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Original article

Changes in the treatment of pediatric acute encephalopathy in Japan between 2015 and 2021: A national questionnaire-based survey

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Abstract

Background: Although acute encephalopathy (AE) is the most serious disorder associated with a viral infection in childhood and often causes death or neurological sequelae, standard treatments have not been established. In 2016, the Japanese Society of Child Neurology published the "Guidelines for the Diagnosis and Treatment of Acute Encephalopathy in Childhood 2016" (AE GL 2016). We conducted a questionnaire survey to evaluate the status of the treatment of pediatric AE in 2021 and the changes in treatment before and after the publication of the AE GL 2016.

Methods: In October 2021, questionnaires were mailed via the web to members of two mailing lists who were involved in the practice of pediatric neurological disorders.

Results: Most Japanese physicians (98 %) engaged in the treatment of pediatric AE used the AE GL 2016 as a clinical reference. From 2015 to 2021, the number of institutions that implemented targeted temperature management (TTM), vitamin administration, and continuous electroencephalographic monitoring increased significantly. Regarding the targeted temperature for TTM, the proportion of patients who were treated with normothermia (36.0–37.0 °C) increased from 2015 (55 %) to 2021 (79 %). The use of corticosteroids in patients with AE caused by a cytokine storm, which is recommended in the AE GL 2016, had already been implemented in most institutions by 2015.

Conclusion: The AE GL 2016 could be used to disseminate the knowledge accumulated to date. Evidence of the efficacy and proper indication criteria for the treatment of AE is insufficient and must be further accumulated.

Abbreviations: AE, acute encephalopathy; JSCN, Japanese Society of Child Neurology; AE GL 2016, Guidelines for the Diagnosis and Treatment of Acute Encephalopathy in Childhood 2016; ANE, acute necrotizing encephalopathy; HSES, hemorrhagic shock and encephalopathy syndrome; AESD, acute encephalopathy with biphasic seizures and late reduced diffusion; AERRPS, acute encephalopathy with refractory, repetitive partial seizures; FIRES, febrile infection-related epilepsy syndrome; MERS, clinically mild encephalitis/encephalopathy with a reversible splenial lesion; TTM, targeted temperature management; EEG, electroencephalography; PICU, pediatric intensive care unit; TI, tracheal intubation; NCS, non-convulsive seizures; NCSE, non-convulsive seizures epilepticus; DWI, diffusion-weighted imaging; CT, computed tomography; MRI, magnetic resonance imaging; SPECT, single-photon emission computerized tomography; HHV-6, human herpesvirus 6; SD, standard deviation; ADEM, acute disseminated encephalomyelitis; CSF, cerebrospinal fluid

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Keywords: Acute encephalopathy; Guidelines; Questionnaire survey; Corticosteroids; Targeted temperature management; Normothermia; Vitamin administration; Continuous electroencephalographic monitoring

1. Introduction

Acute encephalopathy (AE) is a condition characterized by an acute onset and long-lasting disturbance of consciousness [1]. AE is the most serious complication of a common viral infection in childhood, often causing death or sequelae such as motor and intellectual disabilities and epilepsy in survivors [2,3]. Pediatric AE is more common in Japan than in other regions, and has an incidence of 500–900 cases/year [4]. However, in the past, there were no treatment guidelines for AE other than those for influenza-associated encephalopathy [5]. In 2016, the Japanese Society of Child Neurology (JSCN) published the "Guidelines for the Diagnosis and Treatment of Acute Encephalopathy in Childhood" (AE GL 2016), an outline of which was translated into English in 2021, to facilitate the provision of the best and most timely medical care to patients with AE showing rapid disease progression and severe symptoms [1].

In the AE GL 2016, AE is classified into four major groups based on the cause/association: the first group, caused by a metabolic disorder; second, caused by a cytokine storm, including acute necrotizing encephalopathy (ANE) and hemorrhagic shock and encephalopathy syndrome (HSES); third, associated with convulsive status epilepticus, including AE with biphasic seizures and late reduced diffusion (AESD) and AE with refractory, repetitive partial seizures (AERRPS)/febrile infection-related epilepsy syndrome (FIRES); and fourth, associated with miscellaneous syndromes, such as clinically mild encephalitis/encephalopathy with a reversible splenial lesion (MERS). In Japan, AESD was the most common AE syndrome (34 % in 2014–2017), followed by MERS and ANE; unclassified encephalopathy accounted for approximately 40 % of all AE cases [3,6]. At least five years have passed since the AE GL 2016 were published, and we hypothesized that this publication may have affected the practice of managing patients with AE. We conducted a questionnaire-based survey on the status of pediatric AE treatment in 2021 and the changes in treatment from before to after the publication of the AE GL 2016 to understand the current treatment practices for managing pediatric AE in Japan and the impact of the guidelines.

