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Brain & Development 31 (2009) 221–227

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

www.elsevier.com/locate/braindev

Original article

Outcome of acute necrotizing encephalopathy in relation to treatment with corticosteroids and gammaglobulin

Akihisa Okumura [a,*], Masashi Mizuguchi [b], Hiroyuki Kidokoro [c,d], Manabu Tanaka [e], Sinpei Abe [a], Mitsuaki Hosoya [f], Hideo Aiba [g], Yoshihiro Maegaki [h], Hitoshi Yamamoto [i], Takuya Tanabe [j], Eiko Noda [k], George Imataka [l], Hirokazu Kurahashi [d,m]

[a] *Department of Pediatrics, Juntendo University School of Medicine, 2-1-1 Hongo, Bunkyo-ku, Tokyo 113-8421, Japan*
[b] *Department of Developmental Medical Sciences, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan*
[c] *Department of Pediatrics, Anjo Kosei Hospital, 28 Higashihirokute, Anjo, Aichi 446-8602, Japan*
[d] *Department of Pediatrics, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya, Aichi 466-8550, Japan*
[e] *Division of Neurology, Saitama Children's Medical Center, 2100 Magome, Iwatsuki-ku, Saitama-city, Saitama 339-8551, Japan*
[f] *Department of Pediatrics, Fukushima Medical University School of Medicine, Hikarigaoka 1, Fukushima 960-1295, Japan*
[g] *Division of Pediatric Neurology, Shizuoka Children's Hospital, 860 Urushiyama, Shizuoka 420-8660, Japan*
[h] *Division of Child Neurology, Tottori University School of Medicine, 36-1 Nishi-cho, Yonago, Tottori 683-8504, Japan*
[i] *Department of Pediatrics, St. Marianna University School of Medicine, 2-16-1 Sugao, Miyamae-ku, Kawasaki 216-8511, Japan*
[j] *Division of Pediatrics, Hirakata Municipal Hospital, 2-14-1 Kinyahonmachi, Hirakata, Osaka 573-1013, Japan*
[k] *Department of Pediatrics, Nagoya Daini Red Cross Hospital, 2-9 Myoken-cho, Showa-ku, Nagoya 466-8650, Japan*
[l] *Department of Pediatrics, Dokkyo Medical University School of Medicine, 880 Kitakobayashi, Mibu, Shimotsuga, Tochigi 321-0293, Japan*
[m] *Department of Pediatrics, Fukuoka University School of Medicine, 7-5-1, Nanakuma, Jonan-ku, Fukuoka 814-0180, Japan*

Received 24 October 2007; received in revised form 1 March 2008; accepted 21 March 2008

Abstract

Objective. To examine the relation between outcome and treatment with steroids and gammaglobulin in children with acute necrotizing encephalopathy. *Methods.* We retrospectively evaluated the clinical course and outcome of 34 children with acute necrotizing encephalopathy. They were divided into two groups; 17 patients with brainstem lesion and 17 patients without brainstem lesion. Early steroid use was defined as when steroids were administered within 24 h after the onset. The outcome was judged as good when a patient had no or mild cognitive impairment and poor when a patient had more severe sequelae, or died. *Results.* Among patients without brainstem lesions, the outcome was good in 7 of 12 with early steroid, whereas it was poor in all 5 patients without early steroid. There was no significant difference in sex, age, and laboratory data between patients with and without early steroid. The outcome was not correlated with gammaglobulin treatment. As to patients without brainstem lesions, the outcome was not correlated with early steroid or gammaglobulin treatment. *Conclusions.* Steroid within 24 h after the onset was related to better outcome of children with acute necrotizing encephalopathy without brainstem lesions. Early steroid treatment will be an important option of the treatment for acute necrotizing encephalopathy.

Keywords: Acute necrotizing encephalopathy; Outcome; Steroid; Brainstem lesion

1. Introduction

Acute necrotizing encephalopathy (ANE) is a well-defined type of acute encephalopathy described by

* Corresponding author. Tel.: +81 3 3813 3111; fax: +81 3 5800 1580.
E-mail address: okumura@med.juntendo.ac.jp (A. Okumura).

