to 10 years) met the criteria for enrollment in this study, with the onset from March 2010 to February 2011. The clinical and radiological records of the four patients are summarized in Table 1. All were treated with γ-globulin (2 to 6 g/kg) after the diagnosis of KD, the fever being alleviated between day 6 and 25. Two patients exhibiting a poor response to γ-globulin were additionally treated with cyclosporine and infliximab (patient 1), and prednisolone

* Corresponding author at: Department of Pediatrics, Kameda Medical Center, 929 Higashi-cho, Kamogawa-shi, Chiba 296-8602, Japan. Tel.: +81 470 92-2211; fax: +81 470 99 1198.
E-mail address: jtaka@kameda.jp (J. Takanashi).

0022-510X/$ – see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.jns.2011.11.022

Table 1
Data for Kawasaki disease with MERS.

Pt.	Age/Sex	Tx for KD γ-globulin	Other therapies	End of fever	Na level (lowest) follow up	Coronary sequelae	Consciousness disturbance	Duration delirium
1	8/M	2 g/kg×3 (D5, D7, D9)	cyclosporine infliximab	D21	119 (D6) 137 (D40)	AN (5 mm)	Mild drowsiness D1-8	D1-8
2	7/F	2 g/kg (D5)		D6	129 (D3) 139 (D9)	No	Drowsiness D3-5	D3-5
3	10/F	2 g/kg×2 (D3, D5)		D6	127 (D4) 138 (D13)	No	Drowsiness D3-5	D3-5
4	2/F	2 g/kg×2 (D9, D20)	prednisolone	D25	134 (D9) 139 (D45)	No	Drowsiness D10-14	D10-12
	14/F	1.8 g/kg (D5)		D13	128 (D6) 142 (D25)	AN (8 mm)	Mild drowsiness D5-7	D5-7
	7/F	2 g/kg (D4)		D5	131 (D3) 141	No	Drowsiness D2-3	D2-3

ABBREVIATIONS
Pt, patient; Tx, therapy; M, male; F, female; D, day; AN, aneurysm; CC, cell count; WM, white matter; CR, complete recovery.

Delirious behavior Components	Seizure	CSF study	MRI results	EEG results	Neurological outcome	
Incoherent speech, unresponsiveness	No	Normal (D6)	Splenium (D7) Normal (D15)	Frontal slow (D6) Normal (D14)	CR	
Impulsive behavior, visual hallucinations, incoherent speech	No	Normal (D3)	Splenium (D4) Normal (D10)	Diffuse slow (D4) Normal (D9)	CR	
Emotional changes (laughter, weeping, fear), visual hallucinations, incoherent speech	No	Normal (D3)	Splenium + WM (D3) Normal (D7)	Diffuse slow (D3) Normal (D6)	CR	
Visual hallucinations, misperceptions	No	Normal (D10)	Splenium (D10) Normal (D17)	Normal (D10)	CR	
Visual hallucinations	No	CC 16/mm^3 (D7)	Splenium (D10) Normal (D14)	Normal (D11)	CR	[10]
Impulsive behavior, visual hallucinations, incoherent speech	No	Normal (D3)	Sp (D3) Normal (D11)	Diffuse slow (D3)	CR	[11]

(patient 4). One patient (patient 1) had a cardiac aneurysm (5 mm) as a sequela.

All four patients presented with fluctuating delirium with onset between day 1 and 10, and a duration of 3 to 8 days, and all showed mild to moderate drowsiness between the episodes of delirious behavior. The results of neurological examinations were unremarkable except for the delirium and drowsiness. CSF analysis was normal in all patients. The Na level during neurological symptoms decreased to 119–134 mEq/l, which had become normal at the time of follow-up. MRI performed during their neurological manifestations (day 3 to 10) revealed homogenously reduced diffusion in the splenium (patients 1, 2, and 4) (Fig. 1-A) or the splenium and symmetrical subcortical white matter (patient 3), which had completely disappeared by the time of follow-up (day 7 to 17) with an interval of 4 to 8 days (Fig. 1-B). No specific treatment for MERS was performed for any patient; however, their neurological manifestations disappeared completely. EEG showed slow waves in three patients (became normal on follow-up EEG), and normal in another.

