ORIGINAL ARTICLES

Neuropsychological sequelae of haemolytic uraemic syndrome

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Abstract

***Background*—Severe haemolytic uraemic syndrome (HUS) in childhood can cause stroke, hemiplegia, cortical blindness, and psychomotor retardation. These outcomes are evident at the time of discharge immediately after the acute illness. Less is known about the neuropsychological outcomes of less severely affected children who recover from acute HUS.**

***Aims*—This multicentre case control study investigated the hypothesis that children who survive an acute episode of HUS without recognisable neurological injuries have greater impairment of cognitive, academic, and behavioural functions than controls.**

***Design*—Children with HUS were eligible if they had no evidence of severe neurological dysfunction when discharged from one of six Canadian hospitals. Controls had been admitted to hospital for a non-HUS illness and were matched by age, sex, first language, and socioeconomic status. All subjects underwent evaluation of behaviour, academic achievement, cognitive function, and verbal abilities using standardised tests administered by a psychometrist blinded to the case or control status.**

***Results*—Ninety one case control pairs were enrolled. No important differences between patients with HUS and paired controls were evident on tests of IQ, behaviour, verbal abilities, or academic achievement. There was no increased risk of attention deficit disorder among patients with HUS. There was no correlation between the severity of acute renal failure and neuropsychological measures, although scores on some verbal ability tests were lower in those with the highest serum creatinine concentrations during illness.**

***Conclusions*—Children discharged from hospital without apparent neurological injury after an episode of acute HUS do not have an increased risk of subclinical problems with learning, behaviour, or attention.**

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Keywords: haemolytic uraemic syndrome; cognitive function; behaviour

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The haemolytic uraemic syndrome (HUS) is a leading cause of acute renal failure in childhood. Typically, it follows a gastrointestinal illness caused by strains of *Escherichia coli* that elaborate verotoxins (or shigatoxins), and has an annual incidence of 1.44–1.74/100 000 in North American children less than 15 years of age.[1–3] Symptoms of central nervous system dysfunction, ranging from lethargy to coma, were reported among 33–52% of acutely ill patients in earlier series.[4–9] Postulated mechanisms of these symptoms include hyponatraemia, hypertension, uraemia, and consequences of endothelial injury initiated by verotoxin, namely endothelial swelling, microthrombi and, less commonly, large vessel thrombosis.[10] Seizure disorders, hemiplegia, cortical blindness, and psychomotor retardation have been reported in 2–5% of survivors of an acute episode of HUS, but these chronic neurological sequelae have been observed only after severe acute central nervous system involvement.[4–9 11]

Little information is available on the prevalence of clinically important abnormalities in cognitive function, academic performance, and behaviour in those who escape obvious and severe neurological deficits as a consequence of an acute HUS episode. This information would be important for clinicians and for parents of these children. In a pilot investigation of 22 survivors of HUS whose neurological function was grossly normal at discharge from hospital, six of whom had experienced seizures or coma, we identified a non-significant trend toward deficits in some aspects of verbal intelligence, language skills, and behavioural control when survivors of HUS were compared with matched controls.[12] Statistical comparisons were limited by the relatively small sample size. We conducted this large, multicentre study to investigate the hypothesis that children who survive an acute episode of HUS without obvious neurological injury nonetheless have greater impairment of neuropsychological function than controls.

Patients and methods

The study was carried out at six tertiary care hospitals within the reporting network of the Canadian Pediatric Kidney Disease Research Centre (CPKDRC). The participating hospitals were: British Columbia Children's Hospital

(Vancouver), Alberta Children's Hospital (Calgary), University of Alberta Hospital (Edmonton), Winnipeg Children's Hospital (Winnipeg), Hospital for Sick Children (Toronto), and the Children's Hospital of Eastern Ontario (Ottawa).

