Cognitive outcomes following epilepsy in infancy: a longitudinal community based study.

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Summary

Objective: Onset of epilepsy under two years of age is associated with poor cognitive outcome; however the natural course of the range of epilepsies that occur at this age is unknown. The aim of this prospective community-based study was to investigate the neuropsychological development of infants with newly diagnosed epilepsy longitudinally and to identify the clinical factors that predict long-term impairment.

Methods: Sixty six infants less than 24 months of age were enrolled in the baseline phase of this study; 40 were seen again at one year follow-up and 40 at three year follow-up. Children underwent a neurological and neuropsychological assessment at each time point.

Results: Over 55% of children demonstrated impaired cognitive functioning at each assessment, with a similar percentage showing impaired memory and attention at 3-year follow-up. Cognitive scores obtained at each time-point were correlated. Greater than 20 seizures/seizure clusters prior to assessment and an abnormal neurological examination predicted poor cognitive functioning at baseline, while continuing seizures and baseline cognitive score predicted 3-year IQ/cognitive score.

Significance: These findings demonstrate: (a) infants who are performing poorly at baseline continue to display impaired development at follow-up, (b) these children are delayed across a range of neuropsychological functions, (c) a high number of seizures close to initial diagnosis and continuing seizures at follow-up independently predict cognitive impairment. These findings help to identify those infants with new onset epilepsy most at risk for poor developmental outcome and suggest that multimodal

interventions should be instituted early in the course of the disorder to improve outcomes.

Key Words: Epilepsy in infancy, Cognitive development, Cognitive outcome, Neurological predictors

Key Points

1. Cognitive impairment was present at epilepsy onset and was associated with impaired neuropsycholoigcal functioning at 3 year follow-up.

2. A high number of seizures at intitial assessment and an abnormal neurological examination predicted poor cognitive functioning near onset.

3. Cognitive impairment at onset and continuing seizures independently predicted outcomes at 3-year follow-up.

Introduction

The spectrum of underlying aetiologies and electroclinical phenotypes in infant onset epilepsies is wide.[1-3] Despite this heterogeneity a high proportion of these infants present with cognitive impairment.[3-7] Studies of childhood epilepsies suggest age of onset is an important factor in predicting the level of impairment, with earlier onset associated with poorer neuropsychological functioning.[5-10]

In addition to an early age of onset, a number of factors have been associated with negative developmental outcomes such as higher seizure frequency,[5] longer seizure duration,[10] epileptic encephalopathy,[8,11] medication resistant epilepsy,[7,12] as well as abnormalities on neuroimaging/EEG, abnormal neurological examination, and a history of epileptic spasms.[4] The aetiology of the seizures themselves may also underlie this poor development as childhood studies report the presence of cognitive impairment near or at the onset of epilepsy[13-16] and aetiology has been identified as a predictive factor of negative outcome[8,17].

Due to methodological differences, findings vary between studies as to the specific cognitive impairments and risk factors associated with early onset epilepsy. This makes it difficult to identify early those children most at risk for developmental compromise, to target intervention most effectively and also to counsel carers appropriately about long-term outcomes. The aims of this prospective, longitudinal, community-based study of new onset infant epilepsies were to: 1. Identify neurological predictors of poor cognitive functioning close to initial diagnosis. 2. To examine the developmental trajectory of these new onset epilepsies into early childhood and 3. Identify neurological predictors of later developmental outcomes.

Methods:

Recruitment

The recruitment methods have previously been described in detail.[1] In brief, infants between 1 and 24 months of age with newly diagnosed epilepsy (defined as recurrent unprovoked seizures), resident in 15 adjacent boroughs of North London were identified through a survey involving community and hospital based paediatricians over 24 months.

Infants were enrolled if they met the following inclusion criteria (a) aged between 4 weeks and 2 years of age and (b) a history of 2 or more unprovoked seizures greater than 24 hours apart. Infants were excluded if they presented with provoked seizures, i.e. fever, infections, trauma, electrolyte disturbances, transient metabolic or endocrine disorders or seizures only confined to the neonatal period.

