Clinical time course of pediatric acute disseminated encephalomyelitis

Nishiyama, Masahiro ; Nagase, Hiroaki ; Tomioka, Kazumi ; Tanaka, Tsukasa ; Yamaguchi, Hiroshi ; Ishida, Yusuke ; Toyoshima, Daisaku ;…

(Citation)
Brain and Development,41(6):531-537

(Issue Date)
2019-06

(Resource Type)
journal article

(Version)
Accepted Manuscript

Clinical time course of pediatric acute disseminated encephalomyelitis

Masahiro NISHIYAMA[a*], Hiroaki NAGASE[a], Kazumi TOMIOKA[a], Tsukasa TANAKA[a,b], Hiroshi YAMAGUCHI[a,b], Yusuke ISHIDA[a], Daisaku TOYOSHIMA[b], Kyoko FUJITA[c], Azusa MARUYAMA[b], Kaori SASAKI[c], Yoshinobu OYAZATO[c], Taku NAKAGAWA[d], Yuichi TAKAMI[d], Kandai NOZU[a], Noriyuki NISHIMURA[a], Ichiro Nakashima[e], Kazumoto IIJIMA[a]

[a]Department of Pediatrics, Kobe University Graduate School of Medicine, Kobe, Japan

[b]Department of Neurology, Hyogo Prefectural Kobe Children's Hospital, Kobe, Japan

[c]Department of Pediatrics, Kakogawa Central City Hospital, Kakogawa, Japan

[d]Department of Pediatrics, Japanese Red Cross Society Himeji Hospital, Himeji, Japan.

[e]Department of Neurology, Tohoku Medical and Pharmaceutical University, Sendai, Japan

23 text pages, 2 figures, 2 tables

***Corresponding author:**

Masahiro Nishiyama, M.D. Ph.D.

Department of Pediatrics, Kobe University Graduate School of Medicine

7-5-2, Kusunoki-Cho, Chuo-Ku, Kobe, Hyogo 650-0017, Japan

Tel: +81-78-382-6090, Fax: +81-78-382-6099

E-mail: nishiyan0203@yahoo.co.jp

Abstract

The detailed clinical time course in acute disseminated encephalomyelitis (ADEM) from initial symptoms, through exacerbation, to remission has not been widely reported. Hence, this study aimed to investigate the clinical time course of pediatric ADEM. This was a multicenter retrospective study based on registry data from medical chart reviews. The study included children who met the international consensus diagnostic criteria for ADEM. The patients comprised 18 boys and 6 girls, with a mean age of 5.5±3.3 years at onset. From onset, the time until peak neurological symptoms, time until initial improvement, and time until full recovery was 3.1±3.7 days, 6.0±4.5 days, and 26±34 days, respectively. Twenty-three (96%) patients were treated with high-dose methylprednisolone (mPSL) with a mean duration of 4.1±4.0 days from onset. The condition of 15 patients (65%) improved within 3 days of high-dose mPSL initiation, whereas, that of four patients began to improve after >5 days of high-dose mPSL initiation. Only one patient (4%) did not achieve full recovery despite treatment with high-dose mPSL, intravenous immunoglobulin, and plasma exchange. This study presents the detailed clinical time course in pediatric ADEM in Japan. Progression of neurologic deficits typically lasts a few days, with initial improvement in 1 week leading to full recovery within 1 month.

Introduction

Acute disseminated encephalomyelitis (ADEM) is an inflammatory demyelinating disease characterized by polyfocal clinical symptoms and encephalopathy and magnetic resonance imaging (MRI) findings consistent with demyelination [1]. ADEM often occurs after a viral infection between 2 days and 4 weeks [2, 3]. Neurological symptoms have been reported to progress within several days; however, reports on the clinical time course of this disease are limited [4]. Particularly, the duration from onset, through exacerbation and nadir, to remission in ADEM has not been widely reported [5]. Studies have shown that high-dose methylprednisolone (mPSL), which ameliorates central nervous system inflammation, is the main first-line treatment choice for ADEM [2, 3]; other options include intravenous immunoglobulin (IVIg) and plasma exchange [2, 3]. However, the effectiveness of these treatments for ADEM has not been confirmed because no prospective clinical trials have been conducted. Hence, we conducted a multicenter clinical observational study to investigate clinical features of ADEM, especially, the clinical time course and responsiveness to high-dose mPSL.

Materials and Methods

Study design and subjects

This retrospective, clinical observational study was conducted with the approval of the Ethics Committee of Kobe University Graduate School of Medicine, Kobe Children's Hospital, Kakogawa Central City Hospital, and Himeji Red Cross Hospital. As this study project was open to the public via our homepage, the need for formal informed consent from individual participants was waived. Two tertiary referral hospitals and 2 regional central hospitals participated in this study. Patients who were admitted and diagnosed with acquired demyelinating syndrome (ADS) in each hospital between January 2008 and October 2017 were identified and registered in a central database by members of the pediatric ADS study group. We reviewed the medical charts and investigated the clinical course of the disease in each patient, MRI and cerebrospinal fluid (CSF) examination results, treatments, and outcomes of the registered patients. Subsequently, we included patients with a definite diagnosis of ADEM based on the criteria proposed by the International Pediatric Multiple Sclerosis Study Group (IPMSSG) [1]. Patients with prior neurological disease, including intellectual disability, epilepsy, or paralysis were excluded. Patients without complete data to aid in evaluating the clinical time course were excluded from this study.

