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Sequelae of haemolytic uraemic syndrome

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Abstract

Twenty two patients with previous episodes of haemolytic uraemic syndrome (HUS) were investigated for evidence of deficits in cognitive, behavioural, and academic function. Patients were pair matched with 22 controls for age (±1 year), gender, and socioeconomic status. HUS patients had numerically lower cognitive and achievement scores and higher behavioural problem ratings than their controls on every measure. None of the group differences was significant at the 0·01 level. Significance values between 0·10 and 0·01 were obtained for the Wechsler full scale and verbal intelligence quotient scores and for several of the achievement measures and behaviour ratings. These results were conservatively interpreted as trends and are considered to provide preliminary indications of a post-HUS deficit in behaviour, verbal intelligence, and the verbally based skills of reading comprehension and vocabulary. The findings provide interim guidelines for follow up care but require confirmation and elaboration in a larger study.

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The haemolytic uraemic syndrome (HUS) is a leading cause of renal failure in childhood, with an annual incidence of 1·44–1·74/100 000 in North American children of less than 15 years of age.[1–3] During the acute phase of the illness, some degree of central nervous system dysfunction as manifested by lethargy, seizures, or coma is observed in 33–52% of children.[1 4–8] Evidence of raised intracranial pressure is common at necropsy in children with HUS,[1 5 6 8] and postmortem examinations have demonstrated microthrombi and focal areas of infarction in the cerebral cortex.[5 9] A minority of survivors of the acute episode experience chronic seizures, developmental delay, cortical blindness, and hemiparesis.[4 6–8] It is not known whether the acute episode of HUS may also result in less severe central nervous system impairment with concomitant cognitive and behavioural deficits. This study was undertaken as a pilot investigation of the effects of an acute episodè of HUS on cognitive ability, behavioural function, and scholastic achievement.

Methods

SUBJECTS

The study was carried out at the Children's Hospital of Eastern Ontario, Ottawa, and Children's Hospital of Western Ontario, Victoria Hospital Corporation, London, Ontario. Patients were eligible for the study if they met the following criteria: (a) HUS (typical diarrhoeal associated disease) diagnosed by a nephrologist; (b) onset of HUS before the age of 15 years; (c) occurrence of HUS at least six months before entry into the study; (d) current age 4 years or more; (e) first language English or French; and (f) no evidence of mental retardation (intelligence quotient (IQ)<70), documented learning disability, or other conditions associated with learning disability (for example, attention deficit disorder, cerebral palsy, meningitis, or neuromuscular disorder) before the onset of HUS. Thirty nine patients met these criteria. Of these, 22 consented to participate in the study. Seven of the remaining patients could not be located, five were no longer in the area, and five declined to participate.

Controls were selected from the patient lists of the emergency department and the paediatric nephrology clinic at the Children's Hospital of Eastern Ontario. The neuropsychological outcome measures used in this study are known to be sensitive to the influence of socioeconomic status, age, and language; this is particularly true for IQ scores which correlate positively with socioeconomic status. To ensure that patients and controls would be comparable on these important variables we first matched one clinic control to each child with HUS on the basis of age, gender, and first language. We then estimated whether each child constituted an appropriate match on socioeconomic status using data available from the postal code.[10] The latter can be linked to the median income of the households in the census district in which the individual lives. When the difference in median income of the census tracts between HUS patients and prospective matched controls differed by less than $10 000 the parents of the control subject were contacted to determine their willingness to participate in the study. Consenting parents received a telephone interview which included questions about their occupation and education. The Green socioeconomic status scale was used to confirm the match.[11]

Controls were excluded if they had chronic renal insufficiency (as defined by a creatinine value >95th centile for age), documented evidence of mental retardation, or evidence of other conditions associated with learning disability (as listed above). Emergency department controls had acute soft tissue injuries or fractured limbs (n=13). Renal clinic controls had urinary tract infections (n=5), microscopic haematuria (n=1), or minor degrees of proteinuria (n=3). There is no reason to believe that cognitive

outcome measures would be affected by these conditions or their treatment.

