Intravenous methylprednisolone pulse therapy for children with epileptic encephalopathy

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Summary

The aim of this retrospective study of children affected by epileptic encephalopathy was to evaluate seizure frequency, electroencephalographic pattern and neuropsychological status, before and after intravenous methylprednisolone therapy.

Eleven children with epileptic encephalopathy were administered one cycle of intravenous methylprednisolone (15-30 mg/kg/day for three consecutive days, once a month for four months) in addition to constant dosages of their regular antiepileptic drugs.

The treatment resulted in statistically significant reductions of generalized slow spike-and-wave discharges (p<0.0028) and seizure frequency (p<0.013), which persisted even after methylprednisolone pulse therapy was stopped. A globally positive outcome was noted in 9/11 patients (81.8%). This methylprednisolone treatment regimen did not cause significant or persistent adverse effects.

We suggest that children with epileptic encephalopathy without an underlying structural lesion could be the best candidates for intravenous methylprednisolone pulse therapy.

KEY WORDS: epileptic encephalopathy, intravenous methylprednisolone, refractory epilepsy

Introduction

The epileptic encephalopathies are a group of conditions in which the epileptic activity itself – ictal or interictal, clinical or electroencephalographic – contributes to a picture of severe cognitive and behavioral impairments, which are beyond what might be expected from the underlying etiology alone (Wirrell et al., 2005; Berg et al., 2010). This diagnostic category was first introduced in 2001 in the Terminology and Classification Report of the International League Against Epilepsy (ILAE), and formally recognized in the 2006 ILAE Report. The epileptic encephalopathies are age-dependent syndromes that usually begin in infancy and early childhood (Wirrell et al., 2005), and they account for about 40% of all epilepsies occurring in the first three years of life (Guerrini, 2006). Some of these syndromes have a known etiology (e.g., genetic or metabolic/structural), but in most cases the underlying cause is unknown. The epileptic encephalopathies are typically drug resistant; polytherapy leads to seizure freedom in less than 5-10% of patients (Raspall-Chaure et al., 2008; Parisi et al., 2010). Consequently, there is a need to integrate new and specific therapeutic approaches, such as corticosteroid therapy. The corticosteroids most widely used in childhood encephalopathies are adrenocorticotropic hormone, hydrocortisone, prednisone and methylprednisolone. A good response to these drugs has been reported in various studies and case reports (Tsuru et al., 2000; Gupta and Appleton, 2005; Okuyaz et al., 2005; Gallagher et al., 2006; Inutsuka et al., 2006; Urbain et al., 2011; Heyman et al., 2012), as well as in the extended study conducted by Buzatu et al. (2009). However, the available evidence is limited, since it comes from uncontrolled trials and case reports and there is, as yet, no consensus on treatment dosages and durations (Veggiotti et al., 2012). Over the past two decades, high-dose intravenous corticosteroid pulse therapy (an approach already used to treat several neurological syndromes such as multiple sclerosis) has been used in various studies in the field of epilepsy in order to avoid the development of side effects and maintain long-term efficacy (Aykut-Bingol et al., 1996; Tsuru et al., 2000; Okuyaz et al., 2005; Sevilla-Castillo et al., 2009; Lichtenfeld et al., 2010; Mytinger et al., 2010; Heyman et al., 2012; Almaabdi et al., 2014). Administered according to different regimens (dosages ranging from 15 mg/kg/day for three or five days to 30 mg/kg/day for two or three days),
repeated at different intervals (weekly or monthly) (Donetti Dottin et al., 2013), it has been shown to be successful in different disorders (Landau-Kleffner syndrome, absence seizures, infantile spasms, epileptic encephalopathies in general).

The aim of this retrospective study of children with epileptic encephalopathy was to evaluate seizure frequency, electroencephalographic pattern and neuropsychological status, before and after intravenous methylprednisolone therapy.