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doi:10.1016/j.braindev.2008.03.005

Mizuguchi et al. [1–3]. The most prominent feature of ANE is the presence of multiple, symmetric brain lesions in the bilateral thalami and other specific brain regions including periventricular white matter, internal capsule, putamen, upper brain stem tegmentum, and cerebellar medulla, demonstrated by CT or MRI. The onset of ANE is triggered by acute febrile diseases, mostly viral, among which influenza is the most common [2,4]. ANE is often observed among infants and children, but occasional adult cases have also been reported [1,5,6]. Although ANE is common in Japan and Taiwan [2], several reports on ANE have been made from some European and American countries [7–9].

ANE is often associated with severe neurological symptoms. Onset of ANE occurs during the early febrile period of viral infection and runs a fulminant course with rapid development of coma. The neurological outcome of ANE has been reported to be very poor. According to Mizuguchi, among 51 children with ANE, 14 children died, and 20 survived with moderate or severe neurological deficit [2]. Only 17 of them survived with no or mild neurological sequelae [2].

Several authors have suggested that hypercytokinemia is closely related to the development of ANE. Patients with ANE often have signs of systemic inflammatory response syndrome such as shock, multiple organ failure, and disseminated intravascular coagulation. An association of hemophagocytic syndrome has been reported [10]. These facts indicate that macrophage activation and hypercytokinemia will be participated in the pathogenesis of ANE.

There have been no reports on the treatment against ANE. We postulated that anti-inflammatory treatment can be effective for ANE, if the development of ANE is attributable to systemic inflammatory response. We conducted a retrospective study in order to examine the efficacy of anti-inflammatory treatment including steroids and gammaglobulin.

2. Patients and method

We retrospectively evaluated the clinical course and outcome of 38 children with ANE recruited from 17 hospitals. We included all patients with ANE who were serially experienced in each hospital. The diagnosis of ANE was made on the basis of neuroradiological findings according to the criteria proposed by Mizuguchi et al. [2,3]. In this study, we included patients with acute encephalopathy who had multiple focal lesions which were symmetrically distributed in the bilateral thalami and other brain regions such as the putamina, cerebral and cerebellar white matter, and brainstem tegmentum [2,3,11]. We excluded the patients with marked metabolic derangement such as elevated lactate, pyruvate, amino acids, or organic acids levels.

We excluded 4 patients from the study, who were critically ill with severe systemic hypotension and/or multiorgan failure on or within a few hours after admission, because the efficacy of the drug was difficult to evaluate in these patients. They all died within a few days after the onset of ANE. Eventually, the remaining 34 patients were the subject of this study. There were 19 boys and 15 girls. Their median age was 28 months (range, 9–86 months). One patient had a past history of febrile seizure. Five patients had developmental delay before the onset of ANE. None had a prior history of epilepsy.

We assessed the detailed clinical course on the basis of the medical record. The prodromal illness was virologically proven influenza in 11, respiratory illness in 14, gastrointestinal illness in 5, exanthem subitum in 1 and undetermined due to insufficient information in 3. Before the onset of ANE, acetaminophene was used in 12 patients and mephenamate in 5. All patients had severely impaired consciousness and seizure.

Laboratory data were also assessed from the medical records. In this study, the following values were investigated: platelet counts, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, creatinine kinase, and protein in cerebrospinal fluid. Mizuguchi et al. reported that these values may correlate the outcome of patients with ANE [2,12]. No patients had elevated serum ammonia levels and pleocytosis in the cerebrospinal fluid.

We divided the 34 patients into two groups according to the presence or absence of brainstem lesions on CT and/or MRI, because the presence of brainstem lesions is considered to be closely related to poor outcome as reported in previous reports [12]. Brainstem lesion was present in 17 patients and was recognized on the first CT in all of them (Fig. 1).

As to the treatment, we paid an attention to steroids and gammaglobulin. Early steroid use was defined as when steroids were administered within 24 h after the onset of ANE. In our cohort, steroid was used in two regimens: steroid pulse therapy or intravenous dexamethasone. In case with steroid pulse therapy, 30 mg/kg of methylprednisolone was administered for 3 days. As to intravenous dexamethasone, 0.6 mg/kg of dexamethasone was administered in 4 divided doses for 2–4 days. Gammaglobulin was administered at a dose of 1–2 g/kg. Antiepileptic drugs were administered in all patients.