Definitions

All patients in this study fulfilled the diagnosis criteria for ADEM at the first presentation of a demyelinating event; however, some were diagnosed with multiple sclerosis (MS) or multiphasic ADEM (mADEM) during the follow-up period. The diagnosis was conducted based on the definitions proposed by the IPMSSG [1]. To evaluate the clinical time course, several terminologies were defined in this study. The onset of the disease was defined as the day on which a neurological symptom appeared and was established as day 1 in accordance with a previous study [6]. The nadir was defined as the period during which the patient presented with the worst neurological symptoms during the entire duration of the hospital stay. The initial improvement was defined as the first day on which the patient presented with an obvious commencement of improvement in neurological symptoms, which was determined by clinicians. Full recovery was defined as the state in which patients and their parents noticed an absence of neurological symptoms, even if the clinicians observed neurological signs on physical examination. Additionally, abnormal findings on MRI were defined as a high intensity area on a T2-weighted image as identified by radiologists in each hospital.

High dose-mPSL protocol

Subjects in the study were often treated with high dose-mPSL. One course of high dose-

mPSL consisted of 30 mg/kg/day (maximum 1000 mg/day) for 3 continuous days. When patients did not sufficiently recover, an additional course of high-dose-mPSL of 30 mg/kg/day for 3 continuous days after a 4-day interval was administered. Three or more courses of high-dose mPSL were sometimes administered in patients without full recovery.

Results

Symptoms

Twenty-four patients who met the inclusion criteria for ADEM were included in this study. The characteristics of the patients are presented in Table 1. A total of 11 patients (46%) had the following infections within 1 month before onset: upper respiratory inflammation, 8 (33%); gastroenteritis, 2 (8%); and fever, 1 (4%). A specific virus associated with the preceding infections was not identified. Four patients (17%) received vaccinations for the following within 1 month before onset: influenza, 2 (8%); and Japanese encephalitis, 2 (8%). The patients presented with encephalopathy (71%), seizures (21%), motor paralysis (13%), gait disturbance (17%), cranial nerve abnormalities (25%), and/or bladder/rectal disturbance (4%) prior to admission. During the overall hospital stay, the incidence rose for each of: encephalopathy (100%),

seizures (38%), motor paralysis (38%), gait disturbance (42%), cranial nerve abnormalities (38%), and/or bladder/rectal disturbance (29%). Additionally, following onset of the disease, the patients were admitted to the hospital on day 3.0 ± 3.7, and neurological symptoms reached their nadir on day 4.1 ± 3.7. These results indicate that neurological symptoms become progressively diverse and worsen even after admission. Clinical time courses are shown in Figure 1. Symptoms worsened until day 4.1 ± 3.7, and began improving on day 7.0 ± 4.5. Full recovery was achieved on day 27 ± 34.

Examination findings

MRI revealed abnormal findings for all patients. Initial brain MRI, which was conducted on day 4.1 ± 3.0 revealed abnormalities in 21 (88%) patients, and the second brain MRI revealed that these abnormalities remained in 3 (12%) patients (Case 12, 13, 14). The initial MRI was conducted on days 5, 2, and 3 and the second MRI was conducted on days 13, 3, and 9 for cases 12, 13, and 14, respectively. Of 12 patients who underwent spinal MRI, abnormal findings were observed in 2 (17%). Anti-myelin oligodendrocyte glycoprotein (MOG) antibody levels were assessed in 3 patients using cell-based assays as previously described, and the antibody was positive in all 3 patients (Case 3, 13, 17) [7]. Anti-MOG antibody levels were assessed for one patient in the

acute phase while for the other 2 patients, this examination was conducted following repetitive recurrences without encephalopathy. The latter 2 patients were finally diagnosed with MS. Three patients with anti-MOG antibody had abnormal MRI lesions in the following regions: cortex, 1 (33%); subcortical white matter, 3 (100%); deep white matter, 2 (66%); basal ganglia, 2 (66%); brainstem, 1 (33%); cerebellum, 2 (66%); and spinal cord or optic nerve, none. Anti-aquaporin4 (AQP4) antibody levels were assessed in 9 patients, with negative results in all. Pleocytosis, elevated protein levels, elevated myelin basic protein (MBP) levels, and elevated immunoglobulin G (IgG) index were identified in the CSF of 83%, 50%, 57%, and 19% of patients, respectively.