Ethical approval for the study was received from Great Ormond Street Hospital for Children/UCL Institute for Child Health Research Ethics Committee. All parents/carers provided written informed consent to permit their child's participation in this study.

Participants

137 cases of new onset epilepsy in infants less than 2 years of age were notified to the study. Seventy six of these infants were assessed. No clinical or demographic information is available for those children where participation was declined. Ten infants were subsequently excluded as on further review inclusion criteria were not met (7 infants presented with febrile or acute illness related seizures) or the clinical and neuropsychological information obtained at enrolment was insufficient (3 cases).

The data for the remaining 66 children (38 male, mean age 11.9 months [SD 6.9]) are reported here. At baseline infants underwent a neurodevelopmental assessment after a median time interval of 8.5 weeks (interquartile range 12 weeks) following the diagnosis of epilepsy.

Forty of these children (24 male, mean age 26 months [SD = 7.9]) were seen at 1-year follow-up and a further 40 (25 male, mean age 48.8 months [SD = 7.3]) at 3-year follow-up (31 of which were assessed at 1-year follow-up). Data from all 3 time points were available for 31 (47%) children . Six of the 26 children not evaluated at 3 year follow-up had died during the follow up period. The families of remaining children were uncontactable or declined participation.

Neuropsychological Assessment

The Bayley Scales of Infant and Toddler development, third edition[18] were administered at baseline and at 1-year follow-up. It provides developmental composite scores (mean=100, SD=15) across 3 domains: Cognitive, Language and Motor abilities.

At 3-year follow-up the Brief-IQ screen of the Leiter International Performance Scale-Revised[19] was administered (Mean=100, SD=15). A strong correlation (r=0.85) is reported[19] between the Brief IQ screen of the Leiter and the Full Scale IQ of Weschler Intelliegnce Scale for Children, 3rd edition[20]. Children with developmental delay (23/40 children) who could not be assessed with the Leiter were assessed using the Bayley Scales. Composite cognitive scores were calculated for seven of these children using the Bayley standardised norms. The remaining 16 children exceeded the age range of the Bayley scales (< 42 months) so composite IQ scores were calculated using the Leiter scale, with the children receiving a score of zero on each subtest and a

composite IQ score determined according to age. Cognitive age equivalents were also calculated for these 16 children using the Bayley scales to provide an indication of the level at which these children were functioning (See Figure 2 in supplementary data), age equivalents are included for reference only and were not used in any analysis. Memory and attention were assessed using the Leiter-R. The memory screen provides a composite memory score for the child (Mean=100, Standard Deviation=15) and the attention sustained subtest produces a scale score with a mean of 10 and standard deviation of 3. Again for children who could not complete these tasks, a score of zero was assigned and a composite/scale score calculated according to age.

Clinical evaluation

At enrolment the parents/carers were interviewed to obtain clinical information including age of seizure onset, seizure manifestations, number of seizures or seizure clusters experienced prior to current assessment, antiepileptic medication,known medical or genetic conditions, family history and developmental progress prior to seizure onset. Infants underwent a neurological examination. EEG and neuroimaging data as well as investigation results were obtained .

Sixty five of the 66 cases underwent neuroimaging (64 magnetic resonance imaging [MRI](majority 1.5 Tesla systems with variable imaging protocols, performed in different institutions) , one computer tomography [CT]). Where possible neuroimages were reviewed by neuroradiologists unaware of clinical details of cases apart from the inclusion criteria (64 of the 66 cases, 97%). Findings on neuroimages or described in imaging reports were classified as 'aetiologically relevant structural abnormalities' (abnormalities commonly seen in children with epilepsy), 'aetiologically uncertain/incidental finding' (abnormalities commonly seen in a broader range of

neurological and neurodevelopmental disorders not just associated with epilepsy) and 'normal'. EEG data obtained close to diagnosis or baseline assessment were available for 65 infants. EEG recordings (n=62, 92%) or EEG reports were scored according to the presence of epileptiform discharges and abnormal background activity. Aetiology was classified as unknown (n=35), structural/metabolic (n=26) or genetic (n=5).

