Early steroid pulse therapy for children with suspected acute encephalopathy: A historical cohort study

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Abstract

Background

Steroid pulse therapy is widely used for virus-associated acute encephalopathy, especially the cytokine storm type; however, its effectiveness remains unknown. We aimed to investigate the effectiveness of early steroid pulse therapy for suspected acute encephalopathy in the presence of elevated aspartate aminotransferase (AST) levels.

Methods

We enrolled children admitted to Hyogo Children's Hospital between 2003 and 2017 with convulsions or impaired consciousness accompanied by fever (temperature > 38˚C). The inclusion criteria were: refractory status epilepticus or prolonged neurological abnormality or hemiplegia at six hours from onset, and AST elevation > 90 IU/L within six hours of onset. We excluded patients with a neurological history. We compared the prognosis between the groups with or without steroid pulse therapy within 24 hours. A good prognosis was defined as a Pediatric Cerebral Performance Category Scale (PCPC) score of 1–2 at the last evaluation, within 30 months of onset. Moreover, we analyzed the relationship between prognosis and time from onset to steroid pulse therapy.

Results

Fifteen patients with acute encephalopathy and five patients with febrile seizures were included in this study. Thirteen patients received steroid pulse therapy within 24 hours. There was no between-group difference in the proportion with a good prognosis. There was no significant correlation between PCPC and timing of steroid pulse therapy (rs = 0.253, p = 0.405).

Conclusions

Steroid pulse therapy within 24 hours did not improve the prognosis in children with suspected acute encephalopathy associated with AST elevation.

Background

Acute encephalopathy is a serious complication of pediatric viral infections, including influenza. More than 300 patients are diagnosed with virus-associated acute encephalopathy every year in Japan, and the risk of mortality and sequelae is high [1]. There are three main categories of acute encephalopathy. The first category is caused by metabolic derangement, which consists of various inherited metabolic disorders and the classical Reye syndrome. The second category is characterized by a systemic cytokine storm and vasogenic brain edema, and includes Reye-like syndrome, hemorrhagic shock and encephalopathy syndrome (HSES), and acute necrotizing encephalopathy (ANE) [2, 3]. The third category is caused by excitotoxicity and includes acute encephalopathy with biphasic seizures and late reduced diffusion (AESD) [1, 2]. Sequelae of acute encephalopathy are observed in 44% of cases; specifically, sequelae or death was observed in 87% and 90% of ANE and HSES cases, respectively [1]. Several specific treatments for virus-associated acute encephalopathy have been proposed for improving prognosis [4]. Particularly, steroid pulse therapy is widely used for its anti-inflammatory action; however, it has little supporting evidence [4, 5]. Okumura et al. reported that steroid therapy within 24 hours of onset improved prognosis of ANE without brainstem lesions [6]. In contrast, Hayashi et al. reported no correlation between steroid therapy within 48 hours of onset and good outcome in acute encephalopathy with reduced subcortical diffusion [7].

Previously, we reported three risk factors for poor outcome as follows: 1) refractory status epilepticus (RSE); 2) prolonged neurological abnormality at 6 hours from onset; and 3) aspartate aminotransferase (AST) > 90 IU/L within 6 hours of onset [8, 9]. Moreover, we have previously assessed early specific treatment according to the aforementioned criteria and found that targeted temperature management (TTM) might be effective in children with suspected acute encephalopathy without AST elevation (> 90 IU/L within 6 hours of onset) [10]. However, its therapeutic effect in patients with elevated AST remains unknown.

We aimed to investigate the effectiveness of early steroid pulse therapy. We retrospectively compared patients with suspected acute encephalopathy with AST elevation who had received steroid pulse therapy within 24 hours of onset and those who had not.

Methods

Subjects

We enrolled pediatric patients admitted to Hyogo Children's Hospital from January 2003 to December 2017 with convulsions or disturbances of consciousness accompanied by fever (temperature > 38 °C). The inclusion criteria were as follows: 1) RSE, which was defined as convulsions longer than 60 minutes refractory to one or more anticonvulsants, or 2) prolonged neurological abnormality defined as a Glasgow Coma Scale (GCS) score of < 15 or hemiplegia at 6 hours from onset, and 3) AST > 90 IU/L within 6 hours of onset. We excluded patients with a past neurological history (epilepsy, chromosomal abnormality, brain hemorrhage, hydrocephalus, history of intracranial surgery, or intellectual disability), cerebrospinal fluid cell counts > 8/μL, trauma, and asphyxia.