STUDY PARTICIPANTS

Children who had survived an episode of acute HUS and who had been enrolled in previous epidemiological studies conducted by the CPKDRC were eligible for this study if they fulfilled the following criteria: (1) at the time of discharge from hospital after the acute episode of HUS, there was no evidence of stroke, hemiplegia, cortical blindness, seizures requiring daily anticonvulsant treatment, or movement disorder interfering with activities of daily living; (2) no evidence of chronic renal insufficiency requiring dialysis; (3) age 4 to 16 years at the time of psychometric assessment; (4) onset of HUS at least six months before testing; (5) first language English; and (6) no history before the episode of HUS of mental retardation, neurological abnormalities, chronic illnesses associated with learning disabilities, known learning disabilities, or attention deficit disorder. Seizures or coma were not necessary or sufficient reasons for exclusion. Controls were selected from among those who had been admitted to the same hospital for at least five days for treatment of appendicitis, cellulitis, fracture of the femur, osteomyelitis, or pneumonia. These diagnoses were chosen because they had a length of stay in hospital comparable with that required for the treatment of acute HUS, thereby controlling for behavioural changes owing to the hospitalisation itself. Controls were matched to each patient on the basis of age (± 1 year), time since illness (± 6 months), sex, first language, and socioeconomic status. Matching on socioeconomic status was accomplished using postal code data to select subjects living in census tracts with mean annual incomes within $10 000 of the patient.[13] Eligible controls were excluded if they had any of the following: (1) previous HUS; (2) chronic renal insufficiency; (3) a history of mental retardation, neurological abnormalities, chronic illnesses associated with learning disabilities, known learning disabilities, or attention deficit disorder identified before their acute hospitalisation. Our study was approved by the ethics committees of the participating hospitals, and informed consent was obtained from the parents of all subjects.

NEUROPSYCHOLOGICAL ASSESSMENTS

To ensure blinded neuropsychological assessments, survivors of HUS and controls were recruited by a research assistant, and the psychometrist at each centre remained blinded to the patient/control status of the participants. The assessment battery consisted of the following measures of behavioural, cognitive, and academic function.

Behavioural ratings

Child behavior checklist (CBCL)[14]—This scale provides parents with a standard behavioural rating format for children aged 4–16 years, and yields seven behaviour problem scores (anxious, depressed, somatic, social withdrawal, hyperactive, aggressive, and delinquent) and three social competence scores (activities, social, and school).

Teacher report form (TRS)—This rating scale is the teacher's version of the CBCL. It provides a standard behavioural rating format for children between 5 and 18 years of age. The profile includes scales for academic performance, four adaptive characteristics, eight behavioural problems, and summary externalising, internalising, and total scores.

Swanson, Nolan and Pelham checklist (SNAP)[15]—This checklist is a 23 item rating scale that provides separate measures of inattention, impulsivity, overactivity, and peer interaction.

Cognitive abilities

The Wechsler intelligence scales were used to measure the level and pattern of cognitive abilities and provide subtest scores as well as verbal, performance, and full scale IQ scores. Children who were younger than 6 years were evaluated with the Wechsler preschool and primary scale of intelligence–revised (WPPSI-R),[16] and the Wechsler intelligence scale for children–3 (WISC-3)[17] was used for those from 6 years to 16 years 11 months. WPPSI-R and WISC-3 scores were combined for analysis.

Academic achievement

The following brief measures of reading accuracy and comprehension, spelling, computation, and written output were selected to screen for problems in core school subjects.

Wechsler individual achievement test (WIAT)[18]—The three subtests of the WIAT, available as a screening test, were used to measure basic reading, mathematics reasoning, and spelling.

Woodcock reading mastery tests–revised (WRMT-R)[19]—These tests yield measures of reading proficiency from kindergarten to adult levels, and the "brief scale" used for this study combines assessments of word identification and passage comprehension skills.

Test of written language–2 (TOWL-2)[20]—The spontaneous writing sample of the TOWL-2 was used in this study. Subscores for spelling, style, syntax, contextual vocabulary, and thematic content as well as total "spontaneous writing" score are derived from this sample. The measure is appropriate for subjects 7½ years and older.