ASSESSMENT MEASURES

Parents of children 16 years and younger completed the child behaviour checklist (CBCL)[12] and the Swanson, Nolan, and Pelham checklist (SNAP),[13] providing both a comprehensive behavioural rating and a rating of attentional deficit disorder with hyperactivity symptoms (ADD–H) listed in the *Diagnostic and Statistical Manual of Mental Disorders*, 3rd edition.[14] Cognitive ability at all age levels was assessed by the appropriate Wechsler scale: the Wechsler preschool and primary scale of intelligence revised (WPPSI–R),[15] the Wechsler intelligence scale for children, revised (WISC–R),[16] or the Wechsler adult intelligence scale, revised (WAIS–R).[17] Academic achievement in children 5 years and older was measured by the wide range achievement test, revised (WRAT–R)[18] and by the brief scale of the Woodcock reading mastery test-revised (WRMT–R).[19] The spontaneous writing subscale of the test of written language 2 (TOWL–2)[20] was included in the assessment of children 7·5 years and older. These academic measures were selected to provide a brief, objective screening for problems in the core subjects of reading, spelling, mathematics, and written output.

PROCEDURES

One research assistant administered the assessment battery at both centres. The assistant was unaware of the patient/control status of the subjects and did not have access to their medical charts. Relevant medical and background information was obtained by a coinvestigator (EO) and parents were instructed not to mention the child's status during testing.

The assessment measures were carried out in a single visit for each subject and required approximately 1·5 hours for preschool children and 2·5–3 hours for older subjects. The parent accompanying the child filled in the CBCL and SNAP. No behavioural ratings were obtained for subjects 16 years and older.

Medical chart data were used to make two independent ratings of HUS severity based on central nervous system symptoms and peak creatinine values. A four point scale for central nervous system symptoms ranged from 1 (no lethargy) to 4 (coma).

DATA ANALYSIS

Paired t tests were carried out on all continuous assessment measures. χ^2 Comparisons and Pearson's correlations were used to analyse the relationship between HUS severity ratings and test scores. The statistical package for the social sciences (SPSS/PC+ v3·0) statistical software was used to carry out the analyses. Clinical significance was determined by a difference of at least 0·5 SD (medium effect size) or, in the case of academic tests, by a difference of at least one grade level, between the group means.

Statistical significance was interpreted conservatively. As an adjustment for multiple comparisons, $p \leq 0{\cdot}01$ was set as the criterion for significance and values between 0·10 and 0·01 were interpreted as trends.

SAMPLE SIZE AND POWER

The sample size of 44 (22 subjects with pair matched controls) was dictated by the availability of patients with HUS, and had a power of 0·79 to detect a clinically important difference between groups of 0·5 SD on the standardised tests at an alpha level of 0·05. The sample's power was 0·57 when alpha was set at 0·01.[21]

Results

SUBJECT CHARACTERISTICS

Twenty two patients and their controls participated in the study. As expected, patients and controls were well matched with regard to mean (SD) age (10·1 (4.6) *v* 10·1 (4·6) years), gender (17 females per group), and socioeconomic status (Green score, 64·1 (8·0) *v* 64·3 (8·1); p=0·94).

HUS PATIENTS

Medical chart notes described all but four of the HUS patients as having some degree of lethargy during the acute phase of the illness. Five had seizures at some time, two developed hemiparesis, and two developed coma. Six patients received anticonvulsant treatment in hospital. These symptoms were slightly more severe than those of the 17 eligible patients who did not participate in the study in that none of the non-participants developed coma. None of the subjects had a creatinine concentration above 100 μmol/l at the most recent clinic visit, and no patient was being treated with anticonvulsants at the time of the assessment. Table 1 summarises the characteristics of participating HUS patients with comparison data for non-participating eligible patients and for 226 Canadian patients with HUS investigated between 1986 and 1988.[1] In general, subject characteristics are well matched in the three groups. Although the pilot study patients showed a slightly higher median age of onset, age ranges were comparable.