Treatments and outcome

Twenty-three (96%) patients were treated with high-dose mPSL. Six patients were treated with 1 course of high-dose mPSL, 5 patients were treated with 2 courses, 10 patients were treated with 3 courses, and 2 patients were treated with 4 or more courses. High-dose mPSL was initiated on day 5.1 ± 4.0. The clinical time course and initiation of high-dose mPSL for each patient are shown in Figure 2. Fifteen of twenty-three patients (65%) (Case 1, 3, 4, 5, 7, 11, 12, 13, 15, 16, 17, 18, 19, 20, 22) showed an

initial improvement within 3 days of high-dose mPSL initiation. Particularly, three patients (Case 12, 17, 22) showed initial improvement soon after the initiation of high-dose mPSL after 10 days or more of symptom worsening or during the nadir period. Conversely, the nadir period continued for more than 5 days after the initiation of high-dose mPSL in four patients (Case 9, 10, 23, 24), even though these patients had begun taking high-dose mPSL within 4 days of onset. Further, IVIg administration was initiated in four patients on day 12.2 ± 8.3. Plasma exchange was initiated in one patient (Case 24) on day 37; however, this patient did not recover fully and developed persistent motor paralysis, which continued even after discharge. Six (25%) patients exhibited sequelae at discharge; however, all patients, except for the patient treated with plasma exchange, achieved full recovery after discharge.

During the long-term follow-up of 1.9 ± 2.0 years (Table 2), 4 (17%) patients experienced recurrence. Of these 4 patients, 2 were diagnosed with MS and 2 were diagnosed with mADEM. Of the 23 patients with high-dose mPSL therapy, 8 continued taking oral prednisolone (PSL) for more than 30 days (32–69 days); 1 among them experienced recurrence 3 months after stopping PSL. Fifteen patients stopped taking PSL within 1 month after high-dose mPSL; 3 among them experienced recurrence 3 weeks, 5 months, and 12 months after stopping PSL, respectively. The final Expanded

Disability Status Scale scores (EDSS) were 0.0 in 21 (88%) patients. In the remaining 3 patients, EDSS was 1.0, 1.0, and 6.0. The two patients with a final EDSS of 1.0 achieved full recovery in the acute phase; however, they had unexpected decline with epilepsy or attention deficit hyperactivity disorder (ADHD) thereafter. The final diagnosis in these two patients was ADEM, and the relationship between ADEM and the decline was unclear.

Discussion

In contrast to most previous studies of pediatric ADEM [3, 8-12], this study described the clinical time courses after the patients presented with neurological symptoms. To the best of our knowledge, only a few studies have shown the clinical time courses of ADEM [4, 5, 13, 14]. Tenembaum et al. reported that neurological symptoms worsened after a mean period of 4.5 days [4], Schwarz et al. reported a median duration from onset to admission of 4 days (range, 0–14 days) in 26 adults with ADEM [14], and Anlar et al. reported that the initial improvement after high-dose mPSL began after 1–4 days [13]. However, none of these studies examined patients with ADEM after the diagnostic criteria of the 2007 IPMSSG were implemented, and therefore these studies included patients with and without encephalopathy [4, 13, 14].

Omata et al. presented the clinical time course of patients diagnosed with ADEM according to the 2007 IPMSSG criteria; however, the sample sizes were comparatively smaller (7 patients) than those in the present study [5]. In Omata et al.'s case series, the initial MRI was conducted on day 20.7, and disseminated lesions were identified in all cases on initial MRI [5]. In contrast, in our study, the initial MRI was conducted on day 4.1, and abnormalities were not identified in 3 patients on initial MRI; hence, our findings indicate that it is important to conduct a repeat MRI scan, in line with another study reporting that delayed abnormality was observed on MRI in 7 of 13 ADEM cases [6].

Furthermore, the duration from presentation of neurological symptoms to full recovery has comprehensively been described for the first time in this study. The duration of hospital stay in our study was longer than that reported in previous studies [5, 14]. This could be explained by the therapeutic policy of the participating hospital, as high-dose mPSL of 30 mg/kg/day for 3 days/course and 2-3 courses (2-3 weeks) was often administered at our hospital. Another possibility is that our study included several severe cases, which may have influenced the clinical time courses.

Characteristics such as sex, symptoms, and examination results of pediatric ADEM have been well documented in previous studies including studies with the 2007