We divided the outcome of the patients into two groups; good and poor outcome. Nine patients had good outcome. Six of them had no neurological sequelae and three had mild cognitive impairment (intelligence or development quotient $50 \leqslant 70$) without obvious motor impairment. The other 25 patients had poor outcome. Ten of them died, 12 had severe cognitive impairment (intelligence or development quotient <30) with marked motor impairment (all of them could not stand with support), and three had moderate cognitive impairment

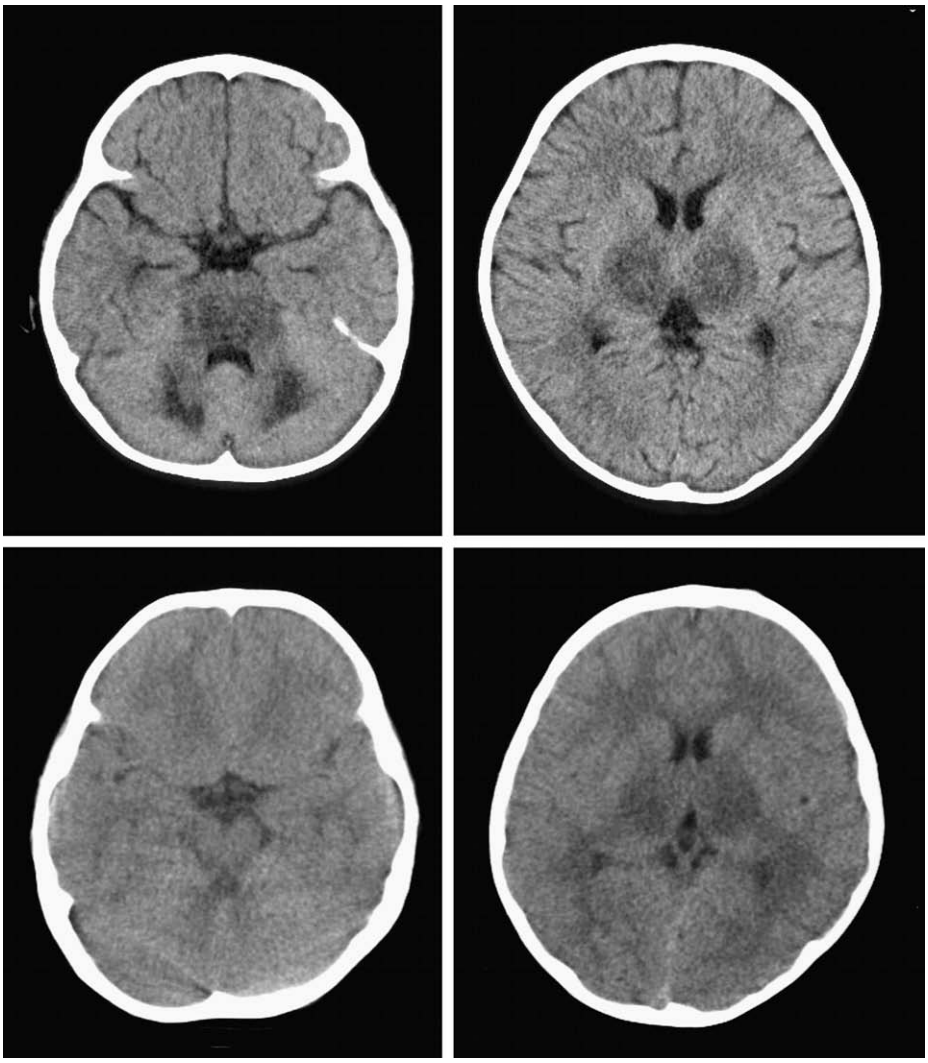

Fig. 1. CT findings. Upper: 21-month-old boy with brainstem lesions. Low density areas are observed in the upper brain stem tegmentum and cerebellar medulla as well as bilateral thalami. Lower: 35-month-old boy without brainstem lesions. Low density areas are present in bilateral thalami, whereas no low density areas are recognized in the brainstem.