Methods

We conducted a historical cohort study using a database. We collected information on patient background, treatment, prognosis, and final diagnosis. We divided the patients into two groups based on whether they had received steroid pulse therapy within 24 hours of onset. Next, we conducted between-group comparisons of the clinical characteristics and prognosis. Moreover, we examined the relationship between prognosis and time from onset to starting steroid pulse therapy. Also, among the steroid pulse group, we compared the clinical characteristics and prognosis between patients who taken steroid pulse within 6 hours of onset and those after 6 hours. The prognosis was determined using the Pediatric Cerebral Performance Category Scale (PCPC) [11] at the last evaluation, within 30 months of onset, with a PCPC score of 1–2 and 3–6 being defined as good and poor, respectively. Onset was defined as the time of initial recognition of neurological symptoms, including convulsions or impaired consciousness, based on previously determined criteria [8, 10, 12, 13].

Moreover, we collected information regarding sex, age at onset, convulsion duration, brainstem imaging abnormalities, blood test values within 6 hours of onset, presence or absence of TTM and a mitochondrial drug cocktail [14], and the number of used anticonvulsants. In case there were no data within 6 hours of onset, the blood test values were treated as missing values. We used the initial result in cases where multiple blood tests were performed.

Treatment protocol

We admitted patients to the pediatric intensive care unit and carefully monitored them. Upon obtaining consent from the parents, the patients underwent treatment for acute encephalopathy. In our institute, patients with AST > 90 IU/L have been receiving steroid pulse therapy since November 2009. We administered methylprednisolone 30 mg/kg (maximum 1000 mg) as steroid pulse therapy for 3 days; subsequently, we administered oral prednisolone for 4 days. Patients with stable cardiovascular dynamics were intubated and underwent TTM under general anesthesia as previously reported [15]. The targeted temperature of the regimen was 34.5 ± 0.5 °C before December 2005 and 36.0 ± 0.5 °C after January 2006. Moreover, patients with AST > 90 IU/L underwent a mitochondrial drug cocktail after March 2016.

Statistical Analysis

We conducted statistical analyses using Fisher's exact test and Mann-Whitney U test in EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (version 3.1.2; The R Foundation for Statistical Computing, Vienna, Austria) [16]. The correlations were examined using Spearman's rank correlation coefficient. The statistical significance level was set at $p < 0.05$.

Ethics Committee

This study was approved by the Ethics Committee of Kobe University Graduate School of Medicine and Kobe Children's Hospital, and was performed in accordance with the Declaration of Helsinki. The informed consent of the treatment for acute encephalopathy was obtained from the parents of participants. The need for informed consent to participate the study was waived due to the design of the observational study.

Results

Characteristics

A total of 1,077 patients were admitted with convulsions or disturbances of consciousness accompanied by fever. Among them, 42 patients had RSE or prolonged neurological abnormality, as well as AST > 90 IU/L within 6 hours from onset. We excluded 17 patients with a past neurological history, three patients with cerebrospinal fluid cells > 8/μL, one patient with trauma, and one patient with asphyxia. Finally, we included 20 patients; among them, 13 received steroid pulse within 24 hours while seven did not. Among those who did not receive steroid pulse therapy within 24 hours, none received it after 24 hours from onset. All the patients who did not receive steroid pulse therapy were admitted before March 2009 while those who did were admitted after October 2009. Two patients who did not receive steroid pulse therapy were given dexamethasone within 24 hours of onset (Table 1).

Table 1
Demographics, clinical course, treatment, and prognosis of all the patients (n = 20)

Steroid pulse	Age (months)	Sex	Convulsion Duration (minutes)	Number of anticonvulsants	Consciousness disturbance at six hours from onset	RSE	Brainstem imaging abnormalities	Maximum AST within 6 hours	Timing of steroid pulse (hours)	Dexamethasone within 24 hours	TTM
1	98	F	0	1	□	□	□	1760	3	□	□
2	17	F	105	4	□	□	□	163	8	□	□
3	27	F	125	3	□	□	□	142	15	□	□
4	1	F	20	2	□	□	□	103	11	□	□
5	8	M	72	4	□	□	□	116	22	□	□
6	19	F	78	4	□	□	□	159	8	□	□
7	137	M	210	4	□	□	□	150	5	□	□
8	2	M	0	3	□	□	□	247	9	□	□
9	62	F	211	4	□	□	□	1798	8	□	□
10	41	F	0	0	□	□	□	110	5	□	□
11	10	F	73	3	□	□	□	100	5	□	□
12	18	F	125	3	□	□	□	106	6	□	□
13	90	F	90	2	□	□	□	107	7	□	□
Non-steroid pulse											
1	13	M	310	2	□	□	□	7230		□	□
2	10	M	555	5	□	□	□	137		□	□
3	19	M	1	4	□	□	□	99		□	□
4	10	M	2	4	□	□	□	166		□	□
5	4	M	3	4	□	□	□	143		□	□
6	19	F	220	3	□	□	□	127		□	□
7	144	M	152	2	□	□	□	121		□	□