2. Material and methods

In October 2021, we mailed a web-based questionnaire to the councilors of the JSCN and members of the annual Zao Conference on Pediatric Neurology, in which most Japanese pediatric neurologists participated. One representative from each institution was asked to respond to the questionnaire. The deadline for survey responses was December 24, 2021, which was 2.5 months after the questionnaires were sent.

The questionnaire items included: (1) how often respondents refer to the AE GL 2016 for their practice; (2) treatment and monitoring information for each AE syndrome as of 2021 and (3) as of 2015 (prior to publication of the AE GL 2016); and (4) target body temperature for targeted temperature management (TTM). AE syndromes were classified into AESD, ANE and HSES, MERS, AERRPS/FIRES, and unclassified AE. The diagnostic criteria for each AE syndrome are shown in Supplementary Material 1 [1,7]. We did not examine metabolic encephalopathy in the present study because of its low incidence. The treatment for each syndrome included steroid pulse therapy, steroid therapy other than steroid pulse therapy, immunoglobulin therapy, TTM, administration of vitamins, free radical scavenger therapy (edaravone), hyperosmotic therapy for intracranial hypertension, plasma exchange therapy, cyclosporine administration, and antithrombin III high-dose therapy. In addition, the respondents were asked to select whether continuous electroencephalography (EEG) and intracranial pressure monitoring were performed. If respondents had no experience in the treatment of a certain syndrome, they were asked to select "no experience" instead of selecting treatment options. A web-based system was used to collect questionnaire responses. In cases of duplicate responses from the same institution, responses received later were excluded. The data were statistically analyzed using the chi-square test or Fisher's exact test for comparisons between 2015 and 2021. P values$<$0.05 were considered statistically significant. This study was reviewed and approved by the Ethical Committee of Tokyo Women's Medical University (No. 2021–0078) and supported by the Joint Research Committee of JSCN (No. 21–01).

3. Results

We received responses from 128 institutions, including 85 of the 151 JSCN-certified educational institutes. Approximately-one-third of the 66 institutions that did not respond were clinics or hospitals that primarily provided rehabilitation services.

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3.1. Characteristics of respondents

Most respondents were affiliated with pediatrics, and the majority were board certified pediatric neurologists. Institutions with pediatric intensive care units (PICU) accounted for 21.5 % (Table 1). Respondents used the AE GL 2016 very frequently (58 %) or frequently (40 %) as a reference for their practice (Table 1).

3.2. The treatments and monitoring used more frequently in 2021 than in 2015

The aggregate results are presented in Table 2. The treatments and monitoring used more frequently in 2021 than in 2015 were TTM for all syndromes other than AERRPS/FIRES, steroid pulse therapy for unclassified AE, administration of vitamins for AESD, AERRPS/FIRES, and unclassified AE, and continuous EEG monitoring for all syndromes other than ANE and HSES.

With regard to TTM, we asked whether tracheal intubation (TI) and ventilation were provided for TTM in cases that did not require TI. Among the 59 institutions that performed TTM, 18 (31 %) performed it without TI in cases that did not require TI in 2021, and this result was not significantly different from that in 2015 (26 %).

With regard to anti-inflammatory therapy in 2015 and 2021, steroid pulse therapy was performed in most institutions (average for all syndromes: 75 % and 82 %, respectively) and immunoglobulin therapy was used in half of the institutions (average for all syndromes: 48 % and 45 %, respectively). We also asked how often the respondents performed steroid pulse therapy for each syndrome. The percentages of the institutions that performed steroid pulse therapy for 75 % or more patients for each AE syndrome in 2021 were as follows: AESD, 66 %; ANE and HSES, 92 %; MERS, 21 %; AERRPS, 71 %; and unclassified AE, 58 %. There were no significant differences in these percentages for any syndromes between 2015 and 2021, except for unclassified AE (41 % in 2015, 58 % in 2021, $P = 0.012$). Steroid pulse therapy was performed in all ANE and HSES cases at most institutions.

