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Influence of Extraneurological Insults on Ventricular Enlargement and Neuropsychological Functioning after Moderate and Severe Traumatic Brain Injury

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ABSTRACT

Extraneurological insults secondary to TBI such as hypotension or hypoxia have been associated with mortality and morbidity. The purpose of this study was to investigate the influence of systemic complications on both neuropsychological outcome and cerebral atrophy. Fifty-seven patients selected from 122 consecutive admissions were studied. Data on the type and severity of injury as well as other systemic insults were collected prior to and during the first 3 days of hospitalization. These data included the presence or absence of a hypoxic episode during the pre-hospital period, the presence and degree of hypoxia, hypercapnia, anemia, hypotension and intracranial hypertension, pupillary reactivity, Glasgow Coma Scale score and coma duration. From the last control CT scan image, performed 6 months post-injury, four different indexes of ventricular dilatation were calculated. Neuropsychological assessment at 6 months included tests of verbal and visual memory, visuoconstructive functions, fine motor speed, and frontal lobe functions. Our results showed that hypoxia and hypotension were related to neuropsychological outcome and long-term ventricular enlargement. Hypoxic episodes prior to hospitalization were related to third ventricle dilatation and to adverse neurological and cognitive outcomes, especially to attention, motor speed, mental flexibility, fluency and verbal memory impairments, suggesting fronto-striatal and hippocampal dysfunction. We conclude that the effect of extraneurological insults on brain structure and function may be as important as the severity of the primary injury.

Key words: head injury; hypoxia; neuropsychology; outcome; ventricular enlargement

INTRODUCTION

THE OUTCOME OF TRAUMATIC BRAIN INJURY (TBI) depends on primary and secondary cerebral damage. Secondary insults can be either neurological (ischemia, hemorrhage, edema, swelling) or extraneurological systemic (hypotension, hypoxia, anemia, malnutrition). Miller et al. (1978) reported that about 44% of patients with severe head injury showed potentially serious systemic insults to the brain that were associated with an increase in mortality and morbidity. Important predictors of poor outcome included early injury severity measures,

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such as the Glasgow Coma Scale (GCS) score, pupillary findings or brain-stem responses, and the presence of systemic factors such as hypoxia or hypotension. Other factors associated with poor outcome are length of unconsciousness (Gilchrist and Wilkinson, 1979; Vilki et al, 1988), age (Levati et al., 1982; Vollmer et al., 1991; Marmarou et al., 1991), GCS scores (Young et al.; 1981; Levati et al., 1982), abnormal motor responses (Jane and Rimel, 1982; Levati et al., 1982), impaired or absent eye movements or pupil light reflexes (Levati et al., 1982; Levin et al., 1990; Marmarou et al., 1991), early onset hypotension (Miller et al., 1981; Levati et al., 1982; Jane and Rimel, 1982; Marmarou et al., 1991), and hypoxemia or hypercarbia (Miller et al., 1981) despite artificial ventilation and intracranial pressure above 20 mm Hg (Jane and Rimel, 1982; Marmarou et al., 1991; Resnick et al., 1997).

After a severe or moderate TBI, almost all patients have some degree of neuropsychological impairment in memory, fine motor coordination, and speech. Although cognitive functions improve markedly during the first year after injury, memory deficits may persist (Tabaddor et al., 1984). Neuropsychological studies have shown that the most important variables influencing the cognitive outcome were coma duration (Vilkki et al., 1988; Wilson et al., 1991), low post-resuscitation GCS score and pupillary reactivity (Levin et al., 1990), increased PTA (Brooks et al., 1980), or elevated ICP (Uzzell et al., 1986).

Neuroimaging studies have shown correlations between ventricular enlargement, coma length, and neuropsychological impairment (Levin et al., 1981; Meyers et al., 1983). The prognostic value of the width of the third ventricle was reported to be superior to any of the other indexes studied, and it was the variable that correlated best with late cognitive status (Reider-Groswasser et al., 1993). Previous studies have reported an association between cognitive outcome and several neuroimaging features, including the size and localization of lesions (Levin et al., 1987), the type of injury (Uzzell et al., 1987) and the presence of focal lesions (Ross et al., 1994). One recent paper reported a relationship between the type of CT scan lesion based on the Traumatic Coma Data Bank classification and both neuropsychological results and ventricular dilatation indices at 6 months post-injury (Mataró et al., 2001).