Materials and methods

This case series consists of 11 children with epileptic encephalopathy (5 females and 6 males), studied at the Child Neuropsychiatry Unit, C. Mondino National Neurological Institute, University of Pavia, between February 2013 and May 2014. All the included patients met the ILAE diagnostic criteria for epileptic encephalopathy (Berg et al., 2010). Five of them (45.5%) had received a diagnosis of Lennox-Gastaut syndrome (LGS) and six (54.5%) a diagnosis of electrical status epilepticus during slow-wave sleep (ESES) according to the ILAE criteria (Berg et al., 2010). Their charts were retrospectively reviewed. Seizure frequency, before and after therapy, was assessed on the basis of parents’ reports (Tables I and II). Applying a neurocognitive assessment protocol already used in similar studies (Veggiotti et al., 2012; Pera et al., 2013), all the patients underwent serial neurological examinations, wake and sleep electroencephalogram (EEG), and at least one nocturnal polygraphic monitoring. Serial cognitive assessments were also performed using the standardized Wechsler scales or Raven’s Progressive Matrices according to the child’s age and degree of collaboration. If a child was unable to perform any of the standardized tests, clinical observation of that child’s behavior was recorded instead. The evaluation also included: blood pressure, body weight, complete blood count, glycemia, liver function and serum electrolytes. Intravenous methylprednisolone was given to the patients in addition to constant dosages of their regular antiepileptic drugs (AEDs). One cycle of pulse therapy consisted of intravenous methylprednisolone administered at 15-30 mg/kg/day for three consecutive days, once a month, for four months (12 infusions in total). Written informed consent was obtained from the children’s parents or legal guardians.

The patients were considered responders when seizure frequency after the pulse therapy was reduced by at least 50%. Descriptive analyses were performed and the variables were examined using chi-square statistics to identify the magnitude of any significant associations.

Results

Eleven children with drug-resistant epilepsy (six females, 54.5%; five males, 45.5%) comprised the study group. Five of them (45.5%) had received a diagnosis of LGS (3 males; 2 females) and six (54.5%) a diagnosis of ESES (3 males; 3 females). At the start of the study they ranged in age from 4.3 years to 16.1 years (mean age 9.1 years). Their mean age at onset of seizures was 47.3 months (range: 0.8-96 months).

In the LGS group, two patients (40%, both males) had a structural etiology, whereas the etiology was unknown in the other three (60%; 2 females and 1 male) (Table I). In the ESES group, two patients (33.3%, 1 female and 1 male) had a structural etiology, and four patients (66.6%, 2 females and 2 males) an unknown etiology (Table II). Overall, four patients (36.4%) presented underlying brain damage prior to the onset of epileptic encephalopathy and seven patients (63.7%) had no cerebral lesion before disease onset.

In the LGS group, three patients (60%) had epileptic spasms, one (20%) had generalized myoclonic seizures, and one (20%) had generalized tonic-clonic seizures. In the ESES group, four patients (66.6%) had focal seizures (complex partial in three and focal motor in one) and two patients (33.3%) had atypical absence seizures.

The frequency of epileptic seizures during the three months before the start of the pulse therapy was more than 50 seizures/month in five (45.5%) patients (4 LGS, 1 ESES), 20-50/month in one (9.1%) patient with LGS, 11-20/month in two patients (18.2%) with ESES, and less than one seizure/month in three patients (27.3%) with ESES. At the onset of seizures, two patients in the LGS group had a global developmental delay with aphasia (18.2%) and two patients (1 LGS, 1 ESES) had only a motor delay (18.2%). The remaining patients showed no developmental delay. In six patients (54.5%) the EEG prior to starting the methylprednisolone therapy showed continuous epileptiform activity occupying more than 85% of non-rapid eye movement (NREM) sleep and persisting for a minimum of three electroencephalographic recordings over a period of at least one month; these patients therefore met the diagnostic criteria for continuous spikes and waves during NREM sleep. In the other five patients electroencephalographic studies showed abnormal generalized spike-slow wave discharges (SWDs) at <2.5 Hz. These occur during both wakefulness and sleep and can show both interictal and ictal patterns. Bursts of fast activity (rhythmic rapid spikes at 10-20 Hz) during sleep are also characteristic.