A comparison of the types of vitamins administered between 2015 and 2021 is presented in Supplementary Material 2. Although the number of institutions that administered vitamins increased, there was no significant change in their contents. Vitamins B1, B6, and carnitine were used in many institutions.

The percentage of institutions using continuous EEG monitoring increased significantly from 2015 to 2021 for all syndromes other than ANE and HSES in which the

Table 1
Characteristics of respondents.

	N	%
Affiliated department		
Pediatrics	107	83 %
Pediatric neurology	20	16 %
Neurology	1	1 %
Professional qualifications		
Pediatric neurologist	105	82 %
Pediatricians specializing in pediatric neurology	17	13 %
Pediatricians not specializing in pediatric neurology	3	2 %
Pediatric emergency physician/ Intensive care physician	1	1 %
Unanswered	2	2 %
Physician experience		
<10 years	4	3 %
10–20 years	57	45 %
20–30 years	48	37 %
>30 years	19	15 %
Availability of PICU at their institution		
Yes	35	27 %
No	93	73 %
Frequency of the AE GL 2016 as a reference for respondents' practice		
Very frequently	74	58 %
Frequently	52	40 %
Less frequently	1	1 %
Not at all	1	1 %

Abbreviations: AE GL 2016, Guidelines for the Diagnosis and Treatment of Acute Encephalopathy in Childhood 2016; PICU, pediatric intensive care unit.

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Table 2
Comparison of the number of institutions that performed each treatment or monitoring method for each acute encephalopathy syndrome in 2015 and in 2021.

Syndrome	AESD			ANE and HSES			MERS		
Treatment	2015 N[a] (%)[b]	2021 N[a] (%)[b]	P value	2015 N[a] (%)[b]	2021 N[a] (%)[b]	P value	2015 N[a] (%)[b]	2021 N[a] (%)[b]	P value
No experience	23	16		59	56		24	19	
Steroid pulse therapy	90/101 (89 %)	95/112 (85 %)	0.355	62/65 (95 %)	69/72 (96 %)	1	55/100 (55 %)	68/109 (62 %)	0.278
Other steroid therapy	9/101 (9 %)	15/112 (13 %)	0.302	11/65 (17 %)	10/72 (14 %)	0.623	12/100 (12 %)	16/109 (15 %)	0.570
Immunoglobulin therapy	49/101 (49 %)	54/112 (48 %)	0.965	45/65 (69 %)	48/72 (67 %)	0.748	17/100 (17 %)	15/109 (14 %)	0.516
TTM	35/101 (35 %)	57/112 (51 %)	0.017*	30/65 (46 %)	47/72 (65 %)	0.024*	7/100 (7 %)	21/109 (19 %)	0.009*
Vitamins	30/101 (30 %)	62/112 (55 %)	0.0002*	17/65 (26 %)	30/72 (42 %)	0.056	12/100 (12 %)	21/109 (19 %)	0.150
Free radical scavengers	31/101 (31 %)	39/112 (35 %)	0.522	17/65 (26 %)	25/72 (35 %)	0.277	8/100 (8 %)	11/109 (10 %)	0.599
Hyperosmotic therapy	46/101 (46 %)	58/112 (52 %)	0.363	35/65 (54 %)	46/72 (64 %)	0.232	15/100 (15 %)	12/109 (11 %)	0.390
Plasma exchange	1/101 (1 %)	2/112 (2 %)	1	10/65 (15 %)	13/72 (18 %)	0.676	0/100 (0 %)	0/109 (0 %)	1
Cyclosporine	7/101 (7 %)	7/112 (6 %)	0.841	3/65 (5 %)	2/72 (3 %)	0.668	1/100 (1 %)	0/109 (0 %)	0.478
Antithrombin III high-dose therapy	3/101 (3 %)	2/112 (2 %)	0.670	8/65 (12 %)	5/72 (7 %)	0.384	2/100 (2 %)	1/109 (1 %)	0.608
Continuous EEG monitoring	50/101 (50 %)	77/112 (69 %)	0.004*	33/65 (51 %)	45/72 (63 %)	0.166	20/100 (20 %)	32/109 (29 %)	0.118*
ICP monitoring	2/101 (2 %)	3/112 (3 %)	1	4/65 (6 %)	7/72 (10 %)	0.538	0/100 (0 %)	0/109 (0 %)	1

