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Neuropsychological function three to six months following admission to paediatric intensive care with meningo-encephalitis, sepsis, and other disorders: A prospective study of school-aged children.

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Abstract

Objective: To assess short-term neuropsychological function and academic performance in school children following admission to intensive care and to explore the role of critical neurological and systemic infection.

Design: A prospective observational case-control study.

Setting: Two Paediatric Intensive Care Units (PICUs).

Subjects: A consecutive sample of 88 children aged 5-16 years (*Mdn* age = 10.00, IQR = 6.00-13.00) admitted to PICU between 2007 and 2010 with meningo-encephalitis, septic illness, or other critical illnesses were assessed three to six months following discharge and performance compared with 100 healthy controls. Patients were without prior neurological or neuro-developmental disorder.

Interventions: None.

Measurements and Main Results: Data encompassing demographic and critical illness details were obtained and children were assessed using tests of intellectual function, memory, and attention. Questionnaires addressing academic performance were returned by teachers. After adjusting for co-variates, the PICU admitted children significantly underperformed on neuropsychological measures in comparison to the healthy controls ($p < .02$). Teachers deemed more PICU children than controls as performing educationally worse and having problems with school work ($p = .001$), as well as performing below average on aspects of executive function and attention ($p < .04$). Analysis of the effect of illness type on outcome revealed that aspects of

neuropsychological function, such as memory function, and teacher-rated academic performance were most reduced in children with meningo-encephalitis and septic illness. In the PICU group, multivariable linear regression revealed that worse performance on a composite score of neuropsychological impairment was more prevalent when children were younger, from a lower social class, and had experienced seizures during their admission ($p < .02$).

Conclusions: Admission to PICU is followed by deficits in neuropsychological performance and educational difficulties, with more severe difficulties noted following meningo-encephalitis and septic illness. These results highlight the importance of future studies on cognition and educational outcome incorporating type of illness as a moderating factor.

Introduction

Advances in paediatric critical care have led to a reduction in mortality and most children are now expected to make a complete physical recovery (1, 2). Indeed, from 2008 to 2010 over 52,000 children aged 0-15 years old were admitted to PICUs in the UK and Ireland, with over 95% leaving alive (3).

In recent years, the outcome of paediatric survivors has become an increasingly important area of investigation. Studies have examined quality of life, functional and physical health, and psychiatric adjustment, demonstrating considerable morbidity (4-11).

Research focusing on neuropsychological function in children following PICU admission is still in its infancy, but it is being encouraged by a wealth of data in the adult population (12, 13). One paediatric study found no evidence of cognitive deficits following PICU admission (14), whilst other studies have demonstrated subtle sequelae (4, 7, 8, 15). Discrepancies may be related to differences in inclusion criteria; length of follow-up; and use or not of healthy controls. Cognitive sequelae have been identified in sub-groups of acutely ill children, including meningitis (16-19), sepsis or septic shock (7, 20, 21), and meningococcal disease (22, 23).

The primary aim of this study was to investigate cognitive function in school-aged children following admission to PICU in comparison to healthy controls, and to examine the contribution of both neurological and systemic infection by contrasting groups of children with meningo-encephalitis, sepsis, and other disorders also leading to PICU admission with healthy controls. It was expected that there would be more anomalies in cognitive function in PICU admitted children than in healthy controls, with sequelae

most prevalent in the group with meningo-encephalitis due to the increased risk of brain damage (24).

Materials and Methods

Patient enrolment

From April 2007 to March 2010 children aged 5 to 16 years old were recruited from the PICUs at St Mary's Hospital and Great Ormond Street Hospital in London, UK.. The PICU cohort was formed of three sub-groups: 1) children admitted with meningo-encephalitis, 2) children admitted with sepsis, and 3) children admitted with non-neurological and non-septic critical illnesses, termed *patient controls*. Cases of meningo-encephalitis and sepsis were classified on the basis of clinical features, with microbiological confirmation sought through cultures or polymerase chain reaction where appropriate. Cases presenting with both were categorised according to the predominant clinical condition.