At the beginning of the pulse therapy, six (54.5%) patients (4 LGS, 2 ESES) were taking three or more AEDs and five (45.5%) patients (1 LGS, 4 ESES) one or two AEDs. It is to be noted that nine patients (81.8%) had, in the course of their disease, tried more than four AEDs. In addition, one patient (2/F) had been implanted with a vagal nerve stimulator since April 2007 and another (3/F) had tried a ketogenic diet for two months. During a brief hospitalization (three days), intravenous methylprednisolone pulse therapy was added to the patients’ ongoing AED therapy,
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which ranged from one to six AEDs. All the patients completed one cycle of pulse therapy, after which they were monitored for a mean of 14.1 months (range: 8-16 months) to evaluate electroencephalographic modifications, seizure frequency, global outcome (behavior, neurological examination, cognitive abilities) and possible side effects. The frequency of epileptic seizures before the pulse therapy ranged from 1 to 90 per month, with a mean of 47.5 seizures/month. At follow-up it ranged from 0 to 80 seizures/month with a mean of 21.2 (p<0.013). In detail, more than 50 seizures/month were recorded in 1/11 patient (9.1%), 20-50/month in 4/11 patients (36.4%), less than one/month in 2/11 patients (18.1%), and no seizures in 4/11 patients (36.4%). Eight patients (72.7%) responded to the cycle of pulse therapy (showing an at least 50% reduction of seizure frequency). The above results show that methylprednisolone pulse therapy significantly reduced seizure frequency and that this significant reduction persisted after methyl-

Table I - LGS group: clinical, therapeutic and electroencephalographic data.

<table>
<thead>
<tr>
<th>Case/sex</th>
<th>1/M</th>
<th>2/F</th>
<th>3/F</th>
<th>4/M</th>
<th>5/M</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Etiology</strong></td>
<td>Structural (bilateral atrophy)</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Structural (PVL)</td>
</tr>
<tr>
<td>Age at onset of seizures (months)</td>
<td>52</td>
<td>3</td>
<td>3</td>
<td>32</td>
<td>23</td>
</tr>
<tr>
<td>Age at start of PT cycle (months)</td>
<td>143</td>
<td>193</td>
<td>177</td>
<td>51</td>
<td>56</td>
</tr>
<tr>
<td>Type of seizures</td>
<td>Spasms</td>
<td>Spasms</td>
<td>Spasms</td>
<td>Generalized (myoclonic-atonic)</td>
<td>GTCS</td>
</tr>
<tr>
<td>Neurological problems before epilepsy onset</td>
<td>Motor delay and aphasia</td>
<td>Motor delay and aphasia</td>
<td>Normal</td>
<td>Normal</td>
<td>CP</td>
</tr>
<tr>
<td>Previous AEDs</td>
<td>VPA, LTG, NZP, HC, RFN</td>
<td>VPA, NZP, RFN, PB, VGB, LGT, FBM, CBZ, CLB, CZP, ESM, TPM, LEV, ACTH</td>
<td>VPA, PB, VGB, LGT, LEV, CBZ, FBM, TPM, HC, LCM, CLB</td>
<td>CLB, VPA, LTG, LEV, RFN, ACTH</td>
<td>VPA, PB, TPM, RFN, ZNS, CLB, ACTH</td>
</tr>
<tr>
<td>AEDs at start of PT</td>
<td>VPA, LTG, NZP, RFN</td>
<td>VPA, NZP, RFN</td>
<td>VPA, LEV, TPM, FBM, CLB, LCM</td>
<td>VPA, LEV</td>
<td>PB, RFN, ZNS, CLB</td>
</tr>
<tr>
<td>EEG before PT</td>
<td>Awake and sleep: very frequent multifocal SWDs (&gt;90%)</td>
<td>Awake and sleep: very frequent multifocal SWDs (&gt;90%)</td>
<td>Sleep: subcontinuous (&gt;90%) SWDs</td>
<td>Awake and sleep: SDs (fronto-parietal right&gt;left)</td>
<td>Awake and sleep: very frequent SWDs (&gt;80%) (bilateral)</td>
</tr>
<tr>
<td>EEG after PT</td>
<td>Awake and sleep: modest reduction of multifocal SWDs (70%)</td>
<td>Awake and sleep: modest reduction of multifocal SWDs (70%). Sleep: significant reduction of SWDs (50%)</td>
<td>Awake and sleep: moderate amplitude of SDs (5%)</td>
<td>Awake and sleep: dramatic reduction of SWDs (5%)</td>
<td>No change</td>
</tr>
<tr>
<td>Seizure frequency before PT</td>
<td>&gt;50 seizures/month</td>
<td>&gt;50 seizures/month</td>
<td>&gt;50 seizures/month</td>
<td>&gt;50 seizures/month</td>
<td>20-50 seizures/month</td>
</tr>
<tr>
<td>Seizure frequency after PT</td>
<td>20-50 seizures/month</td>
<td>20-50 seizures/month</td>
<td>20-50 seizures/month</td>
<td>Seizure free</td>
<td>No change</td>
</tr>
</tbody>
</table>