Syndrome	AERRPS/FIRES			Unclassified AE		
Treatment	2015 N[a] (%)[b]	2021 N[a] (%)[b]	P value	2015 N[a] (%)[b]	2021 N[a] (%)[b]	P value
No experience	73	69		26	22	
Steroid pulse therapy	37/51 (73%)	47/59 (80%)	0.381	62/98 (63%)	91/106 (86%)	0.0002*
Other steroid therapy	5/51 (10%)	7/59 (12%)	0.769	12/98 (12%)	17/106 (16%)	0.438
Immunoglobulin therapy	29/51 (57%)	28/59 (47%)	0.325	48/98 (49%)	50/106 (47%)	0.796
TTM	18/51 (35%)	23/59 (39%)	0.690	29/98 (30%)	49/106 (46%)	0.014*
Vitamins	10/51 (20%)	23/59 (39%)	0.027*	25/98 (26%)	49/106 (46%)	0.002*
Free radical scavengers	10/51 (20%)	15/59 (25%)	0.468	19/98 (19%)	27/106 (25%)	0.299
Hyperosmotic therapy	11/51 (22%)	20/59 (34%)	0.152	37/98 (38%)	46/106 (43%)	0.413
Plasma exchange	5/51 (10%)	6/59 (10%)	1	6/98 (6%)	8/106 (8%)	0.688
Cyclosporine	2/51 (4%)	2/59 (3%)	1	6/98 (6%)	6/106 (6%)	0.889
Antithrombin III high-dose therapy	1/51 (2%)	2/59 (3%)	1	3/98 (3%)	3/106 (3%)	1
Continuous EEG monitoring	32/51 (63%)	50/59 (85%)	0.008*	28/98 (29%)	62/106 (58%)	< 0.0001*
ICP monitoring	0/51 (0%)	1/59 (2%)	1	2/98 (2%)	2/106 (2%)	1

Abbreviations: AESD, acute encephalopathy with biphasic seizures and late reduced diffusion; ANE, acute necrotizing encephalopathy; HSES, hemorrhagic shock and encephalopathy syndrome; MERS, clinically mild encephalitis/encephalopathy with a reversible splenial lesion; AERRPS, acute encephalopathy with refractory, repetitive partial seizures; FIRES, febrile infection-related epilepsy syndrome; AE, acute encephalopathy; TTM, targeted temperature management; EEG, electroencephalography; ICP, intracranial pressure.

[a] 124 physicians responded to questions on treatment in 2015 and 128 responded to those on treatment in 2021.

[b] The number of respondents who chose "no experience" was subtracted from the total number of respondents, and the percentage of institutions that performed each treatment or monitoring was calculated for the remaining respondents.

* Statistically significant difference.

increase was not statistically significant (from 51 % in 2015 to 63 % in 2021).

3.3. Comparison of the target body temperature in TTM between 2015 and 2021

The target body temperature for TTM also changed significantly between 2015 and 2021. The number of institutions that employed brain normothermia (target temperature at 36.0–37.0 °C) increased, and those that employed brain hypothermia (at 35.0 °C or lower) decreased from 2015 to 2021 (Fig. 1).

4. Discussion

In the present study, we compared the actual treatment of AE before (2015) and after (2021) the publication of the AE GL 2016. Considering TTM, the number of institutions that performed TTM increased significantly for all AE syndromes except AERRPS/FIRES. The efficacy of TTM for pediatric AE has not been established, and the AE GL 2016 do not clearly discuss its safety and adverse reactions. To date, no large clinical study has demonstrated the efficacy of TTM for AE in children. Recently, it has been reported that early initiation of TTM for AE, especially within 12 h, leads to a good prognosis [8–10]. In two reports on patients with AE without AST elevation, that is, AE other than that caused by a cytokine storm, none of the patients treated with therapeutic normothermia (36.0 °C) presented neurological sequelae or progressed to AESD, whereas around 25 % patients without TTM developed AESD with neurological sequelae [9,10]. No serious adverse events due to therapeutic normothermia were observed. Although an analysis using the national inpatient database in Japan found that therapeutic hypothermia was administered to<2 % of pediatric patients with AE in both 2010 and 2015, with no significant increase [4], TTM is currently expected to be applied by an increasing number of institutions.