COGNITIVE AND BEHAVIOURAL OUTCOMES

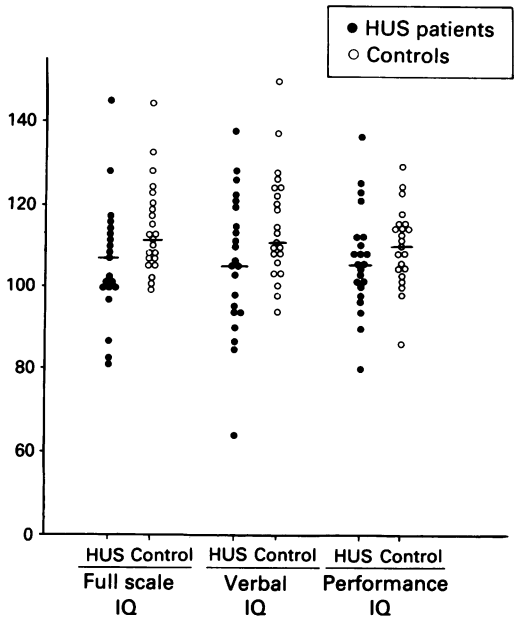
Figure 1 illustrates the distribution of full scale, verbal, and performance IQ scores for the HUS patients and thier controls. Comparisons between the groups for these and other tests are summarised in table 2. Of note, the HUS patients obtained numerically lower mean cognitive and achievement scores and higher behavioural problem ratings than their controls on every measure.

None of the group comparisons yielded significance at the 0·01 level. Trends to significance ($0{\cdot}01 > p \leq 0{\cdot}10$) were obtained on several variables. Differences of this magnitude were evident on the Wechsler full scale (p=0·07) and verbal (p=0·04) IQ scores and on the information (p=0·09), comprehension (p=0·03), and vocabulary (p=0·02) subtests of the Wechsler verbal

Table 1 Characteristics of the study patients

	HUS study patients 1976–90 (n=22)		*Eligible non-participants (n=17)*		*CPKDRC subjects 1986–8 (n=226)*	
	Median	*Range*	*Median*	*Range*	*Median*	*Range*
Age at HUS (years)	5·1	0·6–12	2·4	0·5–10·1	2·75	0·1–15
Peak creatinine (μmol/l)	230	53–749	274	35–1496	329	38–1492
Peak urea (mmol/l)	30·6	9·8–84·4	25·5	7·5–72·1	29·3	2·7–97·8
Lowest haemoglobin (g/l)	64	35–85	63	48–82	61	23–118
Lowest platelet ($\times 10^9$/l)	27	3–380*	55	18–493	34	2–430
Days in hospital	14·5	7–71	20	4–70	11	1–107
Age at testing (years)	9·7	4–21				

CPKDRC, Canadian Pediatric Kidney Disease Reference Centre.
*20/22 had platelet values $\leq 65 \times 10^9$/l.



Wechsler intelligence score for HUS patients and controls. The horizontal lines represent median values.

scale. Differences also were found on the SNAP impulsivity subscale (p=0·10) and on the total SNAP score (p=0·10). The CBCL total score did not yield a group difference but a trend was present on the CBCL total externalising score (p=0·08). Most of the CBCL subscale patient numbers were very small as these scales vary with age level and sex. Subscales with groups of at least 15 were included in the analysis and trends were found on social withdrawal (p=0·05) and hyperactivity (p=0·07). Achievement tests yielded a trend on the WRMT–R brief scale age score (p=0·02) and on the passage comprehension subscale (p=0·07). The TOWL–2 spontaneous writing total score (p=0·06) and the contextual vocabulary subscale (p=0·05) also showed trends to significance. These trends suggest relative deficits in verbal cognitive abilities and in the related areas of word knowledge and reading comprehension as well as difficulties with the modulation of social behaviour.

There was no correlation between selected psychometric measures and age at the time of HUS, years since the HUS, or the severity of the HUS episode. Full scale mean (SD) IQ scores for HUS patients who did (n=6) or did not (n=16) develop seizures or coma showed a clinically important difference (98·3 (13·7) *v* 109·5 (13·4); p=0·12), but the statistical comparison was limited by the small number of patients with severe acute neurological symptoms. Among those with peak creatinine concentrations <300 μmol/l, only 1/16 developed seizures or coma, compared with 5/6 with a peak creatinine >300 μmol/l (p=0·002). However, there was no correlation between peak creatinine values and full scale IQ scores ($r=<0·1$). Similarly the correlation of hypertension and hyponatraemia with full scale IQ was not significant ($r=<0·1$).