206 IPMSSG criteria [8-12, 15-18]. The male:female ratio was 1.0:1 in a US and Israeli
207 study, 1.3:1 in a French or Kuwaiti study, 0.75:1 in a German study, and 2.0:1 in a
208 Japanese study [10-12, 15, 17, 18]. The rates of fever, headache, and vomiting were
209 previously reported to be 42–73%, 19–57%, and 23–38%, respectively [8, 10-12, 15,
210 17]. The rates of motor paralysis, sensory disturbance, and ataxia were 23–70%, 10–
211 15%, and 19–44%, respectively [10, 11, 15, 17]. Previous reports showed the rate of
212 pleocytosis, elevated protein, and elevated MBP to be 51–85%, 34–36%, and 42% in
213 the CSF [10-12, 18]. Our results are consistent with those from these previous studies.
214 The rate of elevated IgG index and presence of oligoclonal bands (OCBs) in our study
215 are also consistent with the findings in previous studies wherein the rate of elevated IgG
216 index and the presence of OCBs were 2–36% and 5–19% [10-12, 17, 18], respectively.
217 MRI findings revealed less cortical involvement in our study than in a previous study
218 (46%) [11]; however, subcortical white matter involvement was higher than that in
219 previous studies (42–67%) [10, 11]. These differences could be explained by the
220 ambiguity in radiological interpretation between our study and previous studies [10, 11].
221 Abnormal lesions in the brainstem and cerebellum, which were previously reported to
222 be more predominant in children than in adults with MS [19], were not as common in
223 our study as compared with those in previous studies (29–54% and 30–35%) [10, 11].

Anti-MOG antibodies were detected in all 3 patients who underwent the examination in this study (Case 3, 13, 17). Because anti-MOG antibodies were not examined in most of the patients in this study, we could not compare the responses in patients with to those without anti-MOG antibody examinations. However, treatment response to high-dose mPSL was rapid in these 3 patients, which supports the previous report that MOG antibody-positive patients appear to respond to steroids rapidly in neuromyelitis optica [20]. Our patients with anti-MOG antibody did not show predominance of MRI lesions in the brainstem and spinal cord as reported by Baumann et al [21], although our sample size was relatively small.

The prognosis of ADEM was reported to be favorable, but varied; the complete recovery rate was reported to be 57%–92% in several pediatric cohorts of ADEM between 2000 and 2004 [3]. A recent pediatric study showed that the rate of sequelae was 17% in pediatric ADEM, 21% in multifocal clinically isolated syndrome (CIS), and 50% in MS [11]. Our results are consistent with those of previous studies and support findings that the outcome of pediatric ADEM was more favorable than that of pediatric multifocal CIS [3, 11, 22, 23]. On the other hand, other recent studies showed that there are lasting neurocognitive and psychosocial deficits including ADHD and epilepsy in pediatric ADEM, and even children who were considered to have fully recovered at

242 discharge may be affected [17, 24, 25]. Our study also included two patients with
243 ADHD or epilepsy, despite them achieving full recovery in the acute phase.
244 High-dose corticosteroids are widely used as a first-line therapy for pediatric
245 ADEM based on expert opinions and observational studies [2, 3, 16]. We observed that
246 more than half of the patients in our study responded rapidly to high-dose mPSL and
247 this is consistent with the observations in a previous study [13]. However, a few patients
248 in this study showed no sign of improvement within several days after initiation of high-
249 dose mPSL. Anlar et al. reported that the period from mPSL administration to initial
250 improvement was not different between those receiving mPSL within 7 days of onset
251 versus later mPSL initiation [13]. Our results were in line with those in this previous
252 report [13]. However, we did not conduct a statistical analysis because of the small
253 number of patients receiving mPSL after 7 days. These findings suggest that it is
254 important to first establish the exact diagnosis and differentially diagnose the disease
255 rather than rapidly initiate high-dose mPSL as many disorders mimic ADS, including
256 genetic/metabolic disorders, infectious diseases, and neoplasms [16, 19]. Moreover,
257 response to corticosteroids was favorable in patients with delayed abnormality on MRI,
258 which was inconsistent with a previous study [6].
259 In our study, 1 of 8 patients with a slow taper of PSL (≥ 30 days) and 3 of 15

patients with a rapid taper of PSL (< 30 days) experienced recurrence. Slow tapering of PSL (4–6 weeks) is recommended because rapid tapering of PSL (≤ 3 weeks) has been shown to increase the risk of relapse [16, 26]. However, these recommendations are based on retrospective studies that included both ADEM and CIS when the diagnostic criteria of the IPMSSG was applied [1, 26]. It is also reported that steroid withdrawal might cause rapid relapse in MOG antibody-positive patients [27]. A prospective study that divides the subjects into ADEM/CIS and MOG antibody-positive/negative groups could clarify the requirements for an adequate tapering of PSL.

The present study had several limitations. First, owing to the retrospective design, the accuracy of the clinical time course of symptoms was limited. Particularly, initial improvement of neurological symptoms was determined less objectively. Second, the sample size was smaller than that of previous studies of pediatric ADEM [4, 12, 16]; therefore, we could only conduct a descriptive study and could not perform statistical analyses. However, considering that these previous descriptive studies applied the 2007 or 2012 IPMSSG criteria, our study was comparatively large [5]. Finally, even if the new IPMSSG criteria are strictly applied, ADEM may still remain a heterogeneous condition [16]. Further, the initial diagnosis of ADEM was modified later in some patients. Although the results obtained in this study should be interpreted with caution,

they still present a detailed clinical time course of pediatric ADEM. Our main findings that 1) progression of neurological symptoms typically lasts a few days, 2) neurological symptoms generally begin improving in 1 week leading to full recovery within 1 month, 3) abnormal lesions may not be identified on initial MRI, and 4) more than half of the patients have a rapid response to high-dose mPSL, will be useful for clinical management of pediatric ADEM.