The clinical information, neuroimaging and EEG data were independently reviewed by 2 paediatric neurologists, who verified the diagnosis of epilepsy, classified electroclinical syndromes[21] and determined if seizure types were "epileptic spasms" or "other seizure types". (See Supplementary Data Tables 4a and 4b for information about epielpsy syndromes/epilepsy types and aetiologies).

At 1-year and 3-year follow-up, information about the clinical progress and medication was obtained from the carers/parents.

Statistical Analysis

Statistical Package for the Social Sciences (SPSS 21, Chicago, IL, USA) for Windows was used for analyses. Univariate analysis was undertaken using Mann-Whitney and Kruskal-Wallis for between-subjects tests and Wilcoxon signed-rank test for repeated measures, with effect sizes reported as *r*. Categorical data was analysed using Chi Square and Fishers exact test. For categorical data analysis, IQ/cognitive score was transformed into two categories: cognitive scores equal to or less than 70, and cognitive score greater than 70. No significant difference was found between genders on cognitive or clinical variables. Multiple linear regression analyses were conducted to identify neurological predictors of cognitive function at baseline, 1-year and 3-year follow-up. A forced entry method was used as other methods such as 'stepwise' are prone to suppressor effects and can be difficult to replicate the results.[22] To protect

against multicollinearity the association between clinical predictor variables was examined using Chi Square, Phi/Cramer's was used to examine the strength of the association with a cut-off value of 0.8 or greater used to identify multicollinearity[22] (See Supplementary Data Table 5).

Results:

Baseline assessment

At baseline assessment 56.1% of children had a Bayley cognitive composite score ≤ 70, greater than 2 standard deviations below the mean. The cognitive composite scores were highly correlated with both the baseline Bayley language composite scores (r_s= 0.777, p<0.01) and Bayley motor composite scores (r_s= 0.865, p< 0.01). See Table 1. The age of epilepsy onset did not correlate with the cognitive score at baseline (r_s= 0.139, p=0.267).

<<<<<<<<<<**TABLE 1**>>>>>>>>>>

All baseline clinical variables investigated significantly impacted on cognitive functioning (See Table 2). As the 'neuroimaging findings' clinical variable had three levels dummy coding was used to investigate this as a categorical variable with two-levels in all further analysis.

<<<<<<<<<<**TABLE 2**>>>>>>>>>>

The 7 clinical variables (known aetiology, >20 seizures prior to baseline assessment, interictal discharges on EEG, grossly abnormal background activity on EEG, abnormal neurological examination, epileptic spasms & >1 AED) were entered into a multiple linear regression model. 'Aetiologically relevant structural abnormality on

MRI' was removed from the analysis due to its high association to 'known aetiology' (Phi= 0.82). 'Abnormal neurological examination' and '> 20 seizures prior to baseline assessment' emerged as significant predictors of Bayley cognitive score. Examination of the two predictor regression model showed that 'Abnormal neurological examination' ($t(60)= -5.85$, $p< 0.001$, $B= -20.3$ (SE B= 3.5)) and '> 20 seizures prior to baseline assessment' ($t(60)= -5.06$, $p< 0.001$, $B= -18.3$ (SE B= 3.6)) accounted for 65.5% of variation in Bayley cognitive composite scores (R^2=.655). The sensitivity and specificity of each of the neurological predictor variables was examined in relation to baseline cognitive functioning. See Table 3 for results. 'Abnormal neurological examination at baseline' had the highest sensitivity at 93.1%. Greater than 20 seizures prior to baseline assessment had the greatest specificity at 90.9%.

