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**Progressive intellectual impairment in children with  
encephalopathy with status epilepticus during sleep  
(ESES).**

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## **Abstract**

We investigated whether Encephalopathy with Status Epilepticus during Sleep (ESES) in childhood was associated with progressive intellectual decline. Participants were identified from the caseload of a single paediatric neurosciences centre and EEG department. A retrospective review of overnight sleep EEG reports (n=2200) over a five-year period identified twenty-two children as having the neurophysiological characteristics of ESES. All had repeat neuropsychological assessment using the WISC-III (UK) and/or WPPSI-R (UK). There was a statistically significant reduction in Full-Scale IQ and Performance IQ across a mean and median time interval of 2 years. Around 1/3 of the participants showed a clinically significant regression in intellectual functioning evidenced by  $\geq 12$  points reduction in IQ. These patients were not distinguishable from the rest of the cohort in terms of clinical history, imaging or duration of ESES. The reduction in IQ reflected reduced processing speed, working memory and overall cognitive efficiency. Children with a history of ESES require close monitoring in order to support educational planning and in providing families with accurate information about prognosis.

**Keywords:** ESES, CSWS, childhood epilepsy, intellectual decline.

**Abbreviations:** WISC-III<sup>UK</sup>: Wechsler Intelligence Scale for children, version 3, UK norms; WPPSI-R: Wechsler Primary and Preschool Scale of Intelligence, revised.

## **Introduction**

Encephalopathy with status epilepticus during sleep or ESES is an age-dependent and self-limited syndrome whose distinctive features include a characteristic age of onset (with a peak around 4-5 years), heterogeneous seizures types (mostly focal motor or unilateral seizures during sleep and absences or falls while awake), a typical EEG pattern (with continuous and diffuse paroxysms occupying a significant proportion of slow wave sleep) and a variable neuropsychological regression consisting of IQ decrease, reduction of language (as in acquired aphasia or Landau-Kleffner syndrome), disturbance of behaviour and motor impairment (in the form of ataxia, dyspraxia, dystonia or unilateral deficit), (Tassinari et al 2000). The favourable seizure outcome is independent of the etiology and is observed also in cases with cortical malformations such as multilobar polymicrogyria (Guerrini et al 1998). The characteristic EEG patterns during slow wave sleep also disappear at approximately the same time, but focal interictal spikes may persist (Morikawa et al 1989; Bureau 1995).

The first description of sub-clinical electrical status induced by sleep in children dates back to 1971 when Patry, Lyagoubi and Tassinari described in 6 children a peculiar EEG pattern occurring almost continuously in sleep characterised by apparently ‘subclinical’ spike and wave for a variable length of time. Tassinari introduced the term “Electrical status epilepticus during slow sleep” and this was originally defined as status epilepticus occurring during at least 85% of slow sleep (Tassinari et al. 1977). More recently the proportion of affected slow sleep required to affect cognition and behaviour has been recognised to be lower, with some authors suggesting a proportion of  $\geq 50\%$  can be associated with cognitive sequelae. The most typical paroxysmal discharges on EEG are

spike wave at 1.5 to 3.5 Hz polyspikes and polyspikes and wave. Secondary bilateral synchrony is the mechanism underlying continuous spikes and waves during slow sleep. In this respect the apparently generalized seizures (absences, tonic-clonic seizures) occurring in this condition have, in fact, a focal onset (Tassinari 1995). ESES can be present in various evolutionary stages of a spectrum of diseases, the prototypes of which are Continuous Spike and Wave in slow Sleep (CSWS), Landau Klefner Syndrome (LKS) & some patients initially presenting with childhood (benign or rolandic) epilepsy with centrotemporal spikes (BECTS) (Galanopolou et al, 2000). Children with ESES generally demonstrate a global neuropsychological disturbance whereas those diagnosed with LKS typically display an isolated language disorder. In both syndromes recovery of language functions may be associated with disappearance of continuous spike and slow wave during slow wave sleep. The neuropsychological disturbances are suspected to be a function of the genetic or symptomatic origin of the underlying epileptic condition, the cortical area of the primary focal paroxysmal activity, the patient's age and the severity and duration of the EEG abnormalities (DeNegri 1997).