Abbreviations: M=male; F=female; LGS=Lennox-Gastaut syndrome; EEG=electroencephalogram; PVL=periventricular leukomalacia; GTCS=generalized tonic-clonic seizures; CP=cerebral palsy; AEDs=antiepileptic drugs; PT=pulse therapy; SWDs=spike slow wave discharges; SDs=spike discharges; VPA=valproic acid; NZP=nitrazepam; HC=hydrocortisone; PB=phenobarbital; VGB=vigabatrin; LGT=lamotrigine; FBM=felbamate; CBZ=carbamazepine; CLB=clobazam; CZP=clonazepam; ESM=ethosuximide; TPM=topiramate; LEV=levetiracetam; ACTH=adrenocorticotropic hormone; LCM=lacosamide; RFN=rufinamide; ZNS=zonisamide.
prednisolone administration was stopped. At the end of the follow-up, electroencephalographic abnormalities were reduced in 8/11 patients (72.7%). In particular, the ESES group, 4/6 patients (66.7%) no longer met the criteria for continuous spikes and waves during NREM sleep. In these four patients, the mean reduction of SWDs was about 78.8%. The other 2/6 patients (33.3%), who showed no changes in SWDs, have a structural etiology underlying their epilepsy. In the LGS group, 4/5 patients (80%) showed improvements of their electroencephalographic abnormalities with an approximately 34% mean reduction in SWDs. The only patient (20%) in the LGS group whose SWDs showed no changes is affected by symptomatic epilepsy. These results show that the reduction in SWDs induced by the pulse therapy, which persisted

Table II - ESES group: clinical, therapeutic and electroencephalographic data.