*Table 2 Paired t test comparisons of cognitive, behavioural, and academic measures**

	HUS Mean (SD)	*Control Mean (SD)*	*Mean difference (SE)*	*p Value*
Weschler (n=22)†				
Verbal IQ	104·5 (16·0)	113·6 (13·5)	9·1 (4·2)	0·04
Comprehension	11·0 (2·9)	12·7 (2·0)	1·6 (0·7)	0·03
Vocabulary	10·0 (3·0)	12·1 (2·6)	2·1 (0·8)	0·02
Information	10·3 (2·6)	11·7 (3·4)	1·4 (0·8)	0·09
Performance IQ	107·6 (13·2)	110·9 (9·8)	3·3 (3·3)	0·34
Full scale IQ	106·5 (14·1)	113·9 (11·3)	7·4 (3·8)	0·07
CBCL (n=20)				
Social competence	50·7 (9·5)	51·1 (9·1)	0·4 (2·8)	0·89
Internalising total	56·2 (10·4)	50·1 (10·2)	6·1 (3·6)	0·11
Social withdrawal (n=16)	61·0 (7·9)	56·0 (3·5)	5·0 (2·3)	0·05
Externalising total	54·3 (9·9)	46·5 (11·0)	7·8 (4·2)	0·08
Hyperactivity (n=16)	61·1 (8·9)	56·1 (2·9)	4·9 (2·5)	0·07
Total behaviour problems	56·8 (11·3)	49·3 (12·2)	7·5 (4·5)	0·11
SNAP, ADD-H rating (n=20)				
Hyperactivity	0·9 (1·6)	0·3 (0·7)	0·6 (0·4)	0·13
Inattention	1·0 (1·8)	0·3 (0·8)	0·7 (0·5)	0·15
Impulsivity	1·0 (1·5)	0·3 (0·9)	0·7 (0·4)	0·10
ADD-H total	2·9 (4·2)	0·9 (2·0)	2·0 (1·1)	0·10
WRAT–R grade scores (n=19)				
Reading	5·5 (4·7)	5·9 (4·7)	0·5 (0·3)	0·20
Spelling	4·8 (4·6)	5·6 (4·9)	0·8 (0·6)	0·20
Mathematics	5·0 (4·2)	5·1 (3·7)	0·1 (0·4)	0·89
WRMT–R age scores (n=18)				
Word identification	12·5 (8·6)	13·1 (8·3)	0·5 (1·4)	0·55
Passage comprehension	13·3 (10·8)	15·1 (11·8)	1·8 (1·1)	0·07
Brief scale total	12·9 (9·6)	14·7 (10·4)	1·8 (0·9)	0·02
TOWL–2 spontaneous writing test‡ (n=15)				
Total score	34·6 (10·1)	40·2 (6·5)	5·6 (2·8)	0·06
Contextual vocabulary	7·1 (4·5)	10·4 (5·1)	3·3 (1·6)	0·05

Abbreviations: see assessment measures section in methods for test abbreviations.
*Subscores are indented and are included only if p≤0·10.
†WPPSI–R (n=7), WISC–R (n=13), and WAIS–R (n=2) scores were combined for analysis.
‡Scores are expressed as percentages to correct for large differences in story lengths.

CLINICAL SIGNIFICANCE

Mean differences of 0·5 SD were obtained on the Wechsler verbal IQ and full scale IQ, the SNAP inattention, impulsivity, and hyperactivity scales, and on the CBCL externalising, internalising, and total behaviour problem scales as well as on several subscale measures. Differences of at least one grade level were obtained for the WRMT–R word identification, passage comprehension, and brief scale total scores.

Discussion

Central nervous system involvement is common in acute childhood HUS. In reported series, 17–24% of patients have developed seizures, 7–40% have developed coma, and up to 52% are described as lethargic in the acute phase of the illness.[1-4-8 22 23] Postulated mechanisms for the central nervous system symptoms include hypertension, hyponatraemia, or the direct toxic effects of uraemia,[8] as well as direct endothelial injury by verotoxin or Shiga-like toxin with resultant endothelial swelling and microthrombosis. Trevathan and colleagues have also demonstrated thrombotic occlusion of large branches of the anterior and middle cerebral arteries.[24] While severe chronic central nervous system impairment is known to persist in a small minority of survivors, the possible extension of milder central nervous system effects beyond the acute HUS episode has been addressed for the first time in this study.

The results of this investigation provide preliminary indications of a post-HUS deficit in verbal intelligence and in the verbally based skills of reading comprehension and vocabulary use, as well as in behaviour. These findings will require confirmation in subsequent investigations. None the less, trends emerged strongly in the present study despite the fact that only six children had seizures or coma during the acute phase of HUS, and that none of the patients had full scale IQ scores below 80.

