Paper

# Response to treatment with methylprednisolone pulses in children with electrical status epilepticus in sleep (ESES)

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## Introduction

Encephalopathy with status epilepticus in sleep (ESES) is a partly reversible, age-related childhood epileptic encephalopathy with heterogenous manifestations affecting cognition, motor abilities, behaviour and speech occurring in association with variable types of seizures. Continuous spike wave in slow wave sleep (CSWS), Landau Kleffner syndrome (LKS), atypical benign rolandic epilepsy (BRE) are different manifestations within this broad spectrum of epileptic encephalopathy due to continued spike wave activity in slow wave sleep. The term ESES for this EEG phenomenon was first introduced by Tassinari et al in 1977 and subsequently converted to status epilepticus in sleep (SES)[1,2]. There is now agreement that CSWS and LKS are within the same spectrum of epilepsy syndromes sharing common characteristics. In CSWS, there is cognitive and/ or behavioral impairment acquired during childhood, associated with strong activation of the interictal epileptiform discharges during non-rapid eye movement (NREM) sleep that is unrelated to any other factor. The syndrome of LKS is considered as a type of CSWS/ESES but with a particular clinical presentation where acquired aphasia is the core symptom.

Although it is considered a self limiting epileptic syndrome, literature on the outcome is sparse; outcome related to therapy is hardly or minimally described. There is no single therapy that is most effective for treatment of seizures in ESES, and most therapies are based on expert consensus guidelines. Some studies describe benefit and improved neuropsychological outcome following long term high dose Benzodiazepines[3], leveteracetam[4], sulthiame and ACTH therapies. Current consensus is that corticosteroids remain the preferred treatment method, however the type of steroids or dose remains to be studied[5,6]. The response to regular administration of methyl prednisolone is not reported or limited to occasional case history[7]. This paper describes the clinical outcome in 10 children following treatment with high dose methyl prednisolone pulses.

## Method

This descriptive study was performed at the University Unit of the Lady Ridgeway Children's Hospital, Colombo, Sri Lanka. Children diagnosed as having CSWS over a two year period (2008-2010) were included in this analysis. The diagnosis of CSWS was made following clinical diagnosis based on history of epilepsy associated with evidence of epilepsy occurring with an encephalopathic state having discriminatory electro-encephalopgraphic findings. The encephalopathic state was defined as neuropsychiatric regression occurring since onset of epilepsy and the characteristic EEG findings as presence of significant activation of spike wave activity in slow wave sleep with spike wave index of at least 50%. These children were prospectively followed up from the time of confirming diagnosis of until completion of the treatment schedule.

All of them were treated with cycles of high dose methyl prednisolone (30mg/kg/day) given for 3 consecutive days. This is followed by a slow taper off with oral prednisolone over the next 4 weeks (oral prednisolone 2mg/kg for 2 weeks followed by 1mg/kg for two weeks). All anticonvulsants that were being used by the patients at the time of diagnosis were continued. The second cycle was repeated after a 4-6 week interval at the same dose. The balance cycles (at same dose) were spaced out (6-12 weeks) according to the degree of reappearance of symptoms.

The therapeutic response was assessed using a modified 40 item epilepsy outcome rating scale developed to assess the impact of the child's epilepsy on the parents (Annex 1). This covered 5 broad areas of dysfunction secondary to the epileptic encephalopathy, i.e. impact due to poor seizure control, impact on independent mobility, impact on communication, impact on cognition and behaviour, impact on overall general wellbeing. These were assessed against a 5-point marking scheme which indicated following scales. 1 = never a problem, 2 = rarely a problem, 3 = sometimes a problem, 4 = frequently a problem and 5 = almost always a problem. This was assessed at the time of the diagnosis when treatment was commenced and repeated after completion of 6th treatment cycle.