Acknowledgments

This work was partly supported by a Grant-in-Aid for Young Scientists (B) (18K15711) of JSPS KAKENHI. The authors thank all participating physicians and nurses who took care of the patients. We also thank the children and their parents for their kind collaboration.

References

[1] Krupp LB, Tardieu M, Amato MP, Banwell B, Chitnis T, Dale RC, et al. International Pediatric Multiple Sclerosis Study Group criteria for pediatric multiple sclerosis and immune-mediated central nervous system demyelinating disorders: revisions to the 2007 definitions. Mult Scler 2013;19:1261-7.

[2] Alper G. Acute disseminated encephalomyelitis. J Child Neurol 2012;27:1408-25.

[3] Tenembaum S, Chitnis T, Ness J, Hahn JS. Acute disseminated encephalomyelitis. Neurology 2007;68:S23-36.

[4] Tenembaum S, Chamoles N, Fejerman N. Acute disseminated encephalomyelitis: a long-term follow-up study of 84 pediatric patients. Neurology 2002;59:1224-31.
[5] Omata T, Fujii K, Tanabe Y, Arai H, Motojima T. Acute disseminated encephalomyelitis: the time until diagnosis and its subsequent course in children. J Child Neurol 2014;29:28-30.
[6] Khurana DS, Melvin JJ, Kothare SV, Valencia I, Hardison HH, Yum S, et al. Acute disseminated encephalomyelitis in children: discordant neurologic and neuroimaging abnormalities and response to plasmapheresis. Pediatrics 2005;116:431-6.
[7] Sato DK, Callegaro D, Lana-Peixoto MA, Waters PJ, de Haidar Jorge FM, Takahashi T, et al. Distinction between MOG antibody-positive and AQP4 antibody-positive NMO spectrum disorders. Neurology 2014;82:474-81.
[8] Torisu H, Kira R, Ishizaki Y, Sanefuji M, Yamaguchi Y, Yasumoto S, et al. Clinical study of childhood acute disseminated encephalomyelitis, multiple sclerosis, and acute transverse myelitis in Fukuoka Prefecture, Japan. Brain Dev 2010;32:454-62.
[9] Hung PC, Wang HS, Chou ML, Lin KL, Hsieh MY, Wong AM. Acute disseminated encephalomyelitis in children: a single institution experience of 28 patients. Neuropediatrics 2012;43:64-71.
[10] Koelman DL, Chahin S, Mar SS, Venkatesan A, Hoganson GM, Yeshokumar AK, et al. Acute disseminated encephalomyelitis in 228 patients: A retrospective, multicenter US study. Neurology 2016;86:2085-93.
[11] Yamaguchi Y, Torisu H, Kira R, Ishizaki Y, Sakai Y, Sanefuji M, et al. A nationwide survey of pediatric acquired demyelinating syndromes in Japan. Neurology 2016;87:2006-15.
[12] Mikaeloff Y, Suissa S, Vallee L, Lubetzki C, Ponsot G, Confavreux C, et al. First episode of acute CNS inflammatory demyelination in childhood: prognostic factors for multiple sclerosis and disability. J Pediatr 2004;144:246-52.
[13] Anlar B, Basaran C, Kose G, Guven A, Haspolat S, Yakut A, et al. Acute disseminated encephalomyelitis in children: outcome and prognosis. Neuropediatrics 2003;34:194-9.
[14] Schwarz S, Mohr A, Knauth M, Wildemann B, Storch-Hagenlocher B. Acute disseminated encephalomyelitis: a follow-up study of 40 adult patients. Neurology 2001;56:1313-8.
[15] Elhassanien AF, Aziz HA. Acute demyelinating encephalomyelitis: Clinical characteristics and outcome. J Pediatr Neurosci 2013;8:26-30.
[16] Pohl D, Alper G, Van Haren K, Kornberg AJ, Lucchinetti CF, Tenembaum S, et

al. Acute disseminated encephalomyelitis: Updates on an inflammatory CNS syndrome. Neurology 2016;87:S38-45.

[17] Shilo S, Michaeli O, Shahar E, Ravid S. Long-term motor, cognitive and behavioral outcome of acute disseminated encephalomyelitis. European Journal of Paediatric Neurology 2016;20:361-7.

[18] Pohl D, Hennemuth I, von Kries R, Hanefeld F. Paediatric multiple sclerosis and acute disseminated encephalomyelitis in Germany: results of a nationwide survey. Eur J Pediatr 2007;166:405-12.

[19] Yeh EA, Chitnis T, Krupp L, Ness J, Chabas D, Kuntz N, et al. Pediatric multiple sclerosis. Nat Rev Neurol 2009;5:621-31.