Children were excluded if they presented with a condition, other than meningo-encephalitis, likely to have an effect on neuropsychological function, such as those admitted with a pre-existing neurological condition or developmental disorder, neurological injury, or psychiatric disorder. Children were also excluded if they were discharged to palliative care; re-admitted to PICU >48hrs after initial discharge; if no discharge summary was available at the time of recruitment; if they lived overseas; or if there were no contact details.

Community based controls

Healthy controls were recruited from the family and/or friends of patients in order to try and match the participants as closely as possible. When this was not possible, we recruited from local mainstream schools, distributing leaflets so that families could opt in. Children included in the control group had no previous history of PICU admission.

Socio-demographics and pre-morbid characteristics

We gathered information on socio-demographic variables, such as ethnicity and socio-economic status. Ethnicity was coded as “white” or “other” for the purposes of analysis because more detailed partitioning produced small groups. Socio-economic status was indexed using the three-class version of National Statistics Socio-Economic Classification (NS-SEC; 25), which is based on the occupation of the main wage-earner in the family. Information was obtained regarding pre-morbid medical history and the presence of prior emotional or behavioural problems.

Clinical indices

Information was gathered from medical records regarding possible risk factors for poor neuropsychological outcome, covering both the pre-morbid and acute illness episodes.

Neuropsychological battery

The battery was administered three to six months following PICU discharge by a research psychologist experienced in neuropsychological assessment or by trained research assistants. This time-frame was chosen in order to provide an indication of

early functioning after full medical recovery. The battery was designed to provide a concise account of cognitive function, with particular focus in the domains of intellectual function, memory, and attention, as they have been highlighted as vulnerable to impairment following critical illness in adults (12). All tests selected are standardised and well validated for use in children.

Intellectual abilities were assessed using the four sub-test Wide Range Intelligence Test (WRIT; 26) for five year olds and the two sub-test version of the Wechsler Abbreviated Scale of Intelligence (WASI; 27) for those aged six years or older. An age-corrected full-scale intelligence score was calculated from scaled scores on the sub-tests, with a mean of 100 and a standard deviation of 15. Verbal abilities were assessed with two sub-tests from the Children's Memory Scale (CMS; 28), which covered the ability to recall and recognise semantically related material (stories) and lists of unrelated material (word pairs). Three age-corrected index scores were calculated, with a mean of 100 and a standard deviation of 15. Visual abilities were assessed using five sub-tests from the Cambridge Neuropsychological Test Automated Battery (CANTAB; CeNes Plc, Cambridge, UK). The sub-tests included measures of recall (paired associates learning) and recognition memory (pattern recognition memory); working memory (spatial working memory) and working memory capacity (spatial span); and sustained attention (rapid visual information processing). Raw scores and age-adjusted Z scores, which expressed each participant's score in relation to an integrated age-matched normative population, were used.

Academic performance

We adapted a questionnaire previously used to assess academic performance in children after traumatic brain injury (29), exploring the child's special educational needs before and after admission and the presence of cognitive difficulties. This questionnaire was also modified for use in the healthy control group.

Protocol

Parents and children were given age-appropriate information sheets and written informed consent and assent was obtained. Ethical permission for the study was granted by the Research Ethics Committee (REC) at Hammersmith Hospital. Assessments were conducted 3 to 6 months following discharge from PICU at the family home, school, or hospital. The battery was completed in a standardised order and took approximately 1-1.5 hours to complete, with a short five minute break mid-way. Head teachers were contacted and asked to pass on the academic questionnaire to the child's teacher.

Statistical analysis

Analyses were carried out using the Predictive Analytics SoftWare (PASW) version 18.0 for Windows (SPSS Inc., Chicago, IL, USA). Comparisons were two-tailed and significance was set at $p < .05$ unless stated otherwise.