<table>
<thead>
<tr>
<th>Case/sex</th>
<th>6/F</th>
<th>7/M</th>
<th>8/F</th>
<th>9/F</th>
<th>10/M</th>
<th>11/M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etiology</td>
<td>Structural (hydrocephaly)</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Structural (cavernous angioma)</td>
<td>Structural (cavernous angioma)</td>
</tr>
<tr>
<td>Age at onset of seizures (months)</td>
<td>36</td>
<td>96</td>
<td>87</td>
<td>93</td>
<td>0.8</td>
<td>94</td>
</tr>
<tr>
<td>Age at start of PT cycle (months)</td>
<td>83</td>
<td>105</td>
<td>124</td>
<td>107</td>
<td>105</td>
<td>95</td>
</tr>
<tr>
<td>Type of seizures</td>
<td>Complex partial</td>
<td>Complex partial</td>
<td>Complex partial</td>
<td>Focal motor</td>
<td>AA</td>
<td></td>
</tr>
<tr>
<td>Neurological problems before epilepsy onset</td>
<td>Mild motor developmental delay</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>Previous AEDs</td>
<td>VPA, LEV, TPM, ESM, LTG, NZP, CLB, DZP, HC, STM</td>
<td>CLB, ESM</td>
<td>LEV, VPA, ESM, CLB</td>
<td>CLB, VPA, LEV</td>
<td>VPA, LEV, CLB, PB, HC, STM, ESM</td>
<td>VPA, NZP, ESM, STM</td>
</tr>
<tr>
<td>AEDs at start of PT</td>
<td>VPA, ESM, CLB</td>
<td>CLB, ESM</td>
<td>VPA, ESM, CLB</td>
<td>LEV</td>
<td>ESM, CLB</td>
<td>VPA, STM</td>
</tr>
<tr>
<td>EEG before PT</td>
<td>Awake: SWDs (central, left&gt;right) Sleep: CSWS (85%)</td>
<td>Awake: rare SWDs Sleep: CSWS (90%)</td>
<td>Awake: frequent SWDs (temporal bilateral) Sleep: CSWS (85%)</td>
<td>Awake: rare SDs (bilateral) Sleep: CSWS (85%)</td>
<td>Awake: SWDs (frontal right&gt;left) Sleep: CSWS (&gt;90%)</td>
<td>Awake: frequent SDs (bilateral), slow activity on right; SWDs right&gt;left Sleep: CSWS (&gt;90%)</td>
</tr>
<tr>
<td>EEG after PT</td>
<td>No change Awake: no change Sleep: dramatic reduction of SWDs (10%)</td>
<td>Awake: rare SWDs (temporal bilateral) Sleep: dramatic reduction of SWDs (20%)</td>
<td>Awake: reduction of SDs Sleep: dramatic reduction of SWDs (10%)</td>
<td>No change Awake: marked reduction of SDs and SWDs Sleep: dramatic reduction of SWDs (10%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seizure frequency before PT</td>
<td>&gt;50 seizures/month</td>
<td>&lt;1 seizure/month</td>
<td>11-20 seizures/month</td>
<td>&lt;1 seizure/month</td>
<td>&lt;1 seizure/month</td>
<td>11-20 seizures/month</td>
</tr>
<tr>
<td>Seizure frequency after PT</td>
<td>No change</td>
<td>Seizure free</td>
<td>Seizure free</td>
<td>No change</td>
<td>Seizure free</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: M=male; F=female; AA=atypical absence seizure; AEDs=antiepileptic drugs; PT=pulse therapy; SWDs=spike-slow wave discharges; SDs=spike discharges; CSWS=continuous spike-and-waves during slow-wave sleep; VPA=valproic acid; NZP=nitrazepam; HC=hydrocortisone; PB=phenobarbital; LTG=lamotrigine; CLB=clobazam; ESM= ethosuximide; TPM=topiramate; LEV=levetiracetam; DZP=diazepam; STM=sulthiame.
even after the end of this therapy, was statistically significant (p<0.0028).
A positive global outcome was noted in 9/11 patients (81.8%). In particular, improvements were found in cognitive function (a gain of between 2 and 15 IQ points, mean 8.8 points) in five patients (45.5%), in attention in 2/11 patients (18.2%), in behavior in 2/11 patients (18.2%), and in language in 3/11 patients (27.3%) (Table III).
No significant or persistent side effects were noted, in particular only a modest transient hyperglycemia in the 24 hours after infusion in 1/11 patient (9.1%) and a modest weight gain in 1/11 patient (9.1%) (this patient had introduced valproic acid therapy one month before the start of the pulse therapy).

Discussion
The results of this study suggest that the intravenous methylprednisolone pulse therapy regimen described herein induces a statistically significant reduction (p<0.013) of seizure frequency in children with epileptic encephalopathy. The frequency of epileptic seizures was reduced by more than 50% in 8/11 patients (72.7%) at the end of the cycle, and in all of them this reduction was sustained even after methylprednisolone therapy was stopped, confirming the efficacy of corticosteroid therapy in reducing seizure frequency. Four of the eight responders became seizure free: one from the LGS group, who presented with myoclonic atonic seizures, and three from the ESES group. The seizure frequency reduction was clinically more significant in the LGS patients, whose seizure frequency was considerably higher than in the ESES patients. The three non-responders all had a structural etiology, suggesting that this treatment is less effective in this group of patients; given the small size of the sample, further studies are needed to confirm this finding in a larger cohort of children with epileptic encephalopathy. Eight patients (8/11, 72.7%) showed a dramatic improvement on EEG with a statistically significant reduction of abnormal SWDs (p<0.0028). The reduction of EEG abnormalities was most marked in patients with ESES, but EEG improvements were also observed in LGS patients with a clinical response. Analyzing the results of the standardized tests and/or caregivers’ reports on attention and behavior, the global outcome was positive in 9/11 patients (81.8%). Even though the severity of the impairment in some of the children meant that this result could not be demonstrated through standardized tests in all the patients, it is nevertheless an important finding since a global improvement increases the quality of life both of affected children and their families. This positive global outcome was associated with reductions in both seizure frequency and interictal EEG abnormalities. Although the Cochrane review on corticosteroids for childhood epilepsy other than epileptic spasms found no evidence for their efficacy or safety in treating childhood epilepsies (Gayatri et al., 2007), our results, along with those of other case reports and retrospective studies on this therapeutic option (Aykut-Bingol et al., 1996; Tsuru et al., 2000; Okuyaz et al., 2005;...
ronal excitability. These mechanisms may also be corticotropin-releasing hormone and decreasing hypothalamic-pituitary-adrenal axis, thus suppressing anticonvulsant effects or systematically through the g-aminobutyric acid [GABA(A)] receptor-mediated ticotropic hormone can affect infantile spasms through the action of corticosteroids in epilepsy. Adrenocorticotropic hormone has been postulated to be responsible for the action of these drugs in Landau-Kleffner syndrome. The same results were confirmed by Okuyaz et al. (2005) in their patient with continuous spike-and-waves during slow-wave sleep (CSWS) and partial epilepsy. Sevilla-Castillo et al. (2009) administered pulse therapy to 14 patients and reported a significant reduction in seizure frequency (>50%) in 12 of them; the two non-responders had a structural etiology. Lichtenfeld et al. (2010) reported a significant reduction in EEG abnormalities in a girl presenting with absence seizures treated with a pulse therapy regimen. Although literature reports have indicated a high relapse rate in patients with epileptic encephalopathy (44-70% within 3-6 months) (Sinclair, 2003; Gupta and Appleton, 2005; Verhelst et al., 2005; Okumura et al., 2006; You et al., 2008), this was not confirmed by the present study.