Verbal abilities

Peabody picture vocabulary test–revised (PPVT-R)[21]—This measure of receptive vocabulary covers the age range of 2½ years to adult. Scores are expressed as age equivalents or standard scores (mean, l00; SD, 15).

Stanford-Binet intelligence scale (4th ed) sentence memory test (SBSM)[22]—This test of memory for meaningful language units is a component test in a widely used intelligence scale. Scores

Table 1 Characteristics of patients with HUS enrolled and not enrolled in the study

	Patients enrolled	*Patients not enrolled*	*Patients with HUS 1991–94*	*p Value*
Number of patients	91	93	205	
Seizures or coma (n)	9	17	22	0.26
Low haemoglobin (g/l)	61.9 (14.6)	62.2 (14.1)	61.8 (13.2)	0.96
Peak WBC ($\times 10^9$/l)	25.1 (13.6)	22.9 (10.9)	23.6 (14.3)	0.52
Peak creatinine (μmol/l)	387 (245)	418 (380)	327 (278)	0.04
Dialysis (n)	51	49	78	0.008
Length of dialysis (days)	12.0 (8.2)	11.1 (10.4)	11.6 (10.4)	0.88
Length of stay (days)	15.4 (11.4)	15.0 (15.2)	14.1 (15.8)	0.75

Values are mean (SD) except where stated.
WBC, white blood cell count.

Table 2 Comparability of patients with HUS and paired controls

	HUS	*Controls*	*p Value*
Age (years)	8.6 (3.1)	9.2 (3.1)	0.20
Sex (M/F) (n)	40/51	40/51	NA
Green score (SES)	63.4 (6.5)	63.8 (6.4)	0.50
Current school grade	3.1 (2.8)	3.5 (2.9)	0.33
Family size	4.6 (1.0)	4.5 (1.2)	0.52
Age at diagnosis (years)	4.3 (3.1)	4.1 (3.1)	0.65
Time since diagnosis (years)	4.1 (2.4)	4.7 (2.6)	0.12

Values are mean (SD) except where stated.
SES, socioeconomic status.

are expressed as standard age scores (SAS; mean, 50; SD, 8).

The supervising psychologist at each site monitored the consistency and accuracy of the assessments and provided appropriate clinical feedback and follow up. The research assistant abstracted pertinent clinical information from the medical records and interviewed parents regarding demographic data, birth history, growth and development, schooling, and socioeconomic status using the method of Green.[23] Central nervous system symptoms during the acute illness were rated on a three point severity scale (no central nervous system symptoms, irritability/lethargy, seizures/coma). Other clinical indicators of interest identified before the study were the peak creatinine concentration during the acute episode of HUS and the number of days of dialysis.

Table 3 Comparisons between patients with HUS and controls on cognitive, behavioural, and academic measures