(intelligence or development quotient $30 \leqslant 50$) with various degree of motor impairment.

Statistical analyses were performed by means of the Mann–Whitney *U* test for numerical variables and the Fisher exact probability test for categorical variables. A p value <0.05 was considered to be statistically significant.

3. Results

3.1. Patient characteristics

Patient characteristics in each group were shown in Table 1. The age, sex, a history of febrile seizure or developmental delay was not significantly different between those with and without brainstem lesions. The use of acetaminophene or mephenamate was not different between the two groups. No laboratory data showed a statistically significant difference between the two groups.

3.2. Patients without brainstem lesions

In this group, outcome was good in 7 patients and poor in 10. Among 7 patients with good outcome, 6 patients had no sequelae and the other had mild cognitive impairment. Among 10 patients with poor outcome, moderate cognitive impairment was observed in 1, severe cognitive impairment with marked motor impairment in 7, and death in 2.

Steroid was administered in 14 patients. Early steroid was given to 12 of them. Steroid was used on the third day in the remaining 2 patients. Steroid pulse therapy was performed in 3 patients, within 24 h after the onset. Gammaglobulin was administered in 5 patients.

The relation between therapy and outcome was summarized in Table 2. In 12 patients with early steroid, the outcome was good in 7 and poor in 5. In contrast, the outcome was poor in all 5 patients in whom steroid

Table 1
Patient characteristics

	With brainstem lesions ($n = 17$)	Without brainstem lesions ($n = 17$)	
Male:female	7:10	12:5	NS
Age (months)	34 (9–86)	25 (11–67)	NS
Past history			
Febrile seizure	0	1	NS
Development delay	3	2	NS
Predromal illness			
Influenza	6	5	Not done
Respiratory illness	6	8	
Gastrointestinal illness	2	3	
Exanthem subitum	0	1	
Not determined	3	0	
Antipyretics			
Acetaminophene	3	9	NS
Mephenamate	4	1	NS
Laboratory data			
Minimum Plt ($\times 10^4/\mu l$)	12.7 (0.3–34.7)	10.5 (3.9–22.1)	NS
Maximum AST (IU/l)	397 (56–29,520)	427 (71–18,088)	NS
Maximum ALT (IU/l)	171 (19–16,510)	414 (41–12,300)	NS
Maximum LDH (IU/l)	1160 (472–52,480)	1386 (315–16,933)	NS
Maximum CK (IU/l)	1020 (61–18,630)	509 (103–53,263)	NS
CSF cell count (/ml)	1 (0–6)	2 (0–6)	NS
Protein (mg/dl)	91 (8–1060)	59 (9–380)	NS

Plt, platelet counts; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; CK, creatinine kinase; CSF, cerebrospinal fluid.

was not administered within 24 h after the onset. Statistical analysis revealed that good outcome was more often in patients with early steroid use. On the other hand, the outcome of patients was not correlated with steroid use, steroid pulse therapy, or gammaglobulin. Major adverse effects of steroids or gammaglobulin were not recognized in any patients.

Between patients with and without early steroid, neither sex, age, nor laboratory data showed a significant difference in any items (Table 3).

Table 2
Therapy and outcome in patients without brainstem lesions

Outcome	Steroid use ($n = 14$)	No steroid ($n = 3$)	
Good	7	0	NS
Poor	7	3	
	Early steroid ($n = 12$)	No early steroid ($n = 5$)	
Good	7	0	$p = 0.044$
Poor	5	5	
	Steroid pulse ($n = 3$)	No steroid pulse ($n = 14$)	
Good	2	5	NS
Poor	1	9	
	Gammaglobulin use ($n = 5$)	No gammaglobulin ($n = 12$)	
Good	2	5	NS
Poor	3	7	

NS, not significant.

3.3. Patients with brainstem lesion

In this group, outcome was good in 2 patients and poor in 15. Two patients with good outcome had mild cognitive impairment. Among 15 patients with poor outcome, moderate cognitive impairment was recognized in 2, severe cognitive impairment with marked motor impairment in 5, and death in 8.

Steroid was administered in 12 patients. Early steroid was given to 9 of them. Steroid pulse therapy was performed in 3 patients, within 24 h after the onset in 2 of them. Gammaglobulin was administered in 3 patients. Major adverse effects of steroids or gammaglobulin were not seen.