Previous studies have found relationships between certain extraneurological insults and neuropsychological outcome. To our knowledge, however, the relationship between the systemic variables indicated above and neuroimaging features of head injury survivors has not been addressed to date. As atrophy measurements are sensitive to injury severity and neuropsychological outcome, it is plausible that neuroimaging data may be related to, and may also reflect, some secondary extraneurological insults. The aim of this study is to investigate the influence of systemic complications on both neuropsychological performance and neuroimaging measurements in a group of moderate and severe head injured patients.

MATERIALS AND METHODS

Patients were selected from a cohort of 122 consecutive cases admitted to the Neurotraumatology Unit of the Vall d'Hebron University Hospital in Barcelona with a GCS score of 13 or less between September 1992 and September 1993. Head injury was moderate in 37 patients and severe in 85. Clinical management was based on current standards of optimal neurosurgical treatment. Thirty-three (38.8%) severe and six (16.2%) moderate patients died as a consequence of the injury. Eighteen patients could not be contacted or refused to participate in the follow-up study, and eight patients were too severely impaired to undergo neuropsychological testing. Fifty-seven patients were finally recruited for the study. Each patient underwent a neuropsychological assessment at 6 months post-injury. Forty-nine (86.0%) were males and eight females (14.0%), and age ranged from 14 to 65 (mean 28.18 years).

Indices of Type and Severity of Injury and Systemic Complications

Data on the type and severity of neurological injury as well as other systemic insults were collected prior to and during hospitalization. The data included the presence or absence of a hypoxic episode during pre-hospital period, pupillary reactivity, Glasgow Coma Scale score at admission, coma duration, and other systemic measures recorded during the first three days of hospitalization, such as the presence and degree of hypoxia, hypercapnia, anemia, hypotension, and intracranial hypertension (Tables 1 and 2).

The operational definitions for the neurological indices of acute injury and systemic variables used in this study are described below.

History of a hypoxic episode prior to hospitalization. We considered the presence of at least one of the following hypoxic signs: abnormal respiration prior to airway control, presence of aspiration, cardiopulmonary arrest, and/or hypoxia ($PaO_2 < 60$ mm Hg, when available).

Pupillary light reflex at admission. Two indices were recorded: Pupillary reactivity, and symmetry. Reactivity

Table 1. Frequency of TBI Patients in Each Systemic, Neurological, and Severity of Injury Variables

	Present	*Absent*	*Unknown*
Hypoxic episode prior to hospitalization	19 (33.3%)	17 (29.8%)	21 (36.8%)
Hypoxia ($PaO_2 < 60$ mm Hg)	6 (10.5%)	50 (87.7%)	1 (1.8%)
Hypercapnia ($PaCO_2 > 45$ mm Hg)	9 (15.8%)	47 (82.5%)	1 (1.8%)
Hemoglobin <12 g/dL	36 (63.2%)	20 (31.5%)	1 (1.8%)
Hematocrit <30%	27 (47.4%)	30 (52.6%)	
Hypotension (SBP ≤ 80 mm Hg)	4 (7%)	53 (93%)	
Intracranial hypertension (ICP > 20 mm Hg)	18 (31.6%)	12 (12.1%)	27 (47.4%)
CPP < 60 mm Hg	12 (12.1%)	18 (31.6%)	27 (47.4%)
Pupillary light reflex at admission	40 (70.2%)	10 (17.5%)	7 (12.3%)
Pupillary symmetry at admission	42 (73.7%)	11 (19.3%)	4 (7%)

was considered normal if both eyes were reactive, and abnormal if either eye failed to react. We also recorded the presence or absence of anisocoria, and the number of non-reactive eyes (0, 1, or 2).

Glasgow Coma Scale and coma duration. Admission Glasgow Coma Scale was used as a measure of severity of patients' neurological status. Eye opening was the criterion used to infer the end of coma.