Test	*HUS*	*Controls*	*p Value*
Wechsler (n = 91)			
*Verbal IQ	103.8 (14.1)	106.7 (14.1)	0.12
Comprehension	10.9 (3.4)	11.2 (3.1)	0.45
Vocabulary	10.6 (3.0)	10.9 (3.0)	0.47
Information	10.8 (2.6)	10.7 (2.6)	0.74
Similarities	10.7 (2.8)	10.9 (3.0)	0.53
Arithmetic	10.0 (2.8)	10.6 (2.8)	0.16
*Performance IQ	105.4 (14.0)	106.3 (13.1)	0.61
Object assembly	10.8 (3.1)	11.2 (2.6)	0.31
Block design	10.9 (2.7)	11.4 (3.0)	0.32
Picture completion	11.4 (2.7)	11.5 (2.8)	0.89
Full scale IQ	105.2 (13.7)	106.7 (12.9)	0.34
PPVT-R (n = 90)	106.3 (14.3)	106.0 (14.8)	0.91
SBSM (n = 91)	52.4 (7.9)	51.6 (7.8)	0.43
CBCL (n = 90)			
*Internalising total	49.5 (10.8)	51.1 (9.7)	0.31
*Externalising total	46.2 (9.8)	49.6 (9.9)	0.02
Total behaviour problems	47.2 (11.2)	50.2 (10.5)	0.06
Total competence (n = 64)	49.5 (9.5)	50.4 (7.6)	0.60
CBCL teacher report form (n = 54)			
Internalising total	48.9 (9.5)	50.3 (10.4)	0.50
Externalising total	47.6 (7.7)	49.3 (8.8)	0.26
Total behaviour problems	47.4 (9.5)	49.6 (10.5)	0.28
Total adaptive functioning	49.3 (8.3)	48.1 (7.8)	0.49
SNAP, ADD-H rating (n = 89)			
Hyperactivity	1.9 (2.5)	2.5 (3.6)	0.16
Inattention	3.0 (3.3)	3.1 (2.9)	0.71
Impulsivity	2.3 (2.6)	2.9 (2.8)	0.12
ADD-H total	7.1 (7.6)	8.6 (8.2)	0.22
WIAT (n = 80)			
*Reading	105.5 (13.9)	102.4 (11.7)	0.13
*Mathematics	101.6 (11.8)	101.0 (11.2)	0.72
*Spelling	101.9 (14.2)	100.6 (11.4)	0.48
WRMT			
Word identification (n = 79)	103.4 (15.4)	101.2 (12.9)	0.35
Passage comprehension (n = 78)	99.7 (13.6)	99.3 (14.3)	0.85
*Total reading (n = 76)	102.1 (15.1)	100.3 (14.7)	0.47
TOWL-2 (n = 52)			
*Story	103.2 (18.6)	100.4 (18.5)	0.42

All values are mean (SD) scores. Some tests were not administered because of the age at the time of testing. One parent of a patient with HUS did not complete the CBCL.
*Primary study outcomes.
CBCL, child behaviour checklist; PPVT-R, Peabody picture vocabulary test–revised; SBSM, Stanford-Binet intelligence scale (4th ed) sentence memory test; SNAP, Swanson, Nolan and Pelham checklist; TOWL-2, test of written language–2; WIAT, Weschler individual achievement tests; WRMT, Woodcock reading mastery tests; ADD-H, attention deficit disorder–hyperactivity.

SAMPLE SIZE AND POWER

Before our study began, we identified the primary study outcomes of interest as the verbal and performance IQ scores, CBCL internalising and externalising standard scores, WIAT and WRMT-R standard scores, and the TOWL-2 standard score. Sample size estimates were conservatively based on independent groups. To detect a clinically important difference of 0.5 SD on standardised tests, with an α level of 0.05 and a power of 0.90, we estimated a need for 100 patients and controls. The recruited sample proved well matched, and therefore had a 0.90–0.95 power to detect the 0.5 SD difference between the pair matched groups.

STATISTICAL ANALYSIS

Paired *t* tests and analysis of variance were used for comparisons of continuous outcome measures between patients and controls. The relation between HUS severity categories and psychometric measures was evaluated using polynomial linear contrast in the analysis of variance procedure. A non-parametric rank correlation (Spearman's rho) was used to examine the association between neuropsychological outcomes and the peak creatinine concentrations during the illness, as peak creatinine was not normally distributed in this sample.

The α level for the main outcomes was established before the study at 0.05. For secondary analyses, a nominal p value is reported. Correlations between -0.4 and -1.0 or between 0.4 and 1.0 were considered clinically important.

Results

PATIENTS

One hundred and eighty four children in participating centres had been identified in previous CPKDRC studies of HUS. Of these, 91 were enrolled, and 93 were not enrolled for the following reasons: 33 could not be located, 28 were ineligible (eight were dead, 11 had obvious neurological injury, five were older than age 16 years, three did not speak English as their first language, and one had chronic renal disease), 17 refused to participate, 15 lived too far from the hospital for participation to be feasible.