ESES is a rare disorder although accurate incidence is difficult to determine. Morikawa et al found an incidence of 0.5% among 12,854 children evaluated during a 10-year period (Morikawa et al, 1995). The Landau-Kleffner syndrome (LKS) and encephalopathy with electrical status epilepticus during sleep (ESES) are rare childhood-onset epileptic encephalopathies in which loss of language skills occurs in the context of an epileptiform EEG activated in sleep. Although in LKS the loss of function is limited to language, in ESES there is a wider spectrum of cognitive impairment. The two syndromes are distinct

but have some overlap. Whether ESES as a whole should be defined as an independent syndrome or as an electroclinical feature of many epilepsy syndromes is a source of debate (see Hirsch et al. in this supplement). The duration of electrical status epilepticus during slow sleep has been correlated with the final neuropsychological outcome (Rousselle & Revol 1995). It has also been suggested that electrical status epilepticus during slow sleep is a model for prolonged cognitive impairment induced interictal paroxysmal activity (Tassinari 1995). "Interictal paroxysmal activity" may interfere with different cognitive processes, as demonstrated by neurophysiological, neuropsychological, and biochemical studies (Binnie 1993; Wasterlain et al 1993). There is now increasing evidence that many autistic children with a history of language regression have epileptiform abnormalities, suggesting a role of subclinical epileptic discharges in relatively common developmental syndromes of infancy (Ballaban-Gil et al 1998; Goldberg et al 1998; De Menezes et al 1998).

Following resolution of ESES, improvement in language dysfunction, learning disability and psychiatric disturbances generally occurs but is variable and individualised. The majority of affected children never return to normal levels, particularly in verbal and attention abilities (Roulet Perez et al 1993; Morikawa et al 1985). Margari et al followed up 25 patients (19 male) from 2 to 16 years of age (mean age 6 years $\pm$ 3 SD) to examine the presence and course of neuropsychiatric disorder (mean duration of follow-up: 3.9 years) (Margari, 2012). At diagnosis of CSWS, 54% of patients had behavioral problems, 37.5% mental retardation, 33% learning disabilities, 17% developmental coordination disorder, 12.5% language disorder, and 8% pervasive developmental disorder. During the follow-up, neuropsychiatric dysfunctions remained unaltered in 52% of the patients,

worsened in 24%, and improved in only 24%. The authors suggest that CSWS may be associated with a broad spectrum of neuropsychiatric disorders and may promote their worsening over time. Despite the apparent developmental impact of the encephalopathy associated with ESES there has been very little published related to neuropsychological outcomes, with only two very small cohort studies e.g. Seegmüller et al (2012) n=10 patients, and Scholtz et al (2005) n=7 patients.

The current study aimed to provide data on a larger series of children with treated ESES using standardised neuropsychological tests. We aimed to provide some preliminary data on the impact of ESES on the developing brain in terms of intellectual development in middle to late childhood.

## **Methods**

Participants were identified by reviewing reports of 24h ambulatory EEG over a period of 5 years (n=2200). The recordings of those who exhibited marked sleep accentuation of epileptiform activity were reviewed. Those who fulfilled the diagnostic criteria for ESES i.e. >85% were identified. We also included were children who had abnormal activity occupying 60-85% of slow wave sleep if there was a history of change in behavior and /or recent loss of skills. Children who were in non-convulsive status with a continuous dysrhythmia awake and asleep were excluded. Clinical records were reviewed to determine seizure types, aetiology, behavioural and EEG features.

This was a retrospective study with cases managed by several clinicians and no uniform or standardized therapeutic paradigm for ESES. Cases were treated with several different anti-epileptic drugs including clobazam, prednisolone and valproate with variability in dose and combination of different treatments. In addition, the sequence and duration of different therapies was not controlled therefore the data on medication use on individual cases is not presented as no valid conclusions can be drawn from this data.