## Results

There were 10 children who were prospectively followed up for this study. Mean age at diagnosis was 7.12 $\pm$ 2.5 years. Male: female ratio was 1:1. Nine of them had symptomatic (MRI proven) aetiology for their epilepsy. Eight children were clearly in stage two of the illness at time of diagnosis but the two older (>11 years) children were most likely reaching end of their second stages at the time of establishment of the diagnosis of

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their epilepsy. Mean duration of follow up for their epilepsy (before and after diagnosis) was 24.6 ± 6.5 months (second stage is when the CSWS is identified on EEG).

**Onset of epilepsy**

Mean age of first seizure was 30.6 ± 14.5 months (range 9-57 months) and were focal seizures with mainly motor manifestations in all. Three of them experienced their first ever seizure as a status epilepticus (30%). Mean age to onset of second stage was 50.6+16.1 months. Average time gap between onset and second stage was 20 ± 10.19 months.

**Neuropsychiatric regression**

The most prominent feature of encephalopathy in this group of was loss of cognitive skills which was noted in all children , acquired hemiplegia in two, complete loss of ambulation in five, severe ataxia in seven, partial regression or complete loss of speech in six, oro-facial manifestations as part of epileptic opercular syndrome in four.

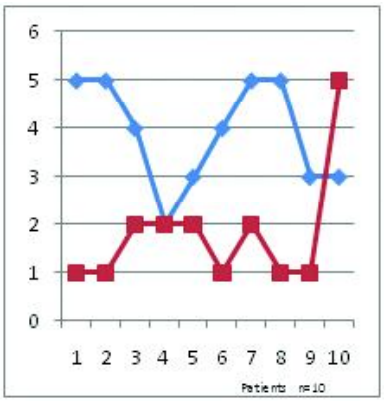
Summary of important findings in each of these ten children is outlined in Table 1.

**Table 1. Clinical profiles in the 10 children diagnosed with ESES**

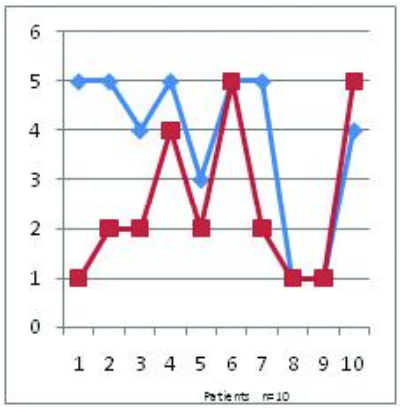
| *Patient* | *Current age* | *Aetiology* | *Pre-morbid development* | *Onset of first stage* | *Onset seizure type* | *Onset age of second state* | *Other seizure types* | *Neuro-dysfunctions* | *Age of onset of pulse therapy* |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 6.5 years | Nil | Nil concerns | 24 months | Simple focal motor (versive) | 30 months | Focal oro-motor seizures, atonic astatic seizures | Ataxia, epileptic opercular syndrome, Cognitive regression | 60 months |
| 2 | 7 years | Ex-Preterm Agenesis of corpus callosum | Normal | 36 months | Prolonged focal motor (mouth) | 48 months | Hemi-facial, hemiconvulsive, generalised clonic seizures Epileptic oper-cular syndrome Cognitive dysfunction | Ataxia with later loss of ambulation, loss of speech | 64 months |
| 3 | 6.6. years | Right congenital arterial ischaemic stroke | Delayed | 26 months | Left sided focal motor (clonic) | 48 months | Hemiclonic seizures, atonic astatic seizures, negative myoclonus | Worsening of left hemiplegia, motor dyspraxia, cognitive dysfunction | 60 months |
| 4 | 7 years | Right sided polymic-rogyria | Delayed months | 32 motor | Focal months | 56 motor | Nocturnal focal seizures, atypical absences, Generalised tonic clonic seizures | Significantly delayed hence acquired dysfunction not reported | 72 months |
| 5 | 7 years and 10 months | Hypoxic ischaemic encephalo-pathy | Delayed | 57 months | Focal status (versive and clonic) | 72 months | Hemifacial, hemiconvulsive Nocturnal convulsive seizures | Acquired hemiplegia, dysarthria | 78 months |
| 6 | 6 years nine months | Hypoxic ischaemic encephalo-pathy | Delayed | 42 months | Focal motor (clonic) | 75 months | Tonic nocturnal seizures, atypical absences | Significantly delayed hence only loss of acquired speech noted | 75 months |