The enrolled participants did not differ from the potentially eligible non-participants (table 1). Compared with a virtually complete sample of 205 Canadian children with HUS studied prospectively from 1991–94,[24] patients enrolled in our study had higher mean (SD) peak

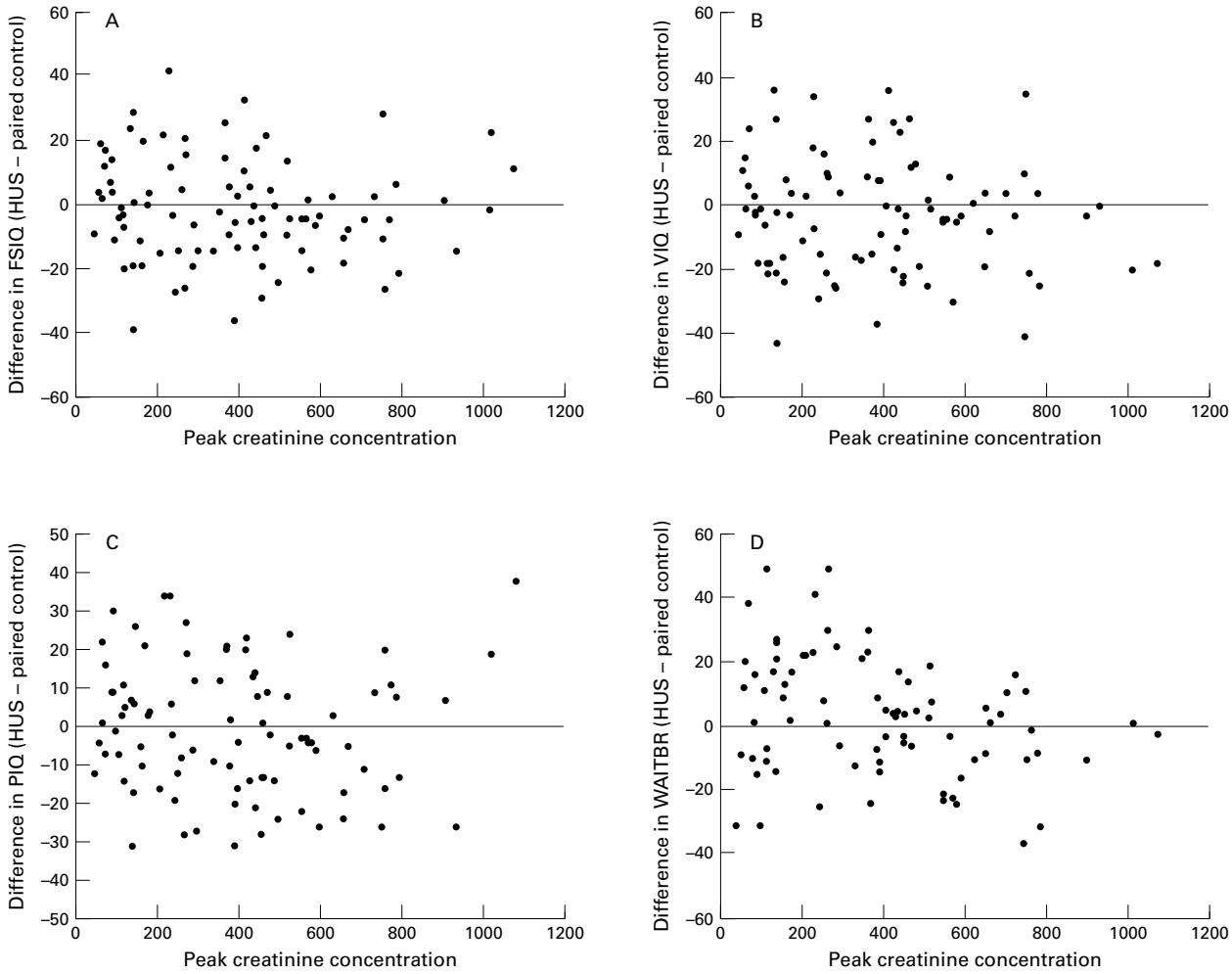

Figure 1 Differences scores (score for patient with HUS minus score for matched control) on selected neuropsychological tests plotted against the peak creatinine concentration for the patient with HUS. A, Wechsler full scale IQ (FSIQ); B, Wechsler verbal IQ (VIQ); C, Wechsler performance IQ (PIQ); D, Wechsler individual achievement basic reading subtest (WAITBR).