### Participants

Twenty-two participants met inclusion criteria (13m/ 9f). The median age of the sample at initial assessment was 6 years (mean 6.8, sd 2.9 years) with a range of 4-16 years. At follow-up, the median age was 7.5 years (mean 9.3, sd 3.4 years) with a range of 6-19 years. This created a mean latency period between assessments of 2.5 years. The clinical histories of all patients are described in Table 1. Thirteen participants were reassessed within 3 years and 8 participants within 3-5 years. 5/22 had a significant neonatal history and 5/22 had abnormal imaging using MRI/CT. There were heterogenous epilepsy types (see Table 1).

### Measures

Participants were assessed using the WISC-III (UK-edition) or the WPPSI-R (UK-edition). Where patients were unable to complete all subtests of the WISC/WPPSI pro-rated scores were derived using statistical techniques outlined within the manual. As this was a retrospective study there was no specified time period between the first and subsequent neuropsychological evaluations.

*Insert table 1*

## **Results**

At the time of their initial assessment, nine participants had a measured IQ within the learning disability range, four within the severe range (IQ 40-49) and five within the mild to moderate range (IQ 50-69). Four participants had an IQ within the borderline range (IQ 70-79), five had an IQ within the low-average range (80-89), and a further four had an IQ within the average range (90-109). At follow-up assessment, thirteen participants had measured IQs within the LD range, three within the severe range, and ten within the mild to moderate range. Four participants had an IQ within the borderline range, one within low-average, and four within the average range. Therefore, 41% of the sample had a measured IQ within the learning disability range at first assessment compared to 55% at second assessment, an increase of 14% (see Figure 1).

*Insert Figure 1*

As the data were not normally distributed a repeated-measures non-parametric analysis (Wilcoxon) was used to compare group median FSIQ, VIQ and PIQ between assessment points (see Figure 2). There were significant differences in Full-Scale IQ with a small effect size ( $p=.042$ ;  $d=0.3$ ); and performance IQ with a medium effect size ( $p=.031$ ;  $d=0.4$ ). There was no significant difference in VIQ across time ( $p=.421$ ).

*Insert Figure 2*

Figure 3 shows the change in IQ for each participant and can be correlated with the clinical histories shown in Table 1 (Identifying numbers for participants 1-22 correspond between Table and Figure).

*Insert Figure 3*

To address the important issue of statistical versus clinical significance regarding change in IQ scores, we analysed the data using a conservative criteria of  $\geq 12$  point difference in IQ. When adopting this more conservative criteria to denote clinically significant change, seven participants were found to show  $\geq 12$  IQ point change with a mean FSIQ at initial assessment of 86 (sd=15), and at follow-up of 67 (sd=14.7) with a large effect size ( $d=1.3$ ). The largest effect was observed in Performance IQ with a mean reduction of 24 points from 92 to 68 ( $p=.018$ ,  $d=1.5$ ). A less dramatic drop in VIQ was observed with an average of 9 points change ( $d=0.4$ ). If excluding those participants who scored at floor value at both time points ( $n=4$ ), our findings suggest that 7/18 participants (38%) showed a highly significant intellectual decline affecting FSIQ and PIQ. These individuals tended to move from the average range to the mild learning disability range. Four individuals had IQ values  $\leq 40$  (floor value on WISC-III) at both assessments and therefore were not able to be rated in terms of on-going cognitive loss using these instruments.

## **Discussion**

We report the largest neuropsychological outcome study of childhood ESES with main findings of a clinically and statistically significant decrease in Full-Scale and Performance IQ despite treatment. Around one-third (7/22) of participants in the current study showed a highly significant loss ( $\Rightarrow$ 12pts) in intellectual performance evident particularly within their Performance IQ scores within a relatively short period of time (2.5 years). These individuals tended to move from the average range to the mild learning disability range and were not distinguishable from the rest of the sample in terms of clinical history, imaging or duration of ESES. Performance IQ (PIQ) effects were more pronounced than verbal IQ, a finding of interest as language difficulties are the most commonly reported difficulties in these children. The drop in PIQ may reflect reduced processing speed, working memory and overall cognitive efficiency.