4. Discussion

Encephalitis or encephalopathy is an extremely rare complication of KD. Actually, none of 540 patients with KD presented with encephalitis/encephalopathy [4]. As far as we know, there have been only six patients with KD complicated by MERS (Table 1) [10,11], including the present four patients, their onset ranging from March 2010 to February 2011. The number of KD patients in 2010 in Japan has been reported to be 12,755, and that over 6 years being 466 [12]. The incidence of MERS in KD over 6 years, therefore, seems to be at least 1% (5/466).

All six patients (mean age, 8.0 years) presented with delirious behavior and drowsiness with hyponatremia (119–134 mEq/l); and a homogenously reduced diffusion in the splenium, all of which completely recovered or disappeared. These clinical, laboratorial, and radiological findings are typical of MERS (mean age, 9.0 years; serum sodium level, 131.8 ± 4.1 mEql/l) [8,13]. MERS has been reported to be an encephalitis or encephalopathy associated with infection, such as influenza or rotavirus [8,9]. It is important for pediatricians to acknowledge that MERS can be observed in patients with KD, which is an acute febrile systemic vasculitis, not directly related to a pathogen.

What is the possible mechanism underlying MERS with KD? The exact pathogenesis of MERS is uncertain, however, MERS seems to comprise cerebral edema due to electrolyte/water imbalance, including hyponatremia, as an underlying pathophysiology [8,13]. Activation of the immune system seems to be a central feature of KD, and the concentrations of many proinflammatory cytokines and chemokines, including tumour necrosis factor α, interleukins 1, 6, and 8, and vascular endothelial growth factor (VEGF), are elevated during the acute phase [1,2]. Elevated VEGF could result in vascular leakage, hypoalbuminemia, and noncardiac edema [14]. Actually, cerebral edema has been histopathologically observed in patients with KD [15], which could possibly progress to MERS.

Two of the six patients with KD complicated by MERS (Table 1, patient 1 and one patient previously reported [10]) had a cardiac aneurysm as a sequela. The duration of a fever has been confirmed to be a predictor of a coronary artery aneurysm in KD [1]. Other independent risk factors have been reported, including an elderly onset and the presence of hyponatremia. Children 6 years and older account only for around 5% of patients with KD [16], however, they often have delays in diagnosis, and an increased incidence of cardiovascular abnormalities (20% vs. 15% under 6 years) [16,17]. The hyponatremia observed in 45% in patients with KD has also been reported to be an independent risk factor for cardiovascular sequelae [18]. Actually, the two patients having a cardiac aneurysm fulfilled the triple risks, prolonged fever (21 and 13 days), elderly onset (8 and 14 years), and hyponatremia (119 and 128 mEq/l). Elderly onset and hyponatremia are also characteristic of MERS, therefore, it is reasonable that patients with KD complicated by MERS likely have risk factors for cardiac abnormalities.

Please cite this article as: Takanashi J, et al, Kawasaki disease complicated by mild encephalopathy with a reversible splenial lesion (MERS), J Neurol Sci (2011), doi:10.1016/j.jns.2011.11.022