*(Continued)*

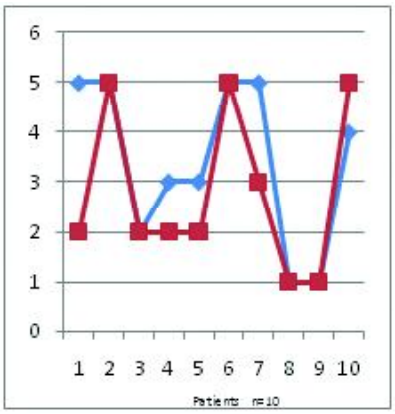
| *Patient* | *Current age* | *Aetiology* | *Pre-morbid development* | *Onset of first stage* | *Onset seizure type* | *Onset age of second state* | *Other seizure types* | *Neuro-dysfunctions* | *Age of onset of pulse therapy* |
|---|---|---|---|---|---|---|---|---|---|
| 7 | 5.5 years | Focal cortical dysplasia | Mild delay | 18 months | Bilateral convulsive seizures | 48 months | Hemifacial, hemiconvulsive, generalised tonic clonic, nocturnal convulsive seizures | Loss of ambulation, loss of speech, epileptic opercular syndrome, poor cognition | 50 months |
| 8 | 12 years | Right sided cortical atrophy | Delayed | 13 months | Tonic (nocturnal) | 24 months | Generalized tonic, drop attacks | Fine motor regression | 144 months |
| 9 | 12.4 years | Cortical dysplasia of R/ occipital region | Mild delay | 9 months | Focal status | 21 months | Generalized tonic clonic, status | Language regression, cognitive regression | 138 months |
| 10 | 6.4 years | R/ hippo-campal sclerosis | Normal | 36 months | Focal status | 60 months | Focal, absence, drop attacks | Arrest in motor development, ataxia, Speech regression | 58 months |



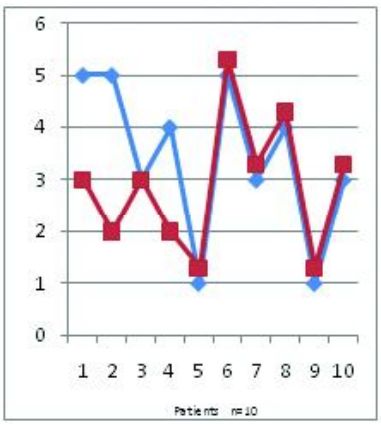

Improvement in seizure control



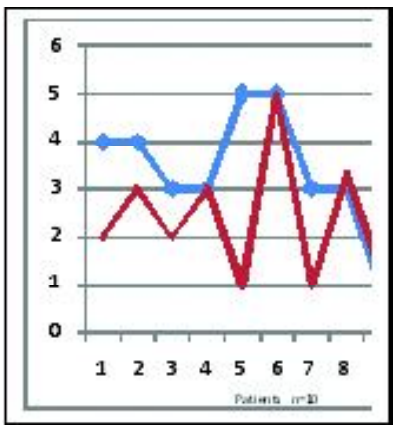

Improvement in independent ambulation




Improvement in speech and communication




Improvement in cognitive functions




Improvement of general well being


**Figure 1. Therapeutic outcome – parental assessment before and after 6 cycles of therapy**

1 = never a problem, 2 = rarely a problem, 3 = sometimes a problem, 4 = frequently a problem and 5 = almost always a problem

**Therapeutic outcome**

All patients were offered methyl prednisolone when diagnosis of ESES was established. Regular anticonvulsants taken at time of establishing the diagnosis were continued. All except one child completed all 6 pulses of methyl prednisolone therapy.