Whilst there have been several descriptions of the clinical and behavioural manifestations of ESES, few have used standardised tests to look at cognitive function. In a report of longitudinal neuropsychological outcome in 10 patients followed from the time of diagnosis into adulthood (mean follow-up duration of 15.6 years) six patients had an IQ  $<70$ , two had a low IQ (77 and 84), and two had an IQ within the average range (103 and 85) (Seegmuller et al. 2012). The authors also describe social, cognitive and attention difficulties in the majority of the patients. They suggest that the initial severity and duration of the acute phase regression and the duration of ESES were most predictive of poorer neuropsychological outcome. In another report it was suggested that the initial diagnosis had little prognostic significance, but that length and the age of onset of CSWS, the site of

epileptiform activity and the individual neuropsychological profile are more useful for predictors long-term cognitive outcome (Veggiotti, 2012).

Our study has limitations as a result of the retrospective nature and lack of control over timing of assessments and therapeutic interventions. The value of the report lies in the serial neuropsychological evaluations in individuals which demonstrate the clinical impact of ESES. Controlled trials in ESES are required to help determine what might be the most effective treatments. Recently the Rescue ESES international European collaboration has developed such a trial. Unfortunately, due to the rarity of the condition, the challenges of multi-centre trial bureaucracy and variability in resources to support the trial assessments, this study has not recruited as well as planned. It is possible that international agreements between collaborating centres to collect data and manage patients in a limited number of standardized paradigms might be the most practical way to generate sufficient clinically useful data on treatment efficacy.

The implications of our study are that whilst some children experience stagnation in development, represented by a plateau in neuropsychological test scores and a corresponding decline in age-normative standard scores, others experience a more significant decline in cognitive function consistent with an active disease process. In this group of children with ESES with a variety of underlying aetiologies and treatments, the underlying encephalopathy resulted in an insidious decline in cognitive ability. It is therefore important that children with ESES have early and continuing neuropsychological assessment and that developmental monitoring is linked with appropriate psychological,

social and psychiatric support to improve mental wellbeing and social participation. Families and educational services should also be provided with accurate information to inform prognosis and support in relation to maximizing learning potential and social integration with peers.

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Table 1. Clinical history showing IQ, seizure type, age of onset, imaging and other clinical phenomena for each participant.

Patient	IQ 1	IQ 2	Neonatal History	Developmental History	Age of Onset	Type Of epilepsy	Age at Diagnosis of ESES	Clinical Presentation at diagnosis	Maximum Epileptic Activity	Imaging
1	77	65	Uneventful	Febrile seizure aged 2.5 years	2.5 years	Generalised and focal epilepsy of unknown aetiology	3 years	No cognitive / behavioural concern	Right hemisphere emphasis	CT normal
2	77	68	Uneventful	Normal; mild dyspraxia	4 years	Atypical Childhood Epilepsy with Centrottemporal Spikes	5 years	Language difficulties	Assymetrical ESES, right hemisphere emphasis	CT normal
3	89	56	Hydrocephalus secondary to aqueduct stenosis	VP shunted 2 months; Right hemiparesis; Global cognitive delay	4 years	Focal epilepsy with structural aetiology	8 years	Language and social communication difficulties	Left hemisphere	CT Left sided peri-ventricular white matter loss; PVL
4	40	69	Uneventful	Uneventful	6 years	Focal epilepsy with unknown aetiology	6 years	Language and social communication difficulties	Left hemisphere emphasis (temporal).	MRI normal
5	105	78	Uneventful	Normal	>1 year	Generalised Epilepsy with myoclonic seizures (unknown aetiology)	4 years	No cognitive regression noted	Bilateral	MRI normal
6	98	99	Uneventful	Delayed motor development	7 months	Focal epilepsy with unknown aetiology	5 years	Poor educational progress	Bilateral	MRI normal
7	108	108	Premature 26 weeks gestation,	Acquired brain injury aged 7 years,	10 years	Generalised and Focal Epilepsy with structural aetiology	11 years	Memory and learning problems	Left hemisphere emphasis (temporal)	MRI normal