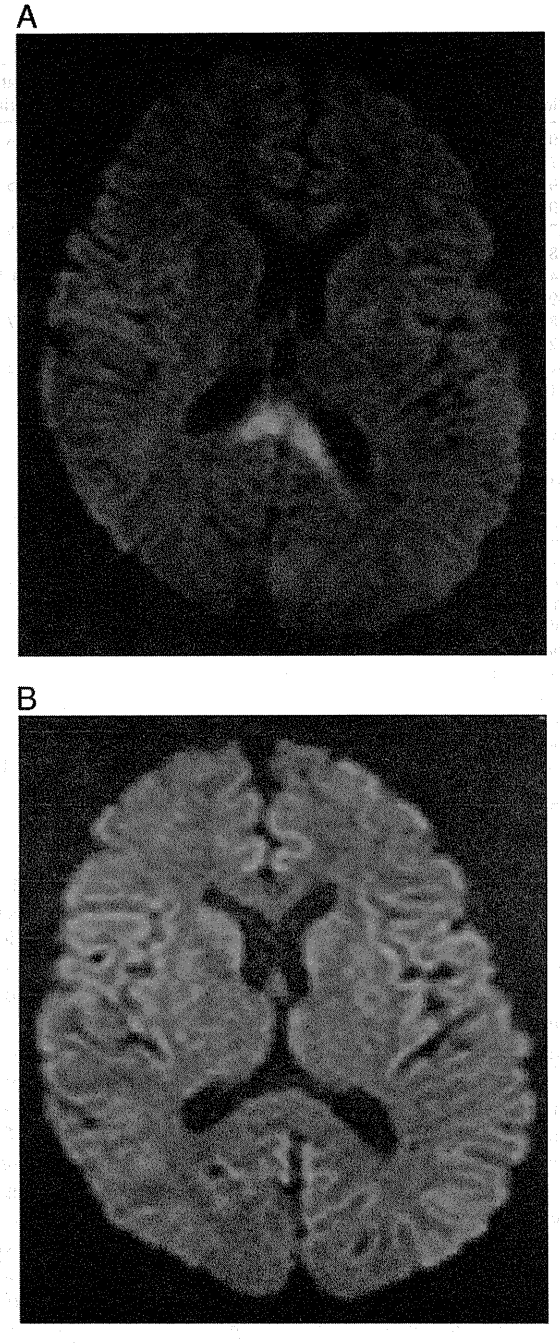

Fig. 1. Diffusion-weighted image of patient 1 on day 7 (A) shows a high signal lesion in the splenium of the corpus callosum, which disappears on day 15 (B).

It seems that cardiac abnormalities are more common in patients with KD having neurological manifestations, for example, two of the six patients with MERS, 2/2 and 2/5 with transient hemiplegia and facial nerve palsy, respectively [4,7]. Those with transient consciousness disturbance during the acute phase of KD have also been reported to have coronary aneurysms in 19% (6/32) [7]. It is possible that the severity of KD (severe vasculitis) may result in neurological manifestations. Further clinical, radiological and immunological studies are necessary to clarify the frequency, mechanism, and prognosis of KD complicated by MERS.

Acknowledgements

We thank Dr. Shinji Itamura at the Department of Pediatric Cardiology, Hiroshima City Hospital, Dr. Tatsuharu Sato at the Department of Pediatrics, Nagasaki University Hospital, and Dr. Daisuke Usui at the Department of Pediatrics, Shizuoka Institute of Epilepsy and Neurological Disorders for their clinical and radiological comments, and the patients and families for their contribution to this study.

This study was supported in part by the Grant-in-aid for the Research on Measures for Intractable Diseases (H23-Nanchi-Ippan-78, H22-Nanchi-Ippan-132), the Research Grant for Nervous and Mental Disorders (21B-5), both from the Ministry of Health, Labor and Welfare of Japan to Dr. Takanashi.

All authors have no conflict of interest.

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Please cite this article as: Takanashi J, et al, Kawasaki disease complicated by mild encephalopathy with a reversible splenial lesion (MERS), J Neurol Sci (2011), doi:10.1016/j.jns.2011.11.022

研究者名簿

区　分	氏　　名	所　　属　　等	職　名
研究代表者	水口　　雅	東京大学大学院医学系研究科発達医科学	教　授
研究分担者	奥村　彰久	順天堂大学医学部小児科学	准教授
	斎藤　義朗	国立精神・神経医療研究センター病院小児神経科	医　長
	高梨　潤一	亀田総合病院小児科	部　長
	廣瀬　伸一	福岡大学医学部小児科学	教　授
	山形　崇倫	自治医科大学医学部小児科学	教　授
	廣瀬　伸一	福岡大学医学部小児科学	教　授
	山形　崇倫	自治医科大学医学部小児科学	教　授
研究協力者	齋藤真木子	東京大学大学院医学系研究科発達医科学	助　教
	種市　尋宙	富山大学医学部附属病院小児科	助　教
	岩崎　博之	東京大学医学部附属病院小児科	助　教

厚生労働科学研究費補助金
難治性疾患克服研究事業
「重症・難治性急性脳症の病因解明と診療確立に向けた研究」
平成23年度　研究報告書

発行：平成24年3月
発行者：水口　雅（研究代表者）
事務局：東京大学大学院医学系研究科　発達医科学教室
〒113-0033　　東京都文京区本郷7－3－1
TEL　03-5841-3515　FAX　03-5841-3628