<<<<<<<<<<**TABLE 3**>>>>>>>>>>

One-year follow-up assessment

No significant difference was found between Bayley cognitive composite score at baseline assessment and one-year follow-up ($z= -0.507$, $p=0.61$, $r= .08$), these scores were also highly correlated ($r_s= 0.772$, $p<0.001$). Mean cognitive score at 1-year follow-up was 71.88 (SD21.18), with a median of 55. 60% of infants assessed had a Bayley cognitive composite score ≤ 70. An exploratory data analysis of the baseline clinical predictor variables and age of onset in relation to Bayley cognitive score at 1-Year follow-up was performed (See Table 2). Known aetiology, >20 seizures prior to baseline assessment, interictal discharges on EEG, grossly abnormal background activity on EEG, abnormal neurological examination, epileptic spasms and baseline cognitive score were entered as predictors in a multiple linear regression model. Again

'aetiologically relevant structural abnormality on MRI' was removed from the analysis due to its high association to 'known aetiology' (Phi=0.95). Bayley baseline cognitive score accounted for 64.1% of variation (R^2=.641) in cognitive score at 1-year follow-up (t(38)= 8.23, p<0.001, B =0.87 (SE B =0.11)). None of the other clinical variables investigated were significant.

3 year follow-up assessment

At 3-year follow-up 57.5% of 40 children had an IQ/Cognitive score ≤70. 57.5% demonstrated attention deficits and 66.7% displayed impairments in memory functioning (IQ/Cognitive score mean=72.8, SD=31.1, Median=55; Memory score mean=68.9, SD=23.33, Median=56; Attention score mean=5.68, SD=2.74, Median=4). Memory composite scores were highly correlated with IQ/cognitive composite scores (r_s= 0.933, p<0.001), as were the attention sustained scale scores (r_s= 0.843, p<0.001).

There was no significant difference between IQ/cognitive score at 3-year follow-up and cognitive composite score at baseline assessment (z= -0.344, p=0.73, r= 0.05) or 1-year follow-up (z= -.285, p=0.78, r= 0.04). A strong correlation between IQ/ cognitive score at 3 year follow-up and Bayley Cognitive Composite score at baseline (r_s= 0.763 (40), p<0.001) and 1-year follow-up (r_s= 0.85 (31), p<0.001) was found, See Figure 1. (The proportion of participants falling within traditional IQ classification categories at each assessment point can be seen in Supplementary Data Figure 3.)

Figure 1: Longitundinal cognitive scores

Analysis of the baseline and 3-year clinical predictor variables and age of onset in relation to IQ/cognitive score at 3-year follow-up was performed (See Table 2).

Baseline cognitive score, known aetiology, interictal discharges on EEG, grossly abnormal background on EEG, neurological examination baseline, > 20 seizures prior to baseline assessment & continuing seizures at 3 year follow-up were entered into a multiple linear regression model. 'Aetiologically relevant structural abnormality on MRI' and 'AED's at 3-year follow-up' were removed from the analysis due to the respective high association to 'known aetiology' (Phi=0.9) and 'continuing seizures' (Phi=0.8). The initial model showed continuing seizures and Bayley Cognitive Composite score at baseline best predicted IQ/cognitive score at 3-year follow-up. Examination of the two predictor regression model showed that these predictors accounted for 72.9% of variation in IQ/cognitive scores at 3-year follow-up (R^2= .729); continuing seizures (t(37)= 4.47, p < 0.001, B = 26.4 (SE B= 5.9)) and Bayley Cognitive Composite Score (t(37) = 5.94, p < 0.001, B = 0.86 (SE B= 0.14)).

The sensitivity and specificity of each of the neurological predictor variables was examined in relation to IQ/cognitive score at 3-year follow-up. See Table 3 for results.

Attrition

Sixty six infants took part in the baseline phase of this study. This reduced to forty children by 3-year follow-up, giving an attrition rate of 39.4%. Children assessed at 1-year and 3-year follow-up were compared to those that dropped out of the study on representation across baseline clinical variables (see Table 1) . There was no significant difference between the groups on any variable (p>.05). No significant difference (p>.05) was found between these same groups on the baseline Bayley composite scores. Reviewing Table 1, the proportion of males to females in the 3 time cohorts are roughly equivalent, as is the mean age of seizure onset. The

percentage of cases represented on each of the neurological variables across the cohorts is again similar.