The target body temperature for TTM has also changed significantly between 2015 and 2021, shifting from hypothermia to normothermia. There is a lack of evidence regarding the appropriate target body temperature for TTM in pediatric patients with AE. In this context, Saji et al. reported no difference in short-term prognosis and adverse events between groups with a body temperature target of 34.0 °C and 36.0 °C for pediatric patients with AE [11]. Therapeutic hypothermia was recommended and was commonly used for managing out-of-hospital cardiac arrest; however, some recent randomized controlled trials in adults and children reported no significant differences in mortality and neurological outcomes between the hypothermia- and normothermia-based strategies [12–14]. Furthermore, a hypothermia group experienced more side effects such as arrhythmia and the need for vasopressor support than a normothermia group [13,15]. In addition, in Japan AE is often treated in hospitals lacking a PICU, and some institutions perform TTM without TI and ventilatory management [9]. This situation and the aforementioned reports on TTM for cardiac arrest may explain why the normothermia-based strategy has become the mainstream pediatric AE treatment in Japan.

Our study revealed little interval changes in frequency of steroid pulse therapy and immunoglobulin therapy for classified AE syndromes between 2015 and 2021. In particular, corticosteroids for AE caused by a cytokine storm had been implemented in almost all institutions by 2015. In the AE GL 2016, early steroid pulse therapy is recommended for AE caused by a cytokine storm, especially ANE (grade B, there is fair evidence to recommend clinical action) [1], based on the report showing early corticosteroid administration has been associated with improved prognosis [16]. Early administration could also be effective for encephalopathy secondary to Shiga toxin-producing *Escherichia coli* O111 infection with inflammatory cytokinemia [17] and influenza-associated encephalopathy [18]. However, there is one report, published after AE GL 2016, which have not shown the effectiveness of corticosteroids in patients with AE presumably due to a cytokine storm [19]. Further studies are therefore needed to determine

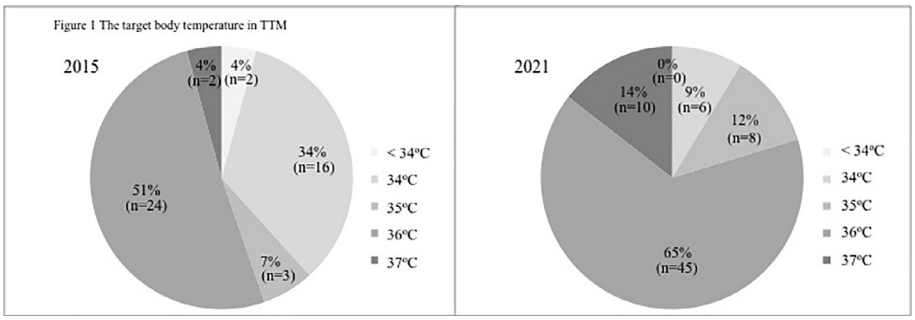

Fig. 1. Target body temperature for TTM. Respondents were asked to choose the target body temperature for TTM as < 34.0 °C, 34.0 °C, 35.0 °C, 36.0 °C, and 37.0 °C. The number of institutions conducting brain normothermia (at 36.0–37.0 °C) increased significantly, and that conducting brain hypothermia (at 35.0 °C or lower) decreased. Abbreviation: TTM, targeted temperature management.

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the efficacy of corticosteroids for AE caused by a cytokine storm. For AESD, the most frequent AE in Japan, corticosteroid and immunoglobulin therapies are currently used in many Japanese hospitals, with little change between 2015 and 2021, although there has been no specific treatment with sufficient evidence. This may be due to the low incidence of serious adverse events, the fact that these therapies can be performed in institutions without a PICU, and the lack of other effective treatment options. A registry for children with AE is now underway, and it is expected to show whether steroid treatment is effective for these AE syndromes.

The AE GL 2016 stated that mitochondrial rescue therapies involving the administration of supplements such as vitamins B1, B2, B6, C, and E, carnitine, coenzyme Q, biotin, and L-arginine may be used for the management of AE possibly associated with metabolic disorders. The number of institutions administering vitamins actually increased significantly for AESD, AERRPS/FIRES, and unclassified AE. Some recent studies showed that early administration of vitamins may be effective for AE not associated with metabolic disorders. Omata et al. showed that the sequelae of AE associated with the onset of febrile convulsive status epilepticus were significantly milder in patients treated with mitochondrial rescue within 24 h of diagnosis than those treated after 24 h or those without therapy [20]. Another study also suggested that early administration of vitamins B1, B6, and carnitine might reduce the risk of AESD [21].