The relation between therapy and outcome was summarized in Table 4. The outcome of patients was not correlated with steroid use, early steroid use, steroid pulse therapy, or gammaglobulin.

4. Discussion

This is the first study that revealed the efficacy of early steroid against ANE. The outcome of patients treated with early steroid was better than those without early steroid, if the patients did not have brainstem lesions. The results of our study highlighted the importance of early treatment for children with ANE. The early diagnosis of ANE will not be difficult in most patients, because CT or MRI demonstrates characteris-

Table 3
Comparison between the patients with or without early steroid

	Early steroid ($n = 12$)	No early steroid ($n = 5$)	
Male:female	9:3	3:2	NS
Age (months)	26.5 (11–58)	15 (11–67)	NS
Laboratory data			
Minimum Plt ($\times 10^4/\mu l$)	10.5 (3.9–22.1)	9.9 (4.9–13.0)	NS
Maximum AST (IU/l)	395 (71–18088)	775 (95–11480)	NS
Maximum ALT (IU/l)	321 (41–10472)	940 (54–12300)	NS
Maximum LDH (IU/l)	1220 (315–16933)	1681 (710–7501)	NS
Maximum CK (IU/l)	642 (103–8400)	481 (218–53263)	NS
CSF protein (mg/dl)	57 (9–299)	94 (37–380)	NS
Outcome			
Good	7	0	$p = 0.044$
Poor	5	5	

Plt, platelet counts; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; CK, creatinine kinase; CSF, cerebrospinal fluid.

tic thalamic lesions from the early stage of the illness. In fact, brain lesions were clearly observed on the CT within a few hours after the patients became comatose. Therefore, early steroid treatment will be practical in children with ANE.

We consider that hypercytokinemia and hyperpermeability of both the blood–brain barrier and the capillary walls of the brain will be closely related to the pathogenesis of ANE, and that early steroid therapy will be effective in these conditions. There have been several reports on cytokine levels in children with influenza-associated encephalopathy including ANE and other subtypes of acute encephalopathy [4,13,14]. Ichiyama et al. measured serum cytokine levels of a patient with ANE due to influenza A [4]. Serum levels of interleukin-6, tumor necrosis factor-alpha and soluble tumor necrosis factor receptor 1 were highly elevated. Akiyoshi et al. reported a girl with ANE associated with hemophagocytic syndrome [15]. Serum and cerebrospinal fluid interleukin-6 and tumor necrosis factor-alpha were markedly elevated in this patient. Concurrent ANE and macrophage activation syndrome had been reported in a patient with juvenile idiopathic arthritis [16]. Histopathological studies of the brain have revealed severe brain edema and perivascular plasma exudation in ANE [2,3]. Thalamic lesions of ANE showed perivascular diapedesis of erythrocytes that suggests a severe injury of intracerebral blood vessels [17]. It is accepted that steroids suppress the pro-inflammatory process including increased cytokine levels and hyperpermeability of the vessels. It is rational that steroids can improve the outcome of ANE, if they are used during the appropriate period.

Table 4
Therapy and outcome in patients with brainstem lesion

Outcome	Steroid use ($n = 12$)	No steroid ($n = 5$)	
Good	0	2	NS
Poor	12	3	
	Early steroid ($n = 9$)	No early steroid ($n = 8$)	
Good	0	2	NS
Poor	9	6	
	Steroid pulse ($n = 3$)	No steroid pulse ($n = 14$)	
Good	0	2	NS
Poor	3	12	
	Gammaglobulin use ($n = 3$)	No gammaglobulin ($n = 14$)	
Good	0	2	
Poor	3	12	

NS, not significant.