Abbreviations: AE, acute encephalopathy; AESD, acute encephalopathy with biphasic seizures and late reduced diffusion; FS, febrile seizure; HSES, hemorrha
mild encephalitis/encephalopathy with a reversible splenial lesion; PCPC, Pediatric Cerebral Performance Category scale; RSE, refractory status epilepticus; T

Regarding the background characteristics of the patients, there were significantly more girls in the group receiving steroid pulse than those in the group not receiving steroid pulse. There was no significant between-group difference in the age of onset, seizure duration, and brainstem imaging abnormalities. Regarding the initial blood test values, there was a lower platelet count in the group receiving steroid pulse therapy. There was no significant between-group difference in the levels of white blood cells, blood glucose, sodium, AST, lactate dehydrogenase, creatine kinase, creatinine, C-reactive protein, base excess, pH, lactic acid, and maximum AST within 6 hours. Regarding treatment, there was no significant between-group difference in the presence or absence of TTM, a mitochondrial drug cocktail, and the number of anticonvulsants used (Table 2). In the steroid pulse group, the background characteristics between patients who received steroid pulse therapy within 6 hours of onset (n = 4) and those who received the therapy after 6 hours (n = 9) were not different (Data not shown).

Table 2
Background characteristics of patients

	Steroid pulse n = 13	Non-steroid pulse n = 7	p-value
Sex, male	3 (23%)	6 (86%)	0.017
Age (months)	19 (10–62)	13 (10–19)	0.633
Convulsion duration (minutes)	78 (20–125)	152 (2.5–265)	0.302
Brainstem imaging abnormalities	2 (15%)	1 (14%)	1.000
WBC (/μL)	11200 (8100–18300)	18820 (15650–35300)	0.097
PLT ($\times 10^4$/μL)	26.3 (17.6–31.8)	37.8 (31.6–49.9)	0.030
Glu (mg/dL)	132 (87–214)	89 (26–165)	0.183
Na (mEq/L)	134 (133–138)	137 (135–143)	0.141
AST (U/L)	110 (100–163)	127 (64–140)	0.937
LDH (U/L)	571 (404–915)	492 (338–652)	0.843
CK (U/L)	231 (141–290)	424 (235–668)	0.234
Cre (mg/dL)	0.35 (0.28–0.61)	0.80 (0.56–0.85)	0.302
CRP (mg/dL)	0.52 (0.14–1.10)	0.20 (0.01–0.65)	0.284
BE	-9.6 (-11.1 to -6.5)	-13.6 (-14.3 to -9.1)	0.142
pH	7.16 (7.08–7.27)	7.19 (7.03–7.24)	0.899
Lac (mmol/L)	3.2 (2.5–5.1)	3.3 (2.2–7.3)	1.000
Maximum AST (U/L) within 6 hours	142 (107–163)	137 (124–155)	0.877
Targeted temperature management	9 (69%)	5 (71%)	1.000
Mitochondrial rescue drugs	5 (38%)	0 (0%)	0.114
Number of anticonvulsants	3 (2–3)	4 (2.5-4)	0.384

Abbreviations: AST, aspartate aminotransferase; BE, base excess; CK, creatinine kinase; Cre, creatinine; CRP, C-reactive protein; Glu, glucose; Lac, lactate; LDH, lactate dehydrogenase; PLT, platelet; WBC, white blood cell

Actual number (%) or median (first-third quartile) values are presented.

Between-group comparisons of the prognosis

The prognosis was good in five out of 13 patients (38%) and three out of seven patients (43%) in the groups with and without steroid pulse treatment, respectively; there was no significant between-group difference (Table 3). There was no significant between-group difference in the timing of the final prognostic evaluation within 30 months, with death cases excluded (Table 3). In the group with steroid pulse, three patients were diagnosed with cytokine storm-type acute encephalopathy, four with excitotoxicity type acute encephalopathy, three with unclassified acute encephalopathy, and three with febrile seizures (FS). In the group without steroid pulse, there were three cases of the cytokine storm type, one case of excitotoxicity, one case of unclassified, and two cases of FS. Table 3 shows the PCPC scores at the last follow-up within 30 months of onset.