The data describing participant characteristics and academic performance were analysed with non-parametric methods, using Mann-Whitney U tests for continuous data and the Chi-square or Fisher's Exact test (FET) for categorical data, as appropriate. Data are expressed as median (IQR) and frequency (percent) respectively.

When post-hoc comparisons were made, a manual bonferroni adjustment was applied by means of dividing the alpha level (.05) by the number of simultaneous comparisons.

The neuropsychological dataset was made up of continuous data and assessed for normality using histograms and the Kolmogorov-Smirnov test. Normally distributed data were analysed using parametric tests and non-normal data were analysed using bootstrapped parametric tests, a form of robust testing which can withstand violations of normality (30). When age-corrected scores were not used, age was included as a covariate. The data are presented as either means $\pm$ (*SEM*) or means $\pm$ bias corrected and accelerated (BCa) *SEM*.

Primary analyses of the neuropsychological and academic data involved between-group comparisons of the PICU cohort and healthy controls. Secondary analyses explored the performance of the three patient sub-groups in comparison to healthy controls; and when significant main effects were present, bonferroni corrected post-hoc comparisons were conducted to locate the source of the effect.

The relationship between neuropsychological measures and associated academic performance indicators were explored using spearman's rank correlations.

For PICU patients only, we examined the relationship between potential predictors and global neuropsychological function using multivariable linear regression. The standardised residuals were confirmed to be normally distributed using histograms and the Kolmogorov-Smirnov test.

Results

Figure 1 depicts our patient recruitment process. Participants and non-participants were similar in age at admission ($Mdn = 10.00$, $IQR = 6.00-13.00$ vs. $Mdn = 10.00$, $IQR = 6.00-13.00$) and days in PICU ($Mdn = 2.00$, $IQR = 1.00-6.00$ vs. $Mdn = 2.00$, $IQR = 1.00-4.00$), but there were more white children (54% vs. 36%) and more males (61% vs. 46%) in the participating group.

In the healthy control group, 64 family members and/or friends and 36 local mainstream school pupils were recruited.

FIGURE_1

Participant demographics and pre-morbid characteristics

Table 1 outlines demographic and pre-morbid characteristics in the participating children. There was a tendency for more males in the patient group (61% vs. 48%), and as some research has shown evidence of sex differences in cognitive abilities (31, 32), we included gender as a covariate in the neuropsychological analyses.

TABLE_1

PICU cohort and patient sub-groups

Most patients in the meningo-encephalitis and sepsis groups had their diagnosis confirmed by laboratory tests (57% and 68% respectively). The patient control group consisted of admissions for respiratory conditions (42%); post-emergency surgery

monitoring (18%); metabolic conditions (16%); post-elective surgery monitoring (11%); cardiac failure (9%), and other (4%).

Table 2 summarises the clinical characteristics of the PICU cohort as a whole and the three patient sub-groups individually. Main effects were explored with post-hoc tests using a manual bonferroni adjusted alpha value of $p=.02$. Days spent in PICU and PIM2 scores were significantly higher in the sepsis group in comparison to the patient controls ($ps \leq .003$). More sepsis patients had shock compared with both meningo-encephalitis cases and patient controls ($ps < .001$). The meningo-encephalitis group differed significantly from the other two groups in demonstrating more neurological complications at the time of their illness (i.e., seizures and raised intracranial pressure) ($ps \leq .001$). Significantly more children in the patient control group than in the other groups had a chronic medical condition (e.g., diabetes) ($ps < .001$). In line with this, significantly more children in the patient control group had a history of previous PICU admissions compared to the sepsis group ($p=.006$). There were no other significant differences.

TABLE_2

Neuropsychological assessment

The median time between discharge from PICU and assessment was 145 days (IQR = 114.50-191.75). The majority of the PICU cohort completed the battery (80/88; 91%). The eight patients that had incomplete datasets comprised of five children that could not complete all tests due to behavioural or neuropsychological difficulties and

three technical malfunctions. If a participant failed to complete three or more sub-tests ($n=3$), their results were not included in the following analyses, leaving 85 patients in the PICU cohort (i.e., 19 meningo-encephalitis, 22 sepsis, and 44 patient controls). All 100 healthy controls completed the full battery.