creatinine values (387 (245) *v* 327 (278); p = 0.04) and higher rates of dialysis (56% *v* 38%; p = 0.02), indicating more severe acute renal injury. The median duration of dialysis was 10 days (range, 2–48 days). Only 9 of the patients in the current study had seizures or coma during the acute HUS episode. Sixty five enrolled subjects had stool culture confirmation of *E coli* O157:H7. As is shown in table 2, patients with HUS and the controls were well matched. The Green scores reflect predominantly middle to upper middle socioeconomic status.

NEUROPSYCHOLOGICAL OUTCOMES

As shown in table 3, there were no differences between patients with HUS and their matched controls with regard to the main cognitive or academic achievement tests. There was a trend towards lower scores among patients with HUS on the externalising behaviour problems subscale of the CBCL, suggesting fewer problems with delinquency and aggressive behaviour, but this difference was not clinically important, as scores for both groups were within the test's parameters for normal. There were no differences between patients and their matched controls on any of the other study assessments (table 3) or on subscales of these tests. Only two patients and three controls had repeated a grade of school (p = 0.56). Sixteen patients with HUS compared with 13 controls were receiving remedial assistance in school (p = 0.69).

On the attention subscale of the CBCL, no difference was noted between mean (SD) scores for patients and their matched controls (53.8 (6.3) *v* 53.6 (8.2); p = 0.92). We used the clinical cut off point score on the CBCL of 67 or higher to assess the prevalence of attention deficit hyperactivity disorder in the sample. Parent CBCL ratings identified six of 90 patients with HUS who had scores of 67 or greater, with the highest score being 72, compared with four of 91 controls, with the

Table 4 Clinical characteristics of HUS patients grouped by the size of the rise in serum creatinine concentration during the acute illness

	Group 1	*Group 2*	*Group 3*
Rise in peak creatinine*	< 4×	4–8×	> 8×
Number of patients	27	31	33
Dialysis	1	18	32
Median days of dialysis	0	4	11
Red blood cell transfusion	16	24	27
Lethargy	15	19	24
Seizures	0	4	5
Coma	0	0	1

*In multiples of the upper limit of the reference range for age.

*Table 5 Case control difference scores on selected measures of cognitive and academic function by creatinine severity group**

	Severity group 1				*Severity group 2*				*Severity group 3*				
Assessment	*n*	*HUS‡*	*Control‡*	*Difference§*	*n*	*HUS*	*Control*	*Difference*	*n*	*HUS*	*Control*	*Difference*	*p Value†*
Wechsler													
Verbal IQ	27	101.7	104.8	−2.6 (3.4)	31	108.8	103.4	−0.4 (3.4)	33	100.8	107.8	−6.0 (2.9)	0.69
Performance IQ	27	105.5	103.9	2.3 (2.7)	31	109.2	105.7	1.3 (3.4)	33	101.8	106.8	−5.1 (2.9)	0.26
Full scale IQ	27	104.1	104.4	0.4 (3.0)	31	110.0	104.6	0.8 (3.2)	33	101.5	107.1	−5.4 (2.3)	0.37
WIAT													
Reading	25	107.6	99.7	6.5 (4.0)	26	111.4	103.1	8.0 (3.7)	29	98.5	101.9	−4.1 (2.6)	0.008
Mathematics	25	101.3	99.8	2.1 (3.4)	26	104.4	102.4	6.3 (5.0)	29	99.3	101.5	−2.6 (2.4)	0.50
Spelling	25	103.4	98.1	4.8 (2.9)	26	106.9	97.8	5.8 (3.7)	29	96.3	102.5	−5.5 (3.2)	0.05
WRMT													
Word identification	25	106.6	98.1	6.1 (4.0)	26	107.2	99.9	5.8 (4.3)	28	97.1	101.1	−4.6 (3.7)	0.02
Passage composition	25	101.3	100.1	0.3 (3.4)	26	103.1	102.0	3.7 (3.9)	28	94.5	98.0	−2.7 (3.5)	0.06
Total reading	24	105.0	100.1	4.3 (4.2)	26	106.0	100.8	5.3 (4.1)	28	95.5	100.0	−4.2 (3.9)	0.02
TOWL-2	18	104.8	97.4	5.1 (5.7)	14	107.7	91.8	18.1 (6.3)	20	97.0	104.6	−10.1 (4.2)	0.18
PPVT-R	27	105.4	105.3	2.3 (4.6)	31	111.6	102.1	5.2 (3.5)	33	102.4	109.6	−6.2 (2.7)	0.34
SBSM	27	52.2	50.3	0.9 (2.0)	31	54.8	52.9	3.6 (1.7)	33	50.3	50.6	−1.8 (1.7)	0.29