Although the participants assessed at each follow-up appear to be similar in clinical characteristics and the above attrition analysis indicates that data is missing at random, different participants were evaluated at each follow-up period. Altogether 31 participants from the overall cohort were assessed at both 1-year and 3-year follow-up. The multiple regression models were repeated evaluating these 31 participants only to examine if variation in participants impacted on findings. The results of both regression analyses identified the same predictor variables at 1-year (cognitive score at baseline ($t(29)= 8.58$, $p<0.001$, $R^2= .717$, B =0.92 (SE B =0.11)) and 3-year follow-up ($R^2= .878$; cognitive score at baseline $t(28)= 8.11$, $p<0.001$, B =1.05 (SE B =0.13) & continuing seizures $t(28)= 4.13$, $p<0.001$, B =21.6 (SE B =5.2)).

Discussion:

This prospective longitudinal study has demonstrated that cognitive impairment in infants with new onset epilepsy is common, affecting over 50%, and that impairment is already present close to initial diagnosis. Despite trajectories of some individuals showing improvement and others deterioration over time (see Figure 1), cognitive function at baseline correlated with that at 1 and 3-years demonstrating that impairments identified at the onset are predominantly stable across early childhood. Previous studies have also found cognitive impairment present near or at the onset of epilepsy in childhood populations[13-16] and persists over time.[14]

Early age of seizure onset is reported to be a significant risk factor for impairment in memory, attention & executive function abilities.[7] In our study 57.5% of the children

demonstrated attention deficits and 66.7% displayed impairments in memory. The memory and attention abilities of the children were highly correlated with their IQ/cognitive scores, which suggests that these abilities are in line with their general level of cognitive functioning rather than specific impairments in otherwise normally functioning children.

At baseline, a high number of seizures/seizure clusters and an abnormal neurological examination predicted poor cognitive functioning. At one year poor cognitive functioning was predicted by low baseline cognitive score; the same was seen at 3-years, along with continuing seizures. Berg et al., (2012) noted that previous studies examining developmental outcomes in childhood epilepsy have been limited in their findings as they investigated surgical candidates with refractory epilepsy rather than the full spectrum of epilepsies that occur in childhood. Our current study prospectively investigated a community based newly diagnosed sample, where the full range of presenting epilepsies and seizure types were examined. Furthermore, observations reported by Berg et al (2012) in their newly diagnosed cohort followed prospectively, showing greater cognitive impairment in children with both early seizure onset and medication resistant epilepsy, are corroborated by our findings.

Continuing seizures was a significant predictor of outcome at 3-years, and was highly associated to medication use. As a result it was not possible to include both predictors in the regression analysis. Thus we cannot disregard the impact of continued use of medication on development of cognitive function. Berg et al., (2008) also reported a high correlation between remission status and AED treatment preventing inclusion of both factors in their regression model. Aetiology, severe epilepsies - 'epileptic encephalopathy', age of onset and AED treatment were all significant predictors of cognitive outcome identified by Berg et al. Variations between our studies in the

identified predicitors could be explained by the broader seizure-onset range of the epilepsy cohort investigated by Berg et al (1 month – 16 years).

Epilepsy resulting from a known cause (symptomatic aetiology) such as an underlying structural brain pathology, has been associated with poor cognitive outcome in previous studies.[8,17] Our univariate analysis showed participants with a known aetiology had significantly poorer cognitive scores than those with an unknown aetiology, however this was not a significant predictor in the linear regression models. At the time our patients underwent investigations some of the more recently used modern genetic technologies, such as next generation sequencing analysis panels and whole exome sequencing technologies, were not available. It is possible that genetic infant onset epilepsies were underreported in this cohort. Further investigation of specific aetiologies in relation to cognitive outcomes in these epilepsies is needed.

Sixteen children who were not able to complete cognitive assessments at 3-years, were assigned the lowest performance scores for their age on the IQ test. Similar strategies have been employed in previous studies.[6,8] The composite IQ scores calculated for these children on the Leiter scale placed all children in the extremely low range of functioning, this is not believed to underestimate the cognitive capabilities of these children considering their cognitive age equivalents (See supplementary data). Excluding these children may have biased the results as the findings would not have reflected the full range of outcomes associated with infant onset epilepsy.

An issue with longitudinal studies is loss to follow-up. This can make inferences about the development of the participants over time inaccurate if cohorts differ on test variables. However the similarities between our cohorts and those children who

dropped out of the study suggests that attrition was widespread across the whole group rather than from a particular subgroup of children. Furthermore a repeat of the regression analyses for those participants with longitudinal data only (N=31) produced the same results.