<b>8</b>	40	40	Uneventful	Global developmental delay, behaviour problems	5 years	Generalised and focal epilepsy of unknown aetiology	5 years	Severe ongoing behavioural problems	bilateral	MRI normal
<b>9</b>	40	40	Uneventful	Global developmental delay	4 years	Focal epilepsy of unknown aetiology	10 years	Increasing concern over poor language and learning	Left emphasis	MRI showed corpus-callosum abnormality
<b>10</b>	81	75	Uneventful	Restricted interests, rigid behaviour	3 years	Focal epilepsy of unknown aetiology	8 years	Continuing concerns	Right sided ESES	MRI abnormal, right-sided periventricular leukomalacia
<b>11</b>	81	75	Uneventful	Specific learning difficulties/clumsy	6 years	Focal epilepsy of unknown aetiology	6 years	Educational difficulties	Bilateral	Awaiting
<b>12</b>	65	50	Uneventful	Global developmental delay	5 years	Focal epilepsy of unknown aetiology	6 years	Continuing developmental concerns	Bilateral	MRI normal
<b>13</b>	79	62	Neonatal seizures	Mild right hemiplegia;	1 <sup>st</sup> week of life	Focal Epilepsy with structural aetiology	7 years	Reduced concentration and deterioration in memory/reading	Left sided (occipital) ESES	MRI Hemi-megalencephaly
<b>14</b>	59	56	Premature 32/40, severe IUGR,	Whooping cough aged 2 years 5 months	Aged 5.5 years	Childhood Epilepsy with Centrottemporal Spikes	7 years	Language difficulties, poor educational progress	Bilateral	none
<b>15</b>	69	69	Neonatal seizures	Left hemiplegia, learning disabilities	15 years	Focal Epilepsy with structural aetiology	15.5 years	Deterioration in school work	Bilateral with Right hemisphere emphasis	MRI Right Schizencephaly
<b>16</b>	78	69	Uneventful	normal	3 years	Myoclonic atonic epilepsy	3 years	Behavioural, motor and cognitive regression	Bilateral	MRI normal

<b>17</b>	82	88	Uneventful	Delayed speech and language development	3 years	Focal epilepsy with unknown aetiology	3 years	Continuing speech delay	Bilateral with shifting emphasis	MRI normal
<b>18</b>	40	40	Uneventful	Mutism aged 4 years, normal speech development prior	Aged 4	Landau Kleffner Syndrome	4 years	Continuing aphasia	Focal ESES left hemisphere	MRI normal
<b>19</b>	106	92	Uneventful	None	5 years	Myoclonic Atonic Epilepsy	5.5 years	Concentration, school difficulties	bilateral	MRI normal
<b>20</b>	82	70	Uneventful	Normal development	3 years	Focal epilepsy with unknown aetiology	8 years	Concentration, school difficulties	bilateral	Awaiting
<b>21</b>	65	69	Uneventful	Mild learning difficulties, late childhood diagnosis of Tourettes Syndrome treated with haloperidol	11 years	Focal epilepsy with unknown aetiology	12 years	Continuing concentration problems	Right sided ESES	Normal MRI
<b>22</b>	110	105	Uneventful	Accidental asphyxia aged 5yrs associated with status epilepticus.	2.5 years	Focal epilepsy with structural aetiology	6.5 years	Memory and learning	Bilateral with right sided emphasis	Normal MRI

Figure 1. Frequency of intellectual ability levels at first and second assessment (mean time interval 2.5 years).