*Creatinine severity groups are defined in table 4.
†Comparison of creatinine severity group mean differences between pairs using weighted linear trend analysis.
‡Values for HUS and controls are the group means.
§Values for differences are the mean (SE) differences between paired patients with HUS and controls.
PPVT-R, Peabody picture vocabulary test–revised; SBSM, Stanford-Binet intelligence scale (4th ed) sentence memory test; TOWL-2, test of written language–2; WIAT, Weschler individual achievement tests; WRMT, Woodcock reading mastery tests.

highest score being 77 ($p = 0.74$). On the CBCL teacher report form, one of 67 patients with HUS and one of 62 controls had scores of 67 or higher ($p = 0.73$). No differences between groups were present on the total problem score for the CBCL teacher report form or for any of its subscales. Similarly, no differences between groups were identified on the brief parent ratings of attention deficit hyperactivity disorder as measured by the SNAP checklists (table 3).

DISEASE SEVERITY AND NEUROPSYCHOLOGICAL OUTCOMES

To examine the study hypothesis that increasingly severe HUS would be associated with worse neuropsychological outcomes, we used the highest recorded creatinine concentration during the acute illness as a proxy for disease severity. Figure 1 shows the distribution of the difference scores (score for the patient with HUS minus the score for the matched control) by the peak creatinine concentration for selected outcomes of interest. No significant correlations (< -0.4 or > 0.4) were identified between the peak creatinine concentration and differences between patients and controls on any neuropsychological tests. The strongest correlations were noted on some tests of verbal ability, such as the WIAT spelling subtest ($r = -0.31$), the WIAT basic reading subtest ($r = -0.28$), and the WRMT total reading subtest ($r = -0.25$), indicating a trend towards a lower score on these tests for patients with HUS who had higher peak creatinine concentrations. No correlation was noted for the other main tests of verbal language, the verbal IQ ($r = -0.09$), the TOWL-2 ($r = -0.20$), or the PPVT ($r = -0.16$).

To explore whether there might be a threshold of HUS severity beyond which neuropsychological deficits were more common, the study population was divided into three roughly equal groups on the basis of age adjusted multiples of the highest recorded creatinine concentration. As shown in table 4, increasing severity of illness as determined by these categories also reflected increasing severity using other clinical and laboratory measures. Table 5 shows differences between cases and controls on cognitive and academic measures between the three creatinine severity categories (no differences were noted on the CBCL or other behavioral measures, and these data are not shown). Although no differences were identified between groups on the Wechsler IQ tests, PPVT-R, SBSM, or TOWL-2, a significant difference was noted on the WIAT basic reading subtest, and trends ($p < 0.10$) were identified in the difference scores on the WRMT-R and on the WIAT spelling subtest. No other methods of classifying the severity of the illness proved more informative, including dividing the study population based on two rather than three creatinine severity classes, on the presence of seizures or coma, or on the basis of the duration of dialysis ($\geq$ 10 days *v* < 10 days of dialysis or no dialysis).