Regarding continuous EEG monitoring, the number of institutions using EEG increased significantly for all syndromes other than ANE and HSES, and this change may have been a beneficial change as a result of the AE GL 2016. According to the AE GL 2016: both conventional and amplitude-integrated EEG are useful for the diagnosis and treatment of AE (grade B) [1]. Consensus guidelines for the use of continuous EEG in adults and children published by the American Clinical Neurophysiology Society also recommend continuous EEG monitoring for the identification of non-convulsive seizures (NCS) and non-convulsive seizures epilepticus (NCSE) in critically ill patients with acute supratentorial brain injury and altered mental status [22]. Based on these recommendations, several studies have detected electrographic seizures in up to 50 % of children who underwent continuous EEG monitoring [23–31]. Reportedly, 34–75 % of such patients have only NCS or NCSE, based on the detection of seizures using continuous EEG [26–29]. Furthermore, children may be at a higher risk of NCS and NCSE than adults [29,32]. Some studies on critically ill children showed that an increased electrographic seizure burden was associated with high mortality or poor neurologic outcomes [23,27,31,33]. These findings suggest that electroconvulsive seizures may independently induce brain damage and exacerbate outcomes, and that continuous EEG monitoring and early antiepileptic drug management are needed for critically ill children. Additionally, EEG has been reported to be useful to distinguish AESD from febrile seizures before the onset of late seizures [34,35]. However, continuous EEG monitoring is not available in all institutions because of the high equipment and personnel costs and the requirement for EEG decoding skills.

According to the survey results, most physicians referred to the AE GL 2016 for the treatment of AE; thus, the influence of the guidelines was expected to be substantial. AE can result in death or serious neurological sequelae, and treatment tends to be aggressive. Some treatments, such as TTM and vitamin therapy, have not been established with sufficient evidence and are therefore not highly recommended in the AE GL 2016. However, these treatments may have gained recognition and implementation due to their inclusion in the guidelines. Further, many new reports have been published since the publication of the AE GL 2016, and the current observed practices are likely based on both the AE GL 2016 and new research. We hope that the guidelines will be revised regularly to include new findings.

Several limitations of this study should be acknowledged. First, there was selection bias. As a questionnaire-based survey for pediatric neurologists, this study did not reflect information from institutions where AE treatment is provided by physicians other than pediatric neurologists. The AE GL 2016 may benefit other specialty physicians more than pediatric neurologists who already have expertise in the field. In addition, survey responses were not obtained from all the institutions that provided AE treatment. However, we received responses from approximately-three-quarters of the JSCN-certified educational institutes that provide AE care, which we believe accurately reflects the broad practice of pediatric neurologists. Second, there was a recall bias because the respondents were asked to recall their practice from 5 years ago. Collecting retrospective data on medical practices at each institution is necessary to increase the survey accuracy. However, currently, no database registers such data from institutions nationwide, making it difficult to undertake such a research project.

In conclusion, from 2015 to 2021, the number of institutions performing TTM, vitamin administration, and continuous EEG monitoring increased significantly, and TTM was mainly managed through normothermia. Evidence on the efficacy and appropriate indication criteria for each treatment of AE is currently insufficient and must be accumulated in the future.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that

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could have appeared to influence the work reported in this paper.

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Author Contributions

Yuka Murofushi, the corresponding author, certifies that all authors participated sufficiently in the conception of the study, acquisition and interpretation of the data, and drafting of the manuscript. All authors have revised the manuscript, approved its final version, and have agreed to take responsibility for the integrity of the data and accuracy of the data analysis.

Specific authors carry a greater burden of responsibility and are listed below:

Yuka Murofushi planned the methodology of the study to reach valid conclusions, drafted the manuscript, and was responsible for the construction of the entire body of the manuscript.

Jun-ichi Takanashi also planned the methodology of the study to obtain valid conclusions and supervised the preparation of this article.

Hiroshi Sakuma, Hiroko Tada, and Masashi Mizuguchi critically revised the manuscript.

Conflict of Interest Disclosures

The authors declare no competing interests.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.braindev.2022.10.008.

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