Hypoxia. Blood gas was recorded on a daily basis during the first three days. We considered hypoxia to be present if Po_2 was less than 60 mm Hg in any of the three measures. We also recorded the lowest value obtained.

Hypercapnia. The cut-off point for the presence of hypercapnia was established at 45 mm Hg. We recorded the presence or absence of hypercapnia and the highest value obtained in the daily-recorded data.

Anemia. To assess anemia we used the daily hemoglobin and hematocrit levels on the first three days. The cut-off points were <12 g/dL for hemoglobin and <30% for hematocrit. We also recorded the lowest value obtained.

Table 2. Mean and Standard Deviation of Extreme Value Measures Recorded

	Mean	*SD*
PaO_2 minimum	97.17	33.70
$PaCO_2$ maximum	40.64	10.21
Hemoglobin minimum	11.16	1.82
Hematocrit minimum	30.22	6.68
Minimum systolic blood pressure	99.72	15.28
Maximum ICP	24.20	10.98
Minimum CPP	60.90	9.26

Hypotension. Blood pressure was collected hourly during the first three days. We recorded the occurrence of hypotension (systolic blood pressure less than 80 mm Hg) and the lowest value obtained in the hourly-collected data during the first three days.

Intracranial pressure and cerebral perfusion pressure. Intracranial pressure monitoring was used in 26 patients. We recorded the initial value and established the cut-off point for intracranial hypertension at 20 mm Hg. Cerebral perfusion rates were also computed. Cut-off level was 60 mm Hg.

Neuropsychological Assessment

Neuropsychological assessment 6 months post-injury was performed with a battery of validated tests previously used in head injury research involving severely injured patients (Clifton et al., 1992). A Spanish version of *The Selective Reminding Test* (Buschke and Fuld, 1974) was used to measure verbal learning and memory. Visual memory was assessed with the 3-min and 30-min delayed recall test from the *Rey-Osterrieth Complex Figure* (Rey, 1959). The copy trial of the Rey *Complex Figure* was used to evaluate the visual-constructional ability. Parts A and B of the *Trail Making Test* (Reitan, 1958) were given to measure visual scanning, motor speed and attention and mental flexibility. Verbal fluency was evaluated using the *Controlled Oral Word Association Test* (Benton, 1994). The number of words starting with the letters F, A, and S recalled in 1 min was recorded. Speed and fine motor coordination were assessed with the *Lafayette Grooved Pegboard Test* (Klove, 1963). Visual scanning, tracking and motor speed were also assessed by the *Symbol Digit Modalities Test* (Smith, 1991). Global adjust-

ment to activities of daily living and general outcome was assessed using the *Glasgow Outcome Scale* (GOS) (Jennett and Bond, 1975). The Galveston Orientation and Amnesia Test (GOAT) (Levin et al., 1979) was also administered as a measure of orientation and amnesia and as an indicator of level of responsiveness. Although this test is designed mainly to reflect resolution of post-traumatic amnesia and is normally used in the acute period to determine the baseline period for initiating formal testing, we administered it at 6 months as an exclusion criterion to be sure that the patient was able to complete the neuropsychological examination.

Neuroimaging Data

Computed tomography (CT) scans were performed in each patient at a mean of 6 months post injury (range 5–9 months). For each CT scan, several measures of ventricular dilation were calculated: Evans index, third ventricle index, cella media index and ventricular score (Fig. 1).

Statistical Analysis

Group comparisons were performed using the Student's *t*-test statistic for independent samples. ANCOVA was included when it was required to control for the effects of severity of injury on neuropsychological and neuroimaging data. Pearson product–moment correlation coefficients were calculated for neuropsychological variables, neuroimaging indices, systemic factors and severity of injury data. For the non-parametric comparisons, Mann Whitney's *U*-Test statistic for independent samples and the Spearman's rank correlation test for the correlation were used. The level of significance was established at $p < 0.01$.

RESULTS

Of the 57 patients, head injury was moderate in 18 (32%; GCS 9–13) and severe in 39 (68%; GCS < 8). Median admission GCS score was 7 [6,9] while mean average time in coma was 5 ± 5 days (range 1–30). According to the Glasgow Outcome Scale at 6 months, 37 (65%) patients achieved a good recovery, 13 (23%) were moderately disabled, and seven (12%) severely disabled.