In the nine children who completed treatment a satisfactory therapeutic outcome was seen in the 5 domains assessed. This is illustrated in Figure 1. The best response was noted for improvement in the seizure frequency. There were three who completely stopped having the habitual seizures which were experienced before the therapy. In others the seizure control can be classified as Modified Engel classification class 2, 3 and 4. In those with complete loss of ambulation or severe incapacitating ataxia affecting independent ambulation (n=8) ability to ambulate with no or some support was noted in five. Mild to moderate improvement in the frequency of oro-facial manifestations was noted in three. Improvement of speech was noted only in three. One patient developed significant deterioration in her gait, speech with significant oral dysfunction (drooling) following administration of first dose of methyl prednisolone. Similar deterioration was noted after large dose of oral steroid therapy (prednisolone) was offered as an alternative.

Though the response to pulse therapy was good it was transient in all due to recurrence of symptoms such as ataxia, drooling and difficulty in ambulation. Duration to commencement of deterioration range between 5-12 weeks after the first three cycles of therapy. Most sustained impact was on control of seizures. Only one child developed a serious adverse reaction (SAR) as a severe pneumonia. At least one or more of the following were experienced by all children: increase in weight, appearance of cushingoid features, hirsuitism, increased appetite, frequent corizal symptoms, and striae.

## Discussion

ESES though resolves in an age limited manner, it leaves catastrophic neuropsychological deficits in the affected children. The pathophysiology of the neuropsychological regression associated with ESES is related to the disturbances caused by continuous spike wave activity during slow wave sleep. It can be considered as a model of clinical effects of a localized disruption of EEG activity during sleep caused by long-lasting sleep-related focal epileptic activity. Depending on area of most spike wave activity variable degrees of impact on learning, cognition, behaviour and motor functions manifest. This highlights the crucial role of slow wave sleep in the neuroplasticity that govern normal neuropsychological development[8]. Positron Emission Tomography studies using 18 F-fluorodeoxyglucose has demonstrated hypermetabolism in the region of focal continued spike wave activity, in children having normal MRI. This finding emphases the role played by frequent spike wave activity[9].

Response to therapy in ESES is difficult to describe due to its prolonged course of illness associated with fluctuation of severity of symptoms. However, apart from the two older children, all others in our group experienced the onset of second stage between 30-75 months making comparison of the response to therapy acceptable. Considering the younger age in this group of 8 children, this response is unlikely to be related to spontaneous resolution of the epileptic encephalopathy as well. Both these features are supportive of a true therapeutic response to the methyl prednisolone therapy rather than random association.

Resolution of ESES had been achieved with high dose corticosteroids or adrenocorticotropic hormone (ACTH) therapy, albeit with transient results in many patients[10,12]. In one of the largest series of 44 children, positive response (clinical or neuropsychological improvement in conjunction with improvement in the EEG tracing gradient) within three months was described in 77% of patients, with normalisation of EEG in 21 patients[5]. The main form of steroid therapy administered to this cohort was hydrocortisone. The children were maintained on high dose steroids over 9 month duration and a sustained response was experienced in only 45% of all children. Forty one percent of those with initial response subsequently relapsed on discontinuation of therapy.

## Conclusion

Based on the response seen we conclude that high dose methyl prednisolone may play a role in control of symptoms (seizures) and haltering the accompanied regression in children with ESES. Although the described response is based on short duration of follow up, repeated pulses at longer intervals may help maintain the children with minimal symptoms and better neuropsychiatric and motor functions. Large scale studies are needed to establish this further.

## Disclosure

The authors of this paper declare no conflicts of interest.