Despite the limitations the present study provides important information as to the early natural history of infant onset epilepsy. The results indicate that later cognitive functioning can be reliably predicted close to seizure onset in infancy and ongoing seizure activity is associated with poor developmental outcome. This could be because the seizures are harmful or that etiologies in which seizures are difficult to control are also the etiologies that are associated with the most cognitive impairment. As it is not possible to distinguish these possibilities, optimizing seizure control should continue to be an important focus for treatment. However, it is also critical that educational and behavioural interventions are instituted early in the course of the disorder as these interventions can have major positive cognitive impacts independently of treatment of seizures. Given the high prevalence of cognitive disability reported, referral for neuropsychological assessment should be standard procedure for all infants presenting with new onset epilepsy.

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Disclosure of Conflicts of interest: Prof J Helen Cross holds an endowed Chair through the University College, London. She has sat on Advisory Panels for Eisai, Vitaflo, Nutricia, Shire, GSK and Takeda for which remuneration has been paid to her department. She has received money to the Department for funding of a PhD from Vitaflo, and has been an investigator for clinical trials with GW Pharma and Zogenix She currently holds grants for research from Action Medical Research, SPARKS, Charles Wolfson Foundation, the Great Ormond Street Hospital Children's Charity, the National Institute for Health and Research and the European Union. She is currently Clinical Advisor to the Children's Epilepsy Surgery Service.

No other conflicts of interest to report.

Ethical Publication Statement: We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Supplementary Data Figure 2. Comparison of current age and cognitive age equivalent of 16 untestable participants

Supplementary Data Figure 3: Percentage of participants falling within each IQ Category

Supplementary Data Table 4a and 4bDistribution of epilepsy syndromes/epilepsy types and aetiologies for patients assessed at baseline (n=66) and for those at 3-year follow-up (n=40)

Supplementary Data Table 5: Association between clinical predictor variables

Figure legends

Figure 1: Longitudinal cognitive scores

Table 1: Participant characteristics across clinical and neuropsychological variables – Baseline, 1-Year & 3-Year cohorts

	Baseline	1-Year	3-Year
Total Number of Participants	66	40	40
Male; Female	38; 28	24; 16	25; 15
Age at Seizure onset [months] : Mean age (SD)	6.18 (5.56)	7.68 (6.11)	6.65 (5.35)
Number of Participants with a Known Aetiology at baseline Number / group n (%)	30/66 (45.5%)	19/40 (47.5%)	19/40 (47.5%)
Number of Participants with Aetiologically Relevant Structural Brain Abnormality at baseline: Number / group n (%)	29/65 (44.6%)	18/40 (45%)	19/40 (47.5%)
Number of Participants displaying interictal epileptiform activity on EEG at baseline: Number / group n (%)	40/64 (62.5%)	24/38 (63.2%)	24/38 (63.2%)
Number of Participants with grossly abnormal background on EEG at baseline: Number/Group N (%)	25/64 (39.1%)	13/38 (34.2%)	12/38 (31.6%)
Number of Participants with Epileptic Spasms at baseline: Number/ group n (%)	23/66 (34.8%)	15/40 (37.5%)	14/40 (35%)

Number of Participants with Abnormal Neurological exam baseline:	29/65	19/40	18/39
Number / group n (%)	(44.6%)	(47.5%)	(46.2%)
Number of Participants with >20 seizures prior to baseline assessment:	41/63	23/39	23/38
Number / group n (%)	(65.1%)	(59%)	(60.5%)
Number of Participants taking >1 AED at baseline assessment:	26/66	-	-
Number / group n (%)	(39.4%)		
Number of Participants with continuing seizures at 3-year follow-up	-	-	21/40
Number/group n (%)			(52.5%)
Number of Participants taking AED's at 3-year follow-up	-	-	26/40
Number/group n (%)			(65%)
Baseline Bayley Cognitive Composite:			
Median/Mean (SD)	65/73.3 (20.1)	67.5/73.6(20.4)	70/74.5 (20.7)
Baseline Bayley Language Composite:			
Median/Mean (SD)	68/70.4 (18)	68/70 (18.1)	72.5/70.7 (17.8)