PICU cohort versus healthy controls

Table 3 shows the main neuropsychological findings. Both the PICU cohort and healthy controls scored in the average range for IQ (i.e., 85 – 115), but the PICU cohort scored significantly lower than controls ($p<.05$). Furthermore, the PICU cohort performed significantly worse than controls on measures of verbal and visual recall and recognition memory; spatial working memory and working memory capacity; and visual sustained attention ($ps<.05$).

We derived a global neuropsychological function index to give an indication of neuropsychological impairment, ranging from 0-1, and corresponding to the proportion of tests in which participants scored at least 1 *SD* below the associated normative means (higher index scores indicating worse performance) (33). The PICU cohort scored significantly higher on this index than the healthy controls ($F(1, 182) = 16.96$, $p<.001$), indicating more widespread impairment (See Figure 2).

TABLE_3

Patient sub-groups versus healthy controls

The neuropsychological sequelae outlined above were then explored in the three patient sub-groups, enabling us to make individual comparisons with the healthy control group. Data are presented as mean (*SEM/BCa SEM*).

Reduced performance was most prevalent in the meningo-encephalitis group, with them performing significantly worse than healthy controls in IQ (95.16 (3.19) vs. 107.25 (1.33), $p=.004$) and memory, including verbal recognition (verbal delayed recognition index: 91.11 (3.75) vs. 101.28 (1.27), $p=.03$), pattern recognition (delayed percentage correct: 68.89 (5.11) vs. 81.47 (1.32), $p=.009$), visual recall (total errors: 31.75 (9.46) vs. 10.90 (1.35), $p=.001$; number of trials to success: 2.93 (0.55) vs. 1.74 (.08), $p<.001$), and spatial working memory (between errors: 46.68 (3.72) vs. 33.80 (1.59), $p=.001$). There was a significant difference between the sepsis group and healthy controls in IQ (98.19 (2.85) vs. 107.25 (1.33), $p=.03$) and verbal recall (verbal delayed index: 97.04 (3.24) vs. 107.91 (1.56), $p=.02$). The patient control group differed significantly from healthy controls in IQ only (100.19 (2.01) vs. 107.25 (1.33), $p=.02$),

In terms of the global neuropsychological index, only the meningo-encephalitis and sepsis groups differed significantly from the healthy controls ($p<.001$ and $p=.03$ respectively) (See Figure 2).

Predictors of poor neuropsychological function in the PICU cohort

The regression used block-wise entry, including known predictors (i.e., patient sub-group, age, gender, and SES) in the first block, followed by potential predictors (i.e., premorbid and acute illness factors) in the second block. Spearman's rank correlations were used to identify potential predictors at $p<.10$. The presence of a chronic medical

condition and seizures during admission were the only two variables significantly correlated with the global index. In the first block, the enter method was used. Stepwise methods (forward variable elimination criterion of $p \leq .05$) were used for the second block as this was exploratory. In the final model (see Table 4), age at admission and SES were found to be significant predictors of the global index, with younger age and lower SES being significantly associated with more widespread impairment ($p < .02$). Of the two exploratory variables entered, presence of a chronic illness was excluded as it did not meet the criterion for entry, thus only seizures remained in the final model, being significantly associated with more widespread impairment ($p = .001$).

FIGURE_2

Academic performance

Response rates were high, with 68/82 (83%) of teachers of PICU children and 89/96 (93%) of teachers of control children returning questionnaires. There was variability in the completion of questions, giving rise to differing *ns*.