Table 3
Prognosis and diagnoses

	Steroid pulse n = 13	Non-steroid pulse n = 7	p-value
Prognosis: Good (PCPC 1 – 2)	5 (38%)	3 (43%)	1.000
Timing of prognostic evaluation (months)	22.6 (19.3–24.3)	23.9 (12.5–24.7)*	0.966
Diagnosis	Acute encephalopathy 10 (77%) Cytokine storm type 3 (23%) AESD 4 (31%) Unclassified 3 (23%) Febrile seizure 3 (23%)	Acute encephalopathy 5 (71%) Cytokine storm type 3 (43%) AESD 1 (14%) Unclassified 1 (14%) Febrile seizure 2 (29%)	

Abbreviations: AESD, Acute encephalopathy with biphasic seizures and late reduced diffusion; PCPC, Pediatric cerebral performance category scale

Actual number (%) or median (first-third quartile) values are presented.

*Excluding one case of death.

Among four patients who had started steroid pulse therapy within 6 hours from onset, two (50%) had a good prognosis. Among nine patients who had started steroid pulse therapy within 6 and 24 hours from onset, three (33%) had a good prognosis. There was no significant between-group difference (p = 1.000).

Relationship between prognosis and time to starting steroid pulse therapy

Figure 1 shows the relationship between prognosis and the timing of starting steroid pulse therapy. There was no significant correlation between PCPC and timing of steroid pulse therapy (rs = 0.253, p = 0.405). After excluding two patients with brainstem lesions, there was no significant correlation between PCPC and timing of steroid pulse therapy (rs = 0.583, p = 0.060).

Discussion

Our findings suggest that steroid pulse therapy is not effective for suspected acute encephalopathy with elevated AST in children, despite early treatment induction. Okumura et al. reported that 58% of 12 patients with ANE without brainstem lesions who received steroid pulse therapy within 24 hours after onset presented no sequelae or mild sequelae. In contrast, all the patients who did not receive steroid pulse therapy within 24 hours had poor outcome, which indicated the possibility of improving prognosis by early steroid administration [6]. Hayashi et al. reported that steroid administration in 73% of children with acute encephalopathy reduced subcortical diffusion (24% received it within 48 hours after onset); however, it was not related to good outcome [7]. Moreover, Takanashi et al. reported that early steroid pulse therapy could be effective for encephalopathy secondary to Shiga toxin-producing *Escherichia coli* O111, which involves inflammatory cytokines [17]. These reports indicate that steroid therapy could be effective for cytokine storm-type acute encephalopathy.

Previous studies enrolled participants with a confirmed final diagnosis, including ANE or AESD. In contrast, we enrolled participants with suspected acute encephalopathy, which is a combination of symptoms (RSE or persistent disturbance of consciousness with AST elevation) within 6 hours of onset. Therefore, the final diagnosis in our study consisted of not only acute encephalopathy but also FS; furthermore, 6 (30%) patients were diagnosed with cytokine storm type-acute encephalopathy. Another unique trait of our study was the early induction of steroid pulse therapy. In this study, steroid pulse therapy was started within 12 hours in the majority of the patients while previous reports started steroid therapy within 24 hours [6] or after several days [17]. Our study included a heterogeneous population in terms of the final diagnosis; however, we included homogenous conditions or symptom combinations at 6 hours from onset. Therefore, it could be more feasible for actual clinical practice given the difficulty in the early differentiation of ANE or AESD from other diseases.

Based on our previous report, we adopted AST > 90 IU/L as the reference value for suspecting cytokine storm type-acute encephalopathy [8, 9]. Specifically, 23% and 43% of participants in the steroid pulse and no steroid pulse group, respectively, had the cytokine storm type. Compared to our previous study, we employed a much lower positive predictive value of AST > 90 IU/L for the cytokine storm type [8]. We hypothesized that an aggressive intervention, especially steroid pulse administration, could modify the final diagnosis from cytokine storm type to a different clinical picture. Nevertheless, early AST elevation seems to be a predictive factor for cytokine storm-type acute encephalopathy since the cytokine type was reported to comprise only 7% of virus-associated acute encephalopathy cases in Japan [1].