Discussion

Over the past four decades, improvements in the recognition and management of childhood HUS have contributed to a substantial reduction in the mortality of the disease, from 100% in Gasser's 1955 series to less than 3% in the last decade.[3 25–27] As the survival rate has improved, attention has shifted to the sequelae of an acute episode. Because there is a spectrum in the severity of renal injury HUS, we hypothesised that a similar spectrum of cerebral injury would result in subclinical problems with learning and behaviour in survivors of HUS who had no obvious neurological impairment at the time of discharge after the acute illness. Our results provide little support for this hypothesis. In this large sample of children who made an uncomplicated recovery from an acute episode of HUS, there was no increase in the risk of clinically important central nervous system sequelae when patients were compared with carefully matched controls. On all main measures of cognitive, academic, and behavioural function, children with HUS fared no worse than controls. These formal observations accord with low rates of grade retention and remedial services in both

groups, and are consistent with more recent reports of good neurological outcome despite prolonged coma[11] and other acute neurological symptoms.[9 28]

However, our results cannot be generalised to children with obvious neurological impairment at the time of discharge from hospital after the acute HUS episode. Because clinicians and families would already be alerted to the possibility of neurological dysfunction in those with chronic renal impairment requiring dialysis,[29] or in those with severe neurological dysfunction (specifically stroke, hemiplegia, cortical blindness, seizures requiring daily anticonvulsant treatment, or movement disorders interfering with activities of daily living), HUS patients with these conditions were excluded from this study. Our main focus was on those who appeared to have recovered completely from their HUS, but who might nonetheless have important subclinical abnormalities in neuropsychological function.

Our study does not provide definitive answers regarding possible mild neuropsychological deficits in those with the greatest rises in serum creatinine among the study population. Consistent with the direction of data in the earlier pilot study, this larger investigation identified weak correlations between the severity of the HUS episode and some measures of verbal ability and language achievement. Although the trend towards a neuropsychological deficit in the most severely affected group makes biological sense, it is not clear why it is restricted to language domains, and is only evident on some tests of language. It remains possible that this is a chance finding specific to the study population, rather than a true trend.

Two other aspects of the study methodology deserve comment. First, although siblings represent an alternative source of controls, and have the advantage of being better matched with regard to socioeconomic status and heritable influences on cognition, we considered it unlikely that we would be able to identify a sufficient number of sibling controls of similar age and sex, and some sibling controls would have been ineligible because they too would have been affected by HUS. The current control group was closely matched on the basis of socioeconomic status, and controls were also matched on the basis of a previous hospitalisation, to exclude the small possibility of a behavioural effect attributable to the hospitalisation itself.[30] Second, the neuropsychological studies performed are widely used and well standardised. It is possible that other tests might have detected deficits not appreciated in our study, but we believe that this is unlikely.

A fruitful focus for subsequent studies will be the clinical, demographic, genetic, or microbiological factors that protect a child with severe HUS from neurobehavioural sequelae. A major challenge in such research will be how to incorporate the influence of heritable disorders in learning and attention on post-HUS function. Such abnormalities in reading and attention are usually identified during the early school years, while the peak prevalence of HUS is in those younger than 5 years, creating the potential for a distortion of the effect of HUS on observed learning or attentional problems. Given that a high number of so called soft neurological signs can be found in ~ 19% of normal schoolchildren,[31] it will be important in future studies to include a control group before it is possible to ascertain whether HUS survivors have a higher rate of clumsiness, poor fine motor coordination, or distractibility, as has been suggested by the authors of one small case series.[28] In fact, with regard to distractibility, our data demonstrate that attentional problems are no more common in HUS survivors who are neurologically normal at discharge than they are in controls.

The knowledge that normal cognitive and behavioural function can be expected for those without obvious neurological deficits following the HUS episode will be reassuring to parents, many of whom have been aware of the possibility of learning problems in the wake of the disorder. In addition, this information will be important to physicians, who need not include neuroanatomical studies or neuropsychological tests as a routine part of the careful follow up of HUS survivors.

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