PICU cohort versus healthy controls

Table 4 shows the main findings from the academic questionnaire. Significantly more PICU children than healthy controls were identified as showing some deterioration in academic performance in the past 3-6 months ($p = .001$). Moreover, a significant proportion of the PICU cohort were reported as having difficulties keeping up with school work ($p = .001$). When we enquired in more detail about specific learning

difficulties, teachers reported significantly more children in the PICU cohort were performing below average in the domains of attention and executive function ($p < .04$).

TABLE_4

Patient sub-groups versus healthy controls

When significant FET main effects were present, post-hoc analyses, using a manual bonferroni adjusted alpha value of $p = .02$, were conducted.

The meningo-encephalitis group were reported to have significantly higher rates of difficulties in completing school work than healthy controls (33% vs. 8%, $p = .01$), with no other significant differences apparent. Teachers noted most problems in the sepsis group, with significantly higher rates of deterioration in academic performance (29% vs. 4%, $p = .007$); as well as difficulties completing school work (33% vs. 8%, $p = .01$); dividing attention (44% vs. 11%, $p = .004$); or considering a variety of possible solutions (44% vs. 8%, $p = .001$) in comparison to healthy controls. There were no significant differences associated with the patient control group ($p > .02$).

Relationship between neuropsychological function and academic performance in the whole sample

Significant associations were noted between a) performance on the test of visual sustained attention and ratings of the ability to focus ($r_s = -.30$, $N = 153$, $p < .001$); b) the strategy score on the spatial working memory task and ratings of the ability to plan ($r_s = .37$, $N = 153$, $p < .001$) and the ability to analyse a task into component parts ($r_s = .36$,

N=154, $p<.001$); and c) performance on the verbal delayed recall index and ratings of the ability to recall events from earlier in the day ($r_s=-.22$, N=151, $p=.006$).

Furthermore, teacher ratings were linked to scores on the global neuropsychological performance index. For most items, children rated as having difficulties scored significantly worse on the index than those not ($ps<.05$).

TABLE_5

Discussion

Our results show that in the three to six months following discharge from PICU, school-aged children significantly underperform on measures of neuropsychological function and teachers deem approximately one fifth as performing academically worse. There were differences between the patient sub-groups, indicative of worse performance following meningo-encephalitis and, to a lesser extent, septic illness.

The sequelae observed in this PICU cohort substantiate those found by Elison and colleagues (7), the only previous study we are aware of that has used formal neuropsychological testing to assess function in a comparable PICU sample, and confirm the adult intensive care literature (12). Whilst underperformance in intellectual function was apparent in all three patient groups under study, specific difficulties in memory and attentional function were most noted in the meningo-encephalitis and sepsis groups. These results corroborate the findings of prior studies in children with these disorders (16-21).

The mechanisms underlying these after-effects are likely to reflect a complex interplay of factors. Post-traumatic stress symptoms have been reported following critical illness (5, 6, 10, 11), with studies indicating that the presence of PTSD symptoms are linked to worse cognitive performance, particularly executive function and attention (36, 37). Thus, it would be appropriate for further study to explore whether neuropsychological deficits are mediated by post-traumatic stress disorder following PICU admission. It may be the case that neuronal damage as a result of neuro-inflammation in meningo-encephalitis and the toxic cerebral effects of systemic inflammation in sepsis account for the more specific neuropsychological deficits observed in these groups (38 - 39).

Global neuropsychological impairment was worst when seizures were reported, with the highest rates being documented in the meningo-encephalitis group. The previous literature on the neuropsychological impact of seizures following meningo-encephalitis is contradictory (40, 41), but our findings suggest that altered brain mechanisms underlying, or related to, seizure activity may play a significant part in the development of subsequent neuropsychological deficits in children with meningo-encephalitis severe enough to lead to PICU admission. The finding that younger age was linked to poorer outcome is contradictory to prior notions of brain plasticity (42), but this has been previously observed in children with meningitis (41), suggesting that the younger brain may be more vulnerable to brain insults caused by infectious critical illness. The links between neuropsychological deficits and lower family socio-economic status are compatible with reduced cognitive functions in deprived healthy populations, and therefore probably unrelated to illness effects (43).