Other reports on the relationship between acute encephalopathy and AST elevation indicate that AST ≥ 46 IU/L on admission is an independent prognostic factor (odds ratio 18.5) for poor outcome in acute encephalopathy [18], while AST elevation on admission in influenza encephalopathy is a predictor of mortality (odds ratio for AST < 100: 100– 500: >500 = 1: 5.45: 17.38) [18, 19]. We found that 60% of participants had severe sequelae, which is consistent with previous reports and indicates that AST elevation predicts poor prognosis early in the disease.

Previously, we reported that clinical symptoms were dramatically worsened between a few and 13 hours from onset in a review on fatal acute encephalopathy [13]. Taken together with the above report and previous reports regarding treatment time-windows for various neuro-critical conditions including hypoxia,

stroke, status epilepticus, and acute encephalopathy [20–25], we hypothesize that very early intervention within several hours is needed for neuroprotection in severe acute encephalopathy. Therefore, in this report, we examined the relationship between prognosis and time from onset to starting steroid pulse therapy. Our study did not show effectiveness of steroid pulse therapy, not only within 24 hours but also within 6 hours, indicating two possibilities: 1) even early administration of steroid pulse therapy for neuro-critical conditions (RSE or persistent disturbance of consciousness with AST elevation) is ineffective, or 2) even earlier intervention is necessary for these neuro-critical conditions. The poor prognosis of Case 1 in Table 1, who had taken steroid pulse therapy within 3 hours of onset, supports the former possibility. On the other hand, the tendency of a better prognosis with the earlier timing of steroid pulse initiation (Fig. 1) may support the latter. To elucidate on this, it is necessary to accumulate data and investigate the relationship between time from onset to administration and prognosis.

All three patients with brainstem lesions had a poor prognosis with or without steroid pulse therapy. This is consistent with a previous report that patients with ANE with brainstem lesions had a poor prognosis regardless of steroid administration [6].

Between-group comparisons of the characteristics indicated that the steroid pulse group had more females, and lower platelet counts. To date, there has been no report on sex-based differences in the diagnosis and prognosis of acute encephalopathy. Regarding the differences in the platelet count, a previous study indicated that levels of $< 10 \times 10^4/\mu L$ were a poor prognostic factor in influenza encephalopathy [19]. However, a previous study reported that the platelet count in acute encephalopathy is higher in the poor prognosis group than in the good prognosis group (median $39.5 \times 10^4/\mu L$ vs. $25.1 \times 10^4/\mu L$) [18]. In this study, there was only one case with a platelet count of $< 10 \times 10^4/\mu L$ in the steroid pulse group, and none in the no steroid pulse group. Therefore, the relationship between a low platelet count and prognosis remains unknown.

Limitations

As mentioned earlier, one of the distinctive traits of our study was that our participants initially had homogenous conditions or symptoms but heterogeneous final diagnoses, which should be considered when interpreting our results. Our results do not directly suggest the ineffectiveness of steroid pulse therapy for a single pathology such as cytokine storm type-acute encephalopathy. This study had other limitations. First, this was a single-center retrospective study with a small sample size. Second, the patients who underwent steroid pulse therapy were admitted after October 2009 while those who did not were admitted before March 2009. Therefore, there might be potential between-group differences in the treatments for acute encephalopathy. Third, two patients received dexamethasone within 24 hours of onset in the no steroid pulse group, which might affect the results. However, given that both patients had a poor prognosis, dexamethasone is unlikely to have affected the conclusions. Finally, our findings cannot be applied to patients without AST elevation (AST $\leq$ 90 IU/L) within 6 hours of onset.

Conclusion

Our findings suggest that early steroid pulse therapy within 24 hours from onset does not improve the prognosis in children with suspected acute encephalopathy associated with AST elevation.

List Of Abbreviations

AESD = acute encephalopathy with biphasic seizures and late reduced diffusion

ANE = acute necrotizing encephalopathy

AST = aspartate aminotransferase

BE = base excess

CK = creatinine kinase

Cre = creatinine

CRP = C-reactive protein

FS = febrile seizure

GCS = Glasgow Coma Scale

Glu = glucose

HSES = hemorrhagic shock and encephalopathy syndrome

Lac = lactate

LDH = lactate dehydrogenase

MERS = clinically mild encephalitis/encephalopathy with a reversible splenial lesion

PCPC = Pediatric Cerebral Performance Category Scale

PLT = platelet

RSE = refractory status epilepticus

TTM = targeted temperature management

WBC = white blood cell

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Kobe University Graduate School of Medicine and Kobe Children's Hospital, and was performed in accordance with the Declaration of Helsinki. The need for informed consent was waived due to the design of the observational study.