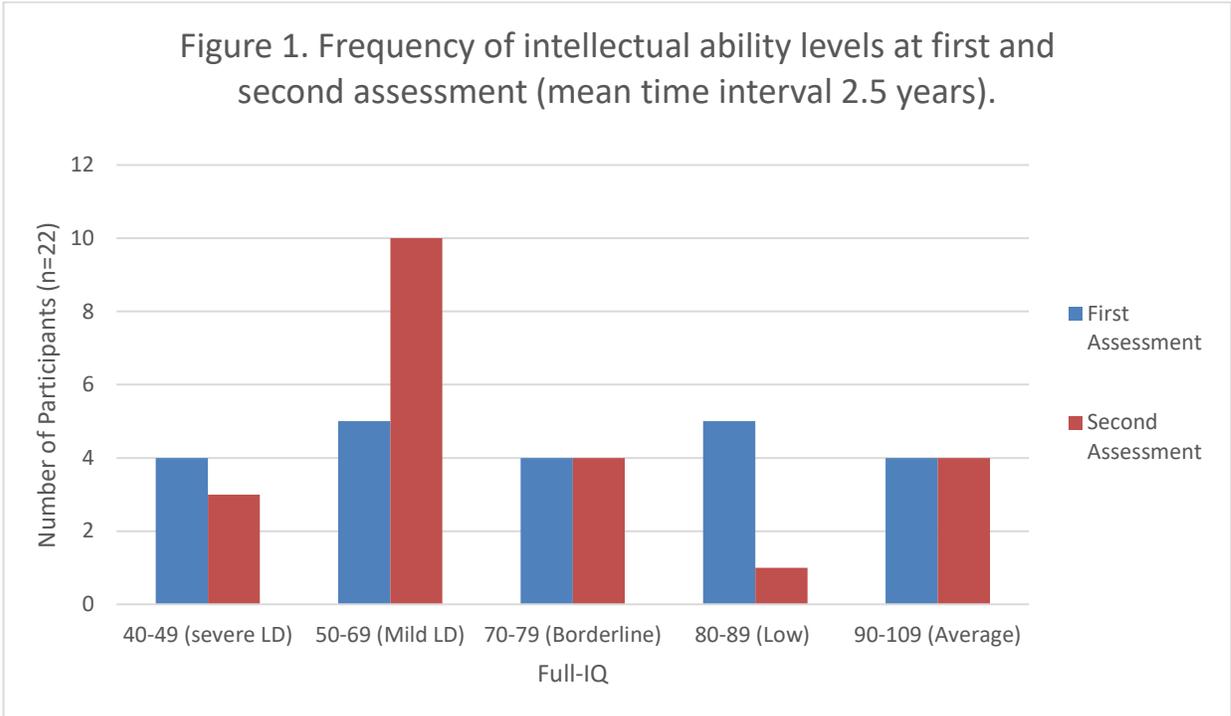


Figure 2. Changes in cohort median Full IQ, Verbal IQ and Performance IQ between first and second assessments.

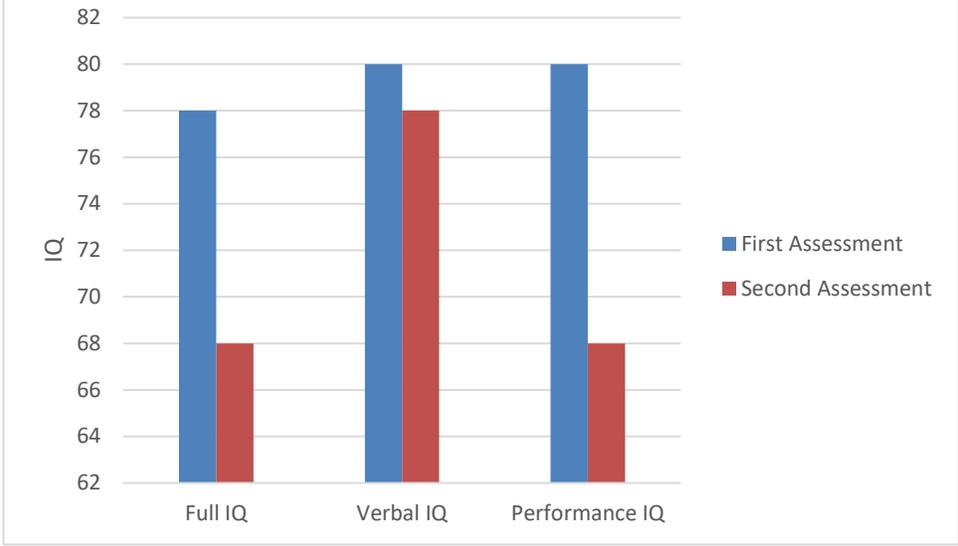


Figure 3. Individual participant change in IQ between first and second assessment.