Unlike previous studies (4, 44), neuropsychological outcome was independent of markers of illness severity (i.e., PICU length of stay and PIM2 scores) in our cohort. However, earlier studies addressed morbidity in children immediately upon discharge from PICU, thus it is possible that effects of illness severity indices weaken over time. Somewhat surprisingly, having a chronic medical condition was not significantly associated with worse performance, even though cognitive deficits have been described in children with disorders such as sickle cell disease and type 1 diabetes (45, 46). However, chronic illness may affect different aspects of neuropsychological function to those studied here.

A number of limitations of our study need to be taken into account. Firstly, the participation rate of families was modest and non-participants were not comparable in terms of gender and ethnicity. However, the demographics of our final PICU cohort were consistent with those reported by the most recent national audit of PICU admissions in the UK and Ireland (3), and thus we can conclude the children in this sample are broadly representative. Secondly, when assessing the effects of type of illness, the resulting sub-groups were small, potentially resulting in type II statistical errors. Thirdly, it is worth highlighting that our results apply to children without obvious major behavioural, emotional, or cognitive anomalies after discharge. And finally, we did not examine the possible effects of delirium on neuropsychological findings. In critically ill adults delirium is associated with worse cognitive outcomes (47, 48). In children measures of delirium had not been validated at the time of this study (49). However, we failed to find associations between drug withdrawal symptoms – a known source of delirium - and our global index of neuropsychological function.

This study is, nevertheless, strengthened by stringent inclusion criteria, a fixed follow-up time, and the use of standardised well-validated objective measures of neuropsychological function. Indeed, the close concordance between teacher observations and aspects of neuropsychological test performance validates and confirms the latter's pragmatic relevance and effects on everyday educational performance. Furthermore, very few studies have chosen a time-point distant enough from the admission to avoid treatment effects, but close enough to measure the initial burden experienced. The short-term follow up and intervention of children is important, as what may initially present as subtle changes in cognitive function, if left untreated, may lead to long-lasting deleterious effects (17).

These findings indicate that a number of children will be struggling to perform at their pre-morbid levels of functioning, suggesting that the recently described “post intensive care syndrome” in adults, which encompasses cognitive deficits, is also apparent in children (50). There is currently no specific guidance in place for the follow-up of survivors of paediatric critical illness (51). Our results highlight that the follow-up of children after critical – particularly infectious – illness should form part of the gold standard of critical care delivery, and provides support for the NICE guidance that children diagnosed with meningitis or sepsis be reviewed for morbidities soon after discharge and appropriate referrals made (52).

Conclusions

Admission to PICU is followed by deficits in intellectual functioning and difficulties in memory, attention, as well as in academic performance. Our findings indicate that

these deficits are more marked in patients with severe infections, especially meningo-encephalitis and septic illness, thus highlighting the importance for future research to take into account type of illness as a moderating variable

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Figure 1. Flow diagram showing patient recruitment.

Figure 2. Quantification of global neuropsychological function index based on impaired performance on the neuropsychological battery in the paediatric intensive care unit cohort and across patient sub-groups in comparison to healthy controls.

Table 1. Socio-demographic and pre-morbid characteristics for paediatric intensive care unit cohort and healthy control children

	PICU cohort	Healthy controls
Age at assessment, yrs	10.00 (7.00-13.75)	10.50 (8.00-12.00)
Gender		
Female	34 (39%)	52 (52%)
Male	54 (61%)	48 (48%)
Socio-economic status		
Level I	30 (40%)	47 (52%)
Level II	17 (23%)	21 (23%)
Level III	19 (25%)	17 (19%)
Not assigned	9 (12%)	5 (6%)
Ethnicity		
White	47 (53%)	57 (58%)
Other	41 (46%)	41 (42%)
Complications during pregnancy		
No	59 (72%)	73 (79%)
Yes	23 (28%)	20 (22%)
Special care when born		
No	69 (84%)	87 (94%)
Yes	13 (16%)	6 (7%)
Family situation		
Intact home	56 (68%)	74 (80%)
Non-intact home	26 (32%)	19 (20%)
Prior emotional or behavioural problems		
No	75 (93%)	84 (90%)
Yes	6 (7%)	9 (10%)

Data are *Mdn* (IQR) or frequency (percent).