Previous studies[1 25 26] have reported relatively high socioeconomic status for HUS patients. This finding was replicated in the present investigation in which the socioeconomic scores reflected predominantly middle to upper middle status. Because there is a positive correlation between socioeconomic status and IQ,[27] we anticipated that IQ scores would be slightly above average in our sample. This was true not for the patients but for their closely matched controls. This difference can reasonably be interpreted as an effect of HUS rather than as a flaw in case-control matching.

The possibility should nevertheless be considered that despite close matching of HUS patients and controls with regard to age, gender, and socioeconomic status we failed to achieve matching of premorbid cognitive levels. Siblings have been used to provide a more stringent control of the cognitive level before illness in studies of central nervous system dysfunction after meningitis[28] and Reye's syndrome.[29] Sibling controls were not considered appropriate for the present investigation because episodes of clinical or subclinical HUS can occur among family members and could obscure true differences on tests of cognitive function. It may be advisable to include siblings as well as pair matched controls in future studies.

The expected correlation between the severity of the acute HUS episode and the degree of central nervous system dysfunction was not evident in this study. We suspect that our sample size of 22 HUS patients together with the relatively small number of subjects with severe central nervous system involvement may have prevented detection of a true relationship. Larger studies will be required to test this hypothesis further. In our study, the trend to cognitive impairment was specific to verbal ability and related functions. If this finding is replicated it will raise important research questions concerning the reason for this functional specificity.

While our findings must be confirmed in future work, they may be considered as interim guidelines for alerting physicians to the clinically less obvious sequelae of HUS, for monitoring quality of life after recovery for the acute illness, and for making available appropriate services as needed.

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Septic shock: no, no, NO

The 6 June 1991 issue of the *New England Journal of Medicine* (pages 1640–3) included an aggressive but intellectually impoverished defence of animal experimentation in medical research. Abusing animal rights campaigners, most of whom are sincere, well intentioned and non-violent, is a policy unlikely to win many friends. Animal experimentation must stand or fall on its results and its utility, that is, its relevance to human disease. It was satisfying, therefore, to see side by side in the *Lancet* of 21/28 December 1991 two papers, one describing animal experiments relating to the treatment of septic shock and the other describing the clinical application of such research in two adult patients.

There is evidence that the unresponsive hypotension of septic shock may be brought about by the accumulation in the tissues of nitric oxide (NO) which is a strong vasodilator. The NO is produced in blood vessel walls from L-arginine by the action of two enzymes (NO synthases), one physiological (called the constitutive enzyme) and one induced by the actions of endotoxin and cytokines (the inducible enzyme). Both kinds of NO synthase are inhibited by the L-arginine analogue, N^G-monomethyl-L-arginine (L-NMMA). In a study performed at the Wellcome Research Laboratories in Kent, Dr E Nava and colleagues (*Lancet* 1991;**338**:1555–7) showed that in anaesthetised rats the prolonged hypotension which followed the intravenous administration of endotoxin was prevented by giving L-NMMA intravenously in a dose of 30 mg/kg 1·5 hours after the endotoxin. The dose was critical as a low dose (3 mg/kg) had no effect and a high dose (300 mg/kg) initially raised the blood pressure but after three hours caused sudden calamitous hypotension.

At St George's Hospital in London Dr Andy Petros and his colleagues (*Lancet* 1991;**338**:1557–8) used L-NMMA and another NO synthase inhibitor, N^G-nitro-L-arginine methyl ester (L-NAME) to treat two men aged 59 and 75 years both of whom had septic shock unresponsive to conventional treatment and were considered unlikely to survive. In both of them the NO synthase inhibitor produced rapid reversal of hypotension and each of them was able to maintain a normal blood pressure without treatment within 48 hours. One patient survived but the other died two days later from the complications of severe sepsis.

NO synthase inhibitors are experimental, unlicensed drugs and there is some way to go before they can be proved to be of use in clinical practice but with the further development of these drugs and of the specific antibodies to endotoxin and the cytokines (see Archivist 1991:1021) some optimism about the future management of septic shock is perhaps not entirely out of place. Dead rats for live people seems to me the sort of bargain only the most incorrigible fanatic would deny.

ARCHIVIST