Consent for publication

Not applicable.

Availability of Data and Materials

Data are not publicly available. However, data may be obtained from the appropriate section in the Kobe Children's Hospital upon reasonable request.

Competing Interests

The authors declare that they have no competing interests.

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Author contributions

YI and MN designed the project and first drafted the manuscript. AM and HN designed and supervised the project and critically reviewed and revised the manuscript for important intellectual content. HY, KY, and HT revised the manuscript for important intellectual content. ST, DT, YS, and KA collected data and critically revised the article. KN, HK, RT, and KI contributed to data analysis and interpretation, critical revision of the article, and final approval of the version to be published. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Figures

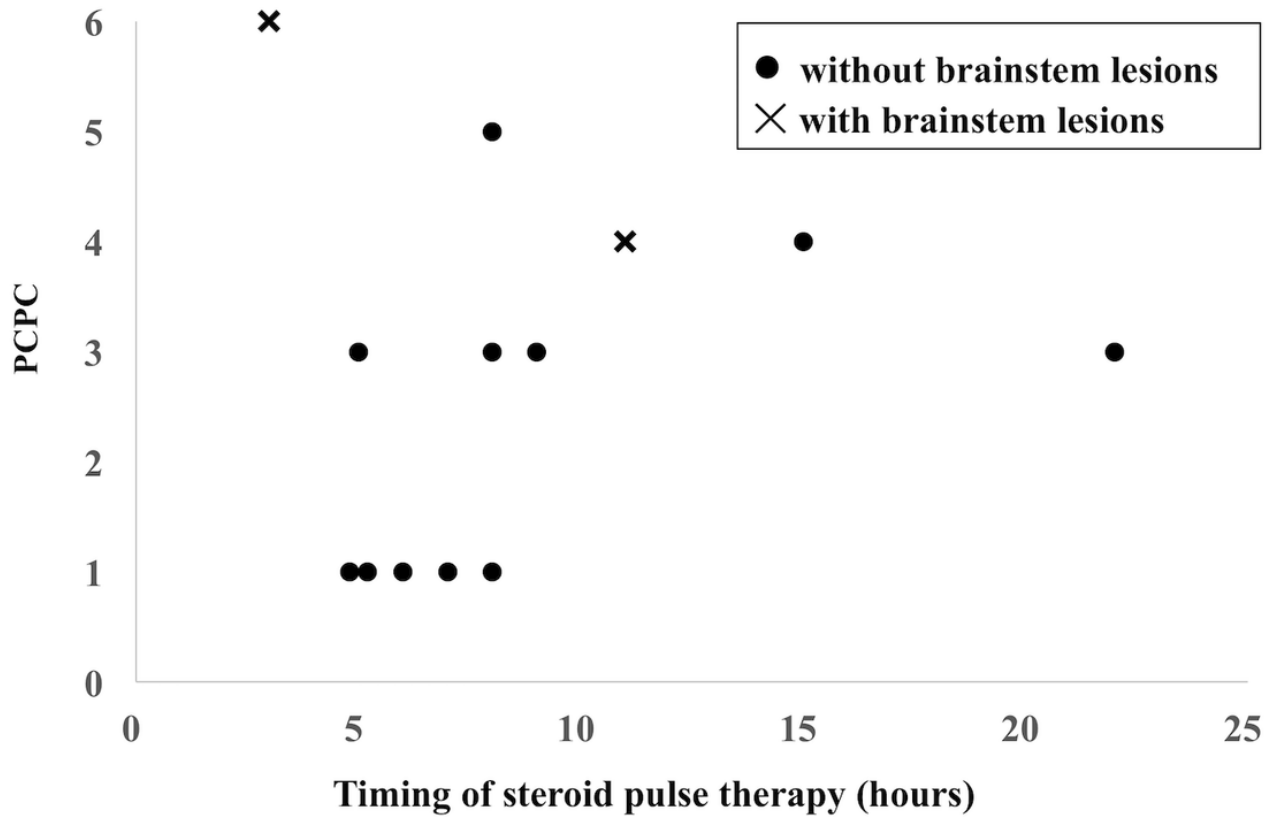

Figure 1

Relationship between prognosis and timing of steroid pulse therapy for suspected acute encephalopathy Abbreviation: PCPC, Pediatric Cerebral Performance Category scale