[20] Kitley J, Woodhall M, Waters P, Leite MI, Devenney E, Craig J, et al. Myelin-oligodendrocyte glycoprotein antibodies in adults with a neuromyelitis optica phenotype. Neurology 2012;79:1273-7.

[21] Baumann M, Sahin K, Lechner C, Hennes EM, Schanda K, Mader S, et al. Clinical and neuroradiological differences of paediatric acute disseminating encephalomyelitis with and without antibodies to the myelin oligodendrocyte glycoprotein. J Neurol Neurosurg Psychiatry 2015;86:265-72.

[22] Ketelslegers IA, Catsman-Berrevoets CE, Neuteboom RF, Boon M, van Dijk KG, Eikelenboom MJ, et al. Incidence of acquired demyelinating syndromes of the CNS in Dutch children: a nationwide study. J Neurol 2012;259:1929-35.

[23] Neuteboom RF, Boon M, Catsman Berrevoets CE, Vles JS, Gooskens RH, Stroink H, et al. Prognostic factors after a first attack of inflammatory CNS demyelination in children. Neurology 2008;71:967-73.

[24] Beatty C, Bowler RA, Farooq O, Dudeck L, Ramasamy D, Yeh EA, et al. Long-Term Neurocognitive, Psychosocial, and Magnetic Resonance Imaging Outcomes in Pediatric-Onset Acute Disseminated Encephalomyelitis. Pediatr Neurol 2016;57:64-73.

[25] Burton KLO, Williams TA, Catchpoole SE, Brunsdon RK. Long-Term Neuropsychological Outcomes of Childhood Onset Acute Disseminated Encephalomyelitis (ADEM): a Meta-Analysis. Neuropsychol Rev 2017;27:124-33.

[26] Dale RC, de Sousa C, Chong WK, Cox TC, Harding B, Neville BG. Acute disseminated encephalomyelitis, multiphasic disseminated encephalomyelitis and multiple sclerosis in children. Brain 2000;123 Pt 12:2407-22.

[27] Ramanathan S, Dale RC, Brilot F. Anti-MOG antibody: The history, clinical phenotype, and pathogenicity of a serum biomarker for demyelination. Autoimmun Rev 2016;15:307-24.

371

372 **Figure legends**

373 **Figure 1.** Clinical time course of pediatric acute disseminated encephalitis. The square

374 represents the mean number of days, and the T-bars represent standard deviation.

375

376 **Figure 2.** Clinical time course for each patient. The filled-bar represents the worsening

377 period, the vertical lined-bar represents the nadir period, and the diagonal lined-bar

378 represents the improving period. The circle represents the initiation of high-dose mPSL.

379 The triangle represents the initiation of IVIg.

380 mPSL: methylprednisolone; IVIg: intravenous immunoglobulin.

381

382

383

Table 1
Characteristics of patients with acute disseminated encephalomyelitis

	ADEM n = 24
Age at onset, years	5.5 ± 3.3
Sex, male	18 (75)
Preceding infection or vaccination	
Infection within 1 month before onset	11 (46)
Days from preceding infection to onset	12 ± 6.2
Vaccination within 1 month before onset	4 (17)

Influenza	2 (8)
Japanese encephalitis	2 (8)
Days from vaccination to onset	13 ± 12
General symptoms	
Fever	15 (63)
Headache	6 (25)
Eye pain	2 (8)
Vomiting	7 (29)
Neurological symptoms	
Encephalopathy	24 (100)
Seizures	9 (38)
Motor paralysis	9 (38)
Sensory disturbance	2 (8)
Gait disturbance	10 (42)
Ataxia	8 (33)
Visual impairment	3 (13)
Nystagmus	3 (13)
Cranial nerve abnormalities	9 (38)
External ophthalmoplegia	2 (8)
Dysphagia	2 (8)
Dysarthria	6 (25)
Facial paresis	2 (8)
Bladder and rectal disturbance	7 (29)
CSF findings*	
Pleocytosis (>5 cells/mm^3)	20 (83)
Protein elevation (>40 mg/dL)	12 (50)
MBP >102 pg/mL	13 (57)**
IgG index >0.73	3 (19)***
Presence of OCBs	0 (0)****
Abnormal findings on MRI	
Cortex	4 (17)
Subcortical white matter	19 (79)
Deep white matter	15 (63)
Basal ganglia	12 (50)
Thalamus	6 (25)

Brainstem	5 (21)
Cerebellum	4 (17)
Spinal cord	2 (17)*****
Optic nerve	2 (8)
Treatment	
High-dose mPSL	23 (96)
Days from onset to initiation of high-dose mPSL	4.1 ± 4.0
IVIg	4 (17)
Plasma exchange	1 (4)
Outcome	
Duration of hospital stay, days	27 ± 22
Sequelae at discharge	6 (25)
Motor paralysis	3 (13)
Cognitive dysfunction	2 (8)
Ataxia	1 (4)
Bladder and rectal disturbance	1 (4)
Full recovery including after discharge	23 (96)
Days from onset to full recovery	26 ± 34

ADEM: acute disseminated encephalomyelitis; CSF: cerebrospinal fluid; MBP: myelin basic protein; IgG: immunoglobulin G; OCBs: oligoclonal bands; MRI: magnetic resonance imaging; mPSL: methylprednisolone; IVIg: intravenous immunoglobulin

Data are represented as mean ± SD or number (%).