In this study, the efficacy was not clearly different between methylprednisolone pulse therapy and intravenous dexamethasone. There have been several studies that revealed beneficial effects of these regimens for inflammatory diseases in the central nervous system. Methylprednisolone pulse therapy against influenza-associated encephalopathy was described in the tentative guideline proposed by the Research Organization for Influenza Encephalopathy Researchers in Japan in 1999. Thereafter, methylprednisolone pulse therapy has been widely applied to children with influenza-associated encephalopathy. A recent questionnaire survey revealed the efficacy of methylprednisolone pulse therapy against influenza-associated encephalopathy, although the subtypes of acute encephalopathy were not determined in these patients [18]. Dexamethasone was often used as an adjunctive treatment in children with acute bacterial meningitis. Several studies and meta-analyses showed that dexamethasone significantly reduces rates of mortality, severe hearing loss, and neurological sequelae in patients with bacterial meningitis [19]. Lebel et al. demonstrated that the patients with bacterial meningitis treated with dexamethasone became afebrile earlier and were less likely to acquire moderate or severe bilateral sensorineural hearing loss, as compared with those who received placebo [20]. Odio et al. reported that intravenous dexamethasone reduced the

risk for neurological and/or audiological sequelae by 1:3.8 [21]. These results indicate that both methylprednisolone pulse therapy and intravenous steroid are effective for hypercytokinemia-mediated brain injuries. However, the efficacy of these two regimens has not been compared. Further studies are necessary in order to clarify which treatment is more beneficial for children with ANE.

There may be a concern about selection bias of patients treated with early steroid. However, there was no significant difference in laboratory data on admission between those treated with early steroid and no early steroid. This indicates that the difference of the severity of ANE will be small, if present, between those who treated with early steroid or not. We do consider that the difference of outcome in patients without brainstem lesions will not be attributable to selection bias of the patients.

The efficacy of steroid was not obvious in children with brainstem lesions, even if the drugs were used within 24 h after the onset. The difference in efficacy of steroids cannot be attributable to the severity of the illness, because no significant difference in patient characteristics was present between those with and without brainstem lesions. In addition, there were no significant differences in the laboratory data that can be correlated with the outcome of various types of acute encephalopathies. Therefore, we consider that brainstem lesions, in themselves, are quite harmful and can be a marker of adverse outcome. Fatal outcome is not uncommon in children with brainstem encephalitis due to enterovirus 71 [22,23]. The patients were characterized by sudden cardiopulmonary collapse, neurogenic pulmonary edema, and extensive damage to the medulla and pons. Therefore, poor outcome will be inevitable in patients with ANE with brainstem lesions. However, there is an anecdotal report that may indicate the efficacy of very early steroids for patients with brainstem lesions. Uematsu et al. reported a 7-month-old girl with ANE with brainstem lesions preceded by bacterial meningitis [24]. In this patient, intravenous dexamethasone was used one day before the appearance of ANE lesions for the treatment against bacterial meningitis. This patient was reported to have no developmental delay at 17 month of age. Thus, we consider that there is a possibility that steroid or other anti-inflammatory treatment may be effective, if they are administered earlier and more intensely. The outcome of patients with brainstem lesion treated with very early steroid pulse therapy should be investigated, before we gave up steroid for ANE with brainstem lesion.

There may be other therapeutic choices, if hypercytokinemia is closely related to the development of ANE. Cyclosporine or other immunosuppressive agents can be drugs of choice. However, the efficacy and safety of these drugs for acute encephalopathy have not yet been established. It is well known that cyclosporine may cause posterior reversible encephalopathy [25,26]. In this study, we could not assess the efficacy of these drugs, because they were not administered in any of our patients. The use of immunosuppressive drugs will be a subject of future studies.

The limitation of this study is a relatively small number of the patients and a retrospective design. In order to obtain firm evidence of therapeutic effects, randomized control trials with a large number of the patients are desirable. However, the incidence of ANE is considered to be low, although it is more frequently observed in Japan or eastern Asia than in the European countries or the North America. In fact, the number of children with ANE was approximately 1 per 3–5 years in the hospitals participating in this study, although they are tertiary referral hospitals where seriously ill children are collected. Therefore, randomized control trials will be quite difficult.

In conclusion, the results of this study strongly suggested the efficacy of early steroid treatment for children with ANE without brainstem lesions. However, no beneficial effects were observed in those with brainstem lesions. Early steroid treatment will be an important option of the treatment for ANE, although further studies are necessary in order to determine the optimal regimen of steroid use.

Acknowledgements

This study was supported by the Grant from the Ministry of Education, Culture, Sports, Science and Technology (17209037).

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