Table 2. Clinical characteristics of paediatric intensive care unit cohort split by patient sub-group.

	PICU cohort (N=88)	Meningo- encephalitis (n=21)	Sepsis (n=22)	Patient controls (n=45)	p Value (df=2)
Age at illness, yrs	10.00 (6.00-13.00)	10.00 (6.00-14.00)	9.50 (6.75-14.00)	10.00 (6.00-13.00)	.87 ^b
Previous critical care admissions	16/83 (19%)	5/20 (25%)	0/22 (0%)	11/41 (27%)	.01 ^d
Chronic medical condition	48/88 (55%)	6/21 (29%)	5/22 (23%)	37/45 (82%)	<.001 ^c
PIM2 ^a	0.05 (0.01-0.13)	0.05 (0.04-0.07)	0.13 (0.03-0.25)	0.04 (0.01-0.07)	.006 ^b
Total days in PICU	2.00 (1.00-5.00)	3.00 (1.00-4.00)	6.00 (2.00-8.25)	1.00 (0.00-2.50)	<.001 ^b
Total days in hospital	10.00 (6.00-17.50)	10.00 (6.50-19.50)	14.50 (8.50-27.25)	8.00 (4.50-15.50)	.05 ^b
Shock	29/88 (33%)	3/21 (14%)	19/22 (86%)	7/45 (16%)	<.001 ^c
ICP	9/88 (10%)	8/21 (38%)	0/22 (0%)	1/45 (2%)	<.001 ^d
Seizures	10/88 (11%)	9/21 (43%)	0/22 (0%)	1/45 (2%)	<.001 ^d
EEG conducted and abnormal	13/19 (68%)	10/13 (77%)	2/3 (67%)	1/3 (33%)	.48 ^d
Intubation	69/88 (78%)	20/21 (95%)	18/22 (82%)	31/45 (69%)	.05 ^d
Steroids administered	39/88 (44%)	12/21 (57%)	12/22 (55%)	15/45 (33%)	.12 ^c
Drug withdrawal symptoms	10/88 (11%)	1/21 (5%)	5/22 (23%)	4/45 (9%)	.21 ^d

PIM2, Paediatric Index of Mortality 2 (34); ICP, raised Intra-Cranial Pressure. All data

presented are *Mdn* (IQR) or frequency (percent); ^a PIM2 data available for 87 patients; ^b

Kruskal Wallis test; ^c Chi Square test; ^d Fisher's Exact test.

Table 3. Neuropsychological performance in paediatric intensive care unit cohort and healthy controls.

	N	PICU cohort	N	Healthy controls	<i>p</i> Value (<i>df</i> =1)	Effect size <i>d</i>
WASI/WRIT						
Full-Scale IQ	84	98.60 (1.46)	100	107.23 (1.33)	<.001 ^a	0.65
Children's Memory Scale						
Verbal immediate index	84	97.82 (1.57)	100	104.03 (1.60)	.007 ^b	0.41
Verbal delayed index	84	99.02 (1.55)	100	107.92 (1.56)	<.001 ^b	0.58
Verbal delayed recognition index	84	94.95 (1.54)	100	101.25 (1.27)	.002 ^b	0.46
CANTAB						
Pattern Recognition Memory						
Percentage correct immediate	85	89.40 (1.55)	100	94.60 (0.92)	.003 ^c	0.44
Percentage correct delayed	85	74.57 (1.99)	100	81.45 (1.29)	.003 ^c	0.45
Spatial Working Memory						
Total between errors	85	40.98 (2.05)	100	33.83 (1.57)	<.001 ^c	0.53
Strategy score	85	35.01 (0.55)	100	34.68 (0.43)	.60 ^c	0.08
Spatial Span						
Span length	83	5.56 (0.15)	100	5.99 (0.14)	.02 ^c	0.37
Rapid Visual Information Processing						
Performance accuracy (A')	83	0.93 (0.01)	100	0.95 (0.01)	.007 ^c	0.41
Paired Associates Learning						
Total errors (adjusted)	85	19.30 (3.01)	100	10.97 (1.29)	.008 ^c	0.40
Number of trials to success	85	2.26 (0.17)	100	1.75 (0.08)	.003 ^c	0.44