**Annex – 1**

## Epilepsy outcome rating scale for Parent/ Carer

Scale definition: 1 = never a problem, 2 = rarely a problem, 3 = sometimes a problem, 4 = frequently a problem and 5 = almost always a problem

| A In relation to your child's seizures how concerned are you about: | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|
| 1. Having one seizure after another | ○ | ○ | ○ | ○ | ○ |
| 2. Having seizures frequently | ○ | ○ | ○ | ○ | ○ |
| 3. Having seizures during day time | ○ | ○ | ○ | ○ | ○ |
| 4. Having seizures during night time | ○ | ○ | ○ | ○ | ○ |
| 5. Having frequent drop attacks | ○ | ○ | ○ | ○ | ○ |
| 6. Having twitching movements in the body | ○ | ○ | ○ | ○ | ○ |
| 7. Developing prolonged seizures | ○ | ○ | ○ | ○ | ○ |
| 8. Having long intervals before recovery | ○ | ○ | ○ | ○ | ○ |
| 9. Seizures causing damage to the brain | ○ | ○ | ○ | ○ | ○ |
| 10. Your child becoming injured due to seizures | ○ | ○ | ○ | ○ | ○ |

| B In relation to your child's mobility and hand functions how concerned are you about: | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|
| 1. Having difficulty in sitting up supported | ○ | ○ | ○ | ○ | ○ |
| 2. Having difficulty in standing unsupported | ○ | ○ | ○ | ○ | ○ |
| 3. Having difficulty in walking unsupported | ○ | ○ | ○ | ○ | ○ |
| 4. Having frequent falls | ○ | ○ | ○ | ○ | ○ |
| 5. Your child injuring his/herself due to falls | ○ | ○ | ○ | ○ | ○ |
| 6. Having difficulty in feeding self | ○ | ○ | ○ | ○ | ○ |
| 7. Having difficulty in playing with toys | ○ | ○ | ○ | ○ | ○ |
| 8. Having difficulty in using a pen | ○ | ○ | ○ | ○ | ○ |
| 9. Your child having difficulty due to toileting | ○ | ○ | ○ | ○ | ○ |
| 10. Having difficulty in dressing | ○ | ○ | ○ | ○ | ○ |

*(Continued)*

| C In relation to your child's speech and communication how concerned are you about the child: | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|
| 1. Having difficulty in talking | ○ | ○ | ○ | ○ | ○ |
| 2. Having difficulty in making any sound | ○ | ○ | ○ | ○ | ○ |
| 3. Having difficulty in expressing needs | ○ | ○ | ○ | ○ | ○ |
| 4. Having difficulty in pointing for his/her needs | ○ | ○ | ○ | ○ | ○ |
| 5. Having speech that is difficult for you to understand | ○ | ○ | ○ | ○ | ○ |
| 6. Having difficulty in talking at normal speed | ○ | ○ | ○ | ○ | ○ |
| 7. Showing no interest in communication (verbal or gestural) | ○ | ○ | ○ | ○ | ○ |
| 8. Having difficulty in understanding what you are saying | ○ | ○ | ○ | ○ | ○ |

| D In relation to your child's other disabilities how concerned are you about: | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|
| 1. Having frequent drooling of saliva | ○ | ○ | ○ | ○ | ○ |
| 2. Him/her being irritable | ○ | ○ | ○ | ○ | ○ |
| 3. Having difficulty in understanding (cognition) | ○ | ○ | ○ | ○ | ○ |
| 4. Having temper tantrums | ○ | ○ | ○ | ○ | ○ |
| 5. Being hyperactive | ○ | ○ | ○ | ○ | ○ |
| 6. Having difficulty in swallowing | ○ | ○ | ○ | ○ | ○ |
| 7. Difficulty in taking out on a trip | ○ | ○ | ○ | ○ | ○ |
| 8. Difficulty in taking him/her in a vehicle | ○ | ○ | ○ | ○ | ○ |
| 9. You having difficulty in falling sleep due to worry | ○ | ○ | ○ | ○ | ○ |
| 10. Taking your child meet relatives and friends | ○ | ○ | ○ | ○ | ○ |
| 11. Difficulties in attending school | ○ | ○ | ○ | ○ | ○ |
| 12. Impact of your child's illness on spouse and other children | ○ | ○ | ○ | ○ | ○ |

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