Baseline Bayley Motor Composite:			
Median/Mean (SD)	68.5/69.2 (21.6)	61/67.1 (21.4)	68.5/69.2 (20.6)

Table 2: Results of univariate analysis of clinical predictors in relation to baseline, 1-year & 3-year follow-up cognitive scores

	Baseline	1-Year	3-Year
Total Number of Participants	66	40	40
Male; Female	38; 28	24; 16	25; 15
Age at Seizure onset	r_s = 0.139, *p* = 0.267	r_s = 0.096, p = 0.554	r_s = - 0.009, p = 0.957
Known aetiology at baseline	U=320.5, p =0.003, r=-0.37	U=96.5, p=0.003, r =-0.47	U=101.5, p =0.008, r=-0.42
Neuroimaging Findings at baseline	H=12.38, p = 0.002	H=8.8, p=0.013	H= 8.87, p = 0.012
Aetiologically relevant structural brain abnormality V Normal MRI	U=115, p< 0.001, r = -0.51	U=104, p=0.006, r =-0.43	U=24.5, p= 0.004, r = -0.53
Aetiologically uncertain/incidental finding V Normal MRI	U=125.5, p = 0.25, r = -0.19	U=145.5, p=0.48, r =-0.11	U=39.5, p = 0.36, r = -0.2
Interictal epileptiform activity on baseline EEG	U=242, p= 0.001, r =-0.43	U=89.5, p=0.01, r =-0.42	U=99.5, p=.037, r =-0.34
Grossly abnormal background on baseline EEG	U=178.5, p < 0.001, r =-0.56	U=60.5, p=0.001, r =-0.55	U=79.5, p=.016, r =-0.39
Epileptic spasms at baseline	U=284.5, p = 0.003, r =-0.37	U=102, p=0.011, r =-0.4	U=135, p=.181, r =-0.21
Abnormal neurological exam at baseline	U=62.5, p < 0.001, r =-0.78	U=44, p <0.001, r =-0.71	U=49, p < 0.001, r =-0.63
>20 seizures/seizure clusters prior to baseline assessment	U=111.5, p < 0.001, r = -0.64	U=67, p<0.001, r =-0.58	U=78, p=.005, r =-0.46
>1 AED at baseline assessment	U=320.5, p = 0.006, r = -0.34	-	-
Continuing seizures at 3-year follow-up	-	-	U=47.5, p < 0.001, r =-0.65
AED's at 3-year follow-up	-	-	U=50.5, p < 0.001, r =-0.59

r_s = Spearman's correlation coefficient; U = Mann-Whitney; H = Kruskal-Wallis; r = Pearson's correlation coefficient

Table 3: Sensitivity & specificity of clinical predictors in identifying cognitive impairment (scores ≤70) at baseline & 3-year follow-up

	Baseline		3-year follow-up	
	Sensitivity	**Specificity**	**Sensitivity**	**Specificity**
Known aetiology at baseline	74.2%	60%	78.9%	61.9%
Aetiologically relevant structural brain abnormality	75.9%	68.4%	78.9%	62.5%
Aetiologically uncertain/incidental finding on MRI	47.1%	68.4%	38.5%	62.5%
Interictal epileptiform activity on baseline EEG	72.5%	66.7%	70.8%	57.1%
Grossly abnormal background on baseline EEG	92%	64.1%	91.7%	53.8%
Epileptic spasms at baseline	82.6%	58.1%	71.4%	50%
Abnormal neurological exam baseline	93.1%	75%	88.9%	66.7%
>20 seizures/seisure clusters prior to baseline assessment	80.5%	90.9%	82.6%	73.3%
>1 AED at baseline assessment	73.1%	55%	-	-
Bayley Baseline Cognitive Score	-	-	85.7%	73.7%
Continuing seizures at 3-year follow-up	-	-	90.5%	78.9%
AED's at 3-year follow-up	-	-	80.8%	85.7%