^a ANCOVA with gender as a covariate; ^b Bootstrapped ANCOVA with gender as a covariate; ^c Bootstrapped ANCOVA with age and gender as covariates. IQ data are presented as estimated marginal means (*SEM*) and all other data are presented as estimated marginal means (*BCa SEM*). Note. An effect size between 0.2 and 0.5 was considered a small effect, 0.5 and 0.8 a moderate effect, and 0.8 and above a large effect (35).

Table 4. Problems and below average classroom abilities in the paediatric intensive care unit cohort and healthy controls as reported by teachers.

	PICU cohort (n/N (%))	Healthy controls (n/N (%))	p Value (df=1)
<i>Problems:</i>			
Visual difficulties	6/63(10%)	7/89 (8%)	.77 ^a
Hearing difficulties	2/64 (3%)	0/86 (0%)	.18 ^b
Deterioration in academic performance	12/57 (21%)	3/86 (4%)	.001 ^a
Difficulties keeping up with school work	18/62 (29%)	7/89 (8%)	.001 ^a
Poor listening skills	10/66 (15%)	6/89 (7%)	.11 ^a
Problems understanding things that are said	7/64 (11%)	4/89 (5%)	.20 ^b
Problems finding the right word	6/63 (10%)	7/88 (8%)	.77 ^a
<i>Below average abilities:</i>			
To focus attention	18/68 (27%)	12/89 (14%)	.04 ^a
To divide attention	17/64 (27%)	10/89 (11%)	.02 ^a
To analyse a task into component parts	19/66 (29%)	8/89 (9%)	.002 ^a
To consider a variety of possible solutions	17/65 (26%)	7/88 (8%)	.003 ^a
To plan activities	16/65 (25%)	9/89 (10%)	.03 ^a
To recall events from earlier in the day/previous days	10/65 (15%)	7/89 (8%)	.19 ^a

Data are frequency (percent); ^a Chi Square test; ^b Fisher's Exact test.

Table 5. Predictors of the global neuropsychological function index.

	<i>b</i>	<i>SE b</i>	β
<i>Step 1</i>			
Constant	0.20	0.13	
Patient Sub-group:			
Meningo-encephalitis vs. patient controls	0.20	0.07	.35*
Sepsis vs. patient controls	0.05	0.07	.10
Age	-0.02	0.01	-.29*
Gender ^a	0.09	0.06	.18
SES ^b	0.12	0.06	.24*
<i>Step 2</i>			
Constant	0.17	0.13	
Patient Sub-group:			
Meningo-encephalitis vs. patient controls	0.10	0.08	.18
Sepsis vs. patient controls	0.06	0.06	.11
Age	-0.02	0.01	-.26*
Gender ^a	0.09	0.06	.17
SES ^b	0.13	0.05	.26*
Seizures ^c	0.25	0.10	.31*

Note. Patient sub-group was represented by two dummy variables with patient controls serving as the reference group. $R^2 = .23$ for step 1, $\Delta R^2 = .07$ for Step 2 ($ps < .05$).

* $p < .05$. ^a Male versus female: a positive regression coefficient means worse outcome for females than males; ^b SES Class I and II versus all other categories: a positive coefficient means worse outcome for the lower SES classes; ^c Seizures experienced versus not experienced: a positive coefficient means worse outcome following seizures.