There are several theories regarding the mechanism of action of corticosteroids in epilepsy. Adrenocorticotropic hormone can affect infantile spasms through g-aminobutyric acid [GABA(A)] receptor-mediated anticonvulsant effects or systematically through the hypothalamic-pituitary-adrenal axis, thus suppressing corticotropin-releasing hormone and decreasing neuronal excitability. These mechanisms may also be related to the effects of steroids on absence seizures and LGS. Possible immunomodulatory effects may include correction of deficient or dysfunctional enzymes, changes in intracellular-extracellular electrolyte ratios, correction of low intracellular glucose, reduction in cerebral water content, and modulation of intracellular adenosine and neurosteroid production (Marchi et al., 2011).

The immunomodulatory or anti-inflammatory properties of corticosteroids have been postulated to be responsible for the action of these drugs in Landau-Kleffner syndrome and ESES. Since the anticonvulsant effect of corticosteroids persists after drug discontinuation, it has been suggested that in addition to allowing acute seizure control, corticosteroids may reset a deranged cerebral homeostatic mechanism, thus increasing refractoriness to seizure recurrence (Vezzani and Granata, 2005; Özkara and Vigevano, 2011). A major concern related to corticosteroids, especially in children and adolescents, is the possible development of side effects. The most frequent ones are excessive weight gain, hyperphagia, water retention with edema, Cushingoid appearance, hypertension, behavioral disturbances, increased infection susceptibility, leukopenia, electrolyte disturbances, hyperglycemia, glycosuria, impaired glucose tolerance, frank diabetes and sleep disorders. Furthermore, long-term side effects such as hypothalamic-pituitary axis suppression, psychosis, osteoporosis, nephrocalcinosis, brain atrophy, cataracts and, in children, growth retardation, have also been reported (Gupta and Appleton, 2005; Malphrus and Wilfong, 2007). Since methylprednisolone treatment did not cause significant or persistent adverse effects in our case series [1/11 patient (9.1%) showed a modest transient hyperglycemia in the 24 hours after infusions; 1/11 patient (9.1%) a modest weight gain], methylprednisolone treatment, administered according to the regimen herein described, seems to be safe. Taking into account the negative prognosis of severe childhood epilepsies, pulse therapy may be a safe and effective therapeutic option for children who show resistance to conventional AEDs. It is therefore important to identify a priori those who are more likely to benefit from the treatment and to avoid unnecessary exposure of other patients. We suggest that children with epileptic encephalopathy without an underlying structural lesion could be the best candidates for intravenous methylprednisolone pulse therapy. Larger randomized controlled studies in children are needed to establish the long-term efficacy and safety of this treatment.

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References


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