*The maximum values of all examinations are presented. **n=23. ***n=16. ****n=21. *****n=12

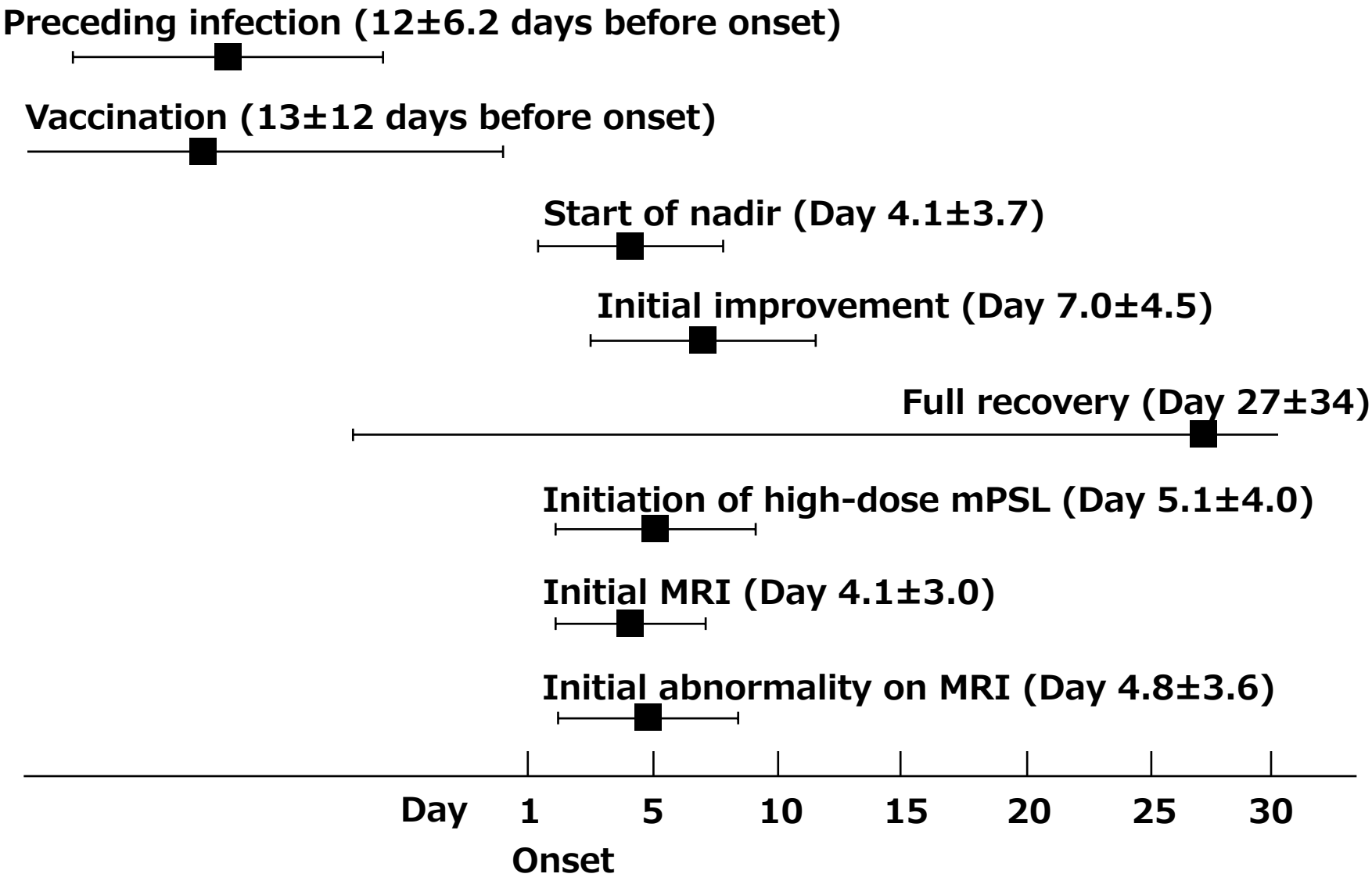
Table 2

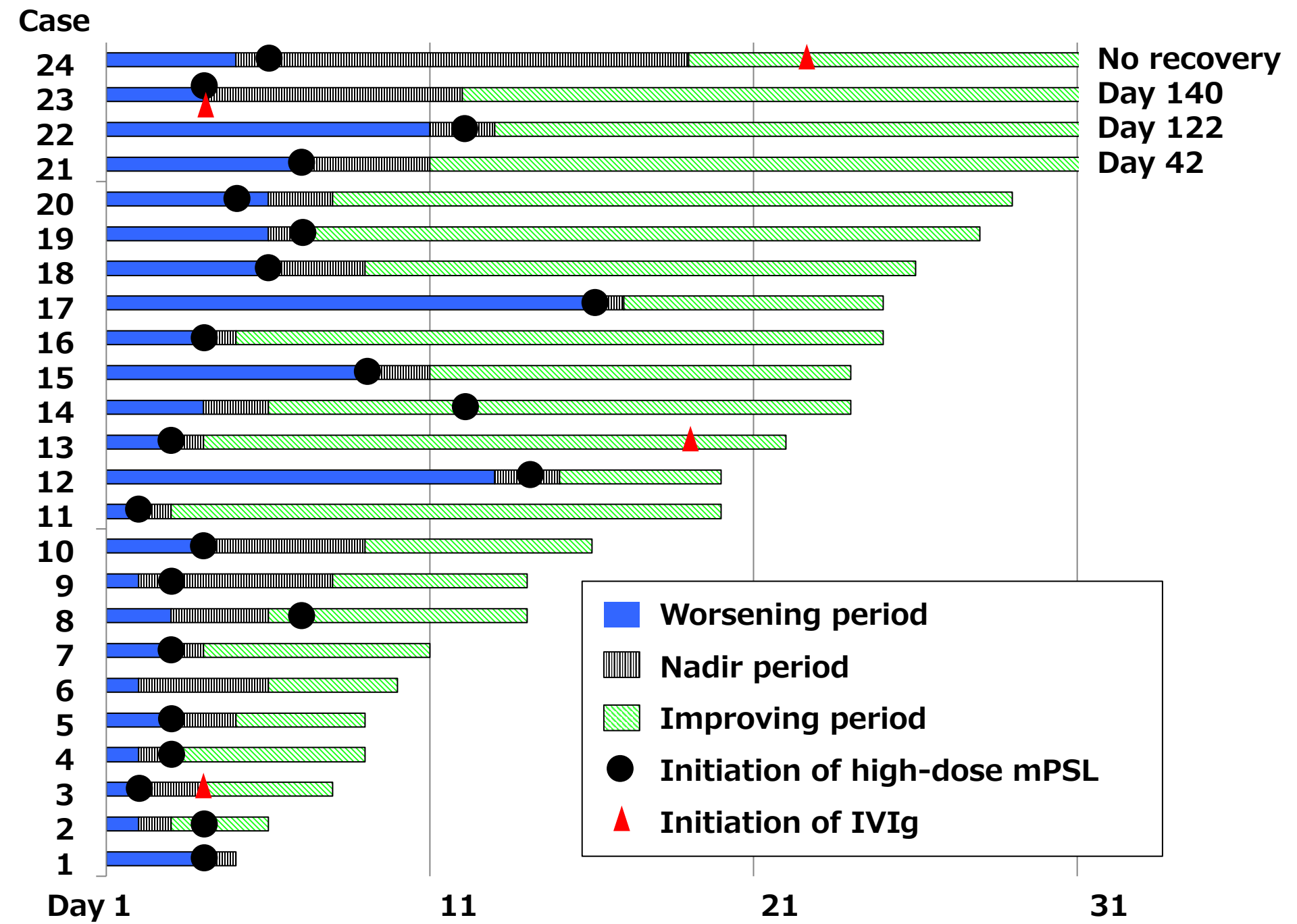
Long-term outcome of patients with acute disseminated encephalomyelitis

	ADEM (n = 24)
Follow-up duration, years	1.9 ± 2.0
Recurrence	4 (17)
Interval between first and second attack, years	0.5 ± 0.4
Final diagnosis during follow-up period	
ADEM	20 (83)
MS	2 (8)
mADEM	2 (8)
Sequelae during follow-up period	3 (13)
Motor paralysis	1 (4)
ADHD	1 (4)
Epilepsy	1 (4)
Final EDSS	
0.0	21 (88)
1.0	2 (8)
6.0	1 (4)

ADEM: acute disseminated encephalomyelitis; MS: multiple sclerosis; mADEM: multiphasic acute disseminated encephalomyelitis; ADHD: attention deficit hyperactivity disorder; EDSS: Expanded Disability Status Scale

Data are represented as mean ± SD or number (%).


Preceding infection (12±6.2 days before onset)
Vaccination (13±12 days before onset)
Start of nadir (Day 4.1±3.7)
Initial improvement (Day 7.0±4.5)
Full recovery (Day 27±34)
Initiation of high-dose mPSL (Day 5.1±4.0)
Initial MRI (Day 4.1±3.0)
Initial abnormality on MRI (Day 4.8±3.6)
Day
1
5
10
15
20
25
30
Onset


Case
24
23
22
21
20
19
18
17
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
No recovery
Day 140
Day 122
Day 42
Worsening period
Nadir period
Improving period
Initiation of high-dose mPSL
Initiation of IVIg
Day 1
11
21
31