Severity of injury (GCS motor score and pupillary reactivity) differed significantly between the pre-hypoxia groups. We did not find any significant differences in the severity of injury in the remaining groups according to the other systemic variables. Therefore, in the pre-hypoxia groups, we performed an analysis of covariance by entering the GCS as a covariate to rule out the effect of injury severity on cognitive outcome and ventricular enlargement.

Extraneurological Variables

History of a hypoxic episode prior to hospitalization. As shown in Table 3, differences in neuropsychology and neuroimaging indexes between patients with a pre-hospital hypoxic episode and those without history of hypoxia were analysed by an ANCOVA controlling for the effects of severity of injury (GCS and pupillary reactivity). Patients with a pre-hospital hypoxic episode showed significantly worse global outcome according to the GOS and a tendency to perform worse on attention and mental flexibility (TMT A and SDMT), fluency, and verbal memory than the group without a history of hypoxia. The neuroimaging analysis showed the IIIrd ventricle to be significantly larger in the pre-hospital hypoxic group.

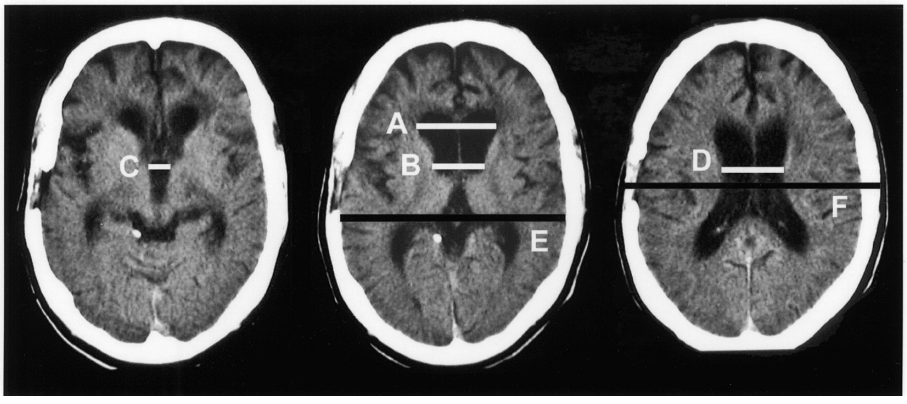

FIG. 1. CT images of the brain of a patient with TBI. Measures of ventricular size: Evans Index = A/E; III Ventricle Index = C/D; Cella Media Index = D/F; Ventricular Score = [(A + B + C + D)/E] × 100.

Table 3. Neuropsychological and Neuroimaging Mean and Standard Deviation Scores of TBI in Relation to Extraneurological Variables

	Prior hypoxic episode			*$PaO_2 < 60$ mm Hg*			*$PaCO_2 > 45$ mm Hg*		
	Absent	*Present*	*F*	*Absent*	*Present*	*t/Z*	*Absent*	*Present*	*t/Z*
Memory									
Sum recall	44 (10.9)	38 (12.7)	3.9*	42.06 (13.08)	40.83 (11.37)	0.82	41.53 (12.90)	44.00 (12.90)	0.52
Delayed free recall	6.82 (3.59)	5.47 (3.7)	2.42	6.50 (3.68)	6.33 (2.65)	0.91	6.38 (3.63)	7.00 (3.39)	0.47
Figure 3-min recall	21.21 (5.8)	16.81 (9.1)	1.30	18.65 (7.85)	18.50 (8.08)	0.96	18.25 (7.79)	20.92 (8.00)	0.83
Frontal functions									
FAS	34.35 (9.7)	24.84 (9.01)	4.58*	28.44 (9.92)	35.50 (9.77)	0.10	29.34 (10.44)	28.44 (8.32)	−0.24
TMT A	48.47 (20.3)	92.39 (67.8)	4.23*	83.23 (68.97)	70.33 (34.77)	0.65	80.16 (62.47)	89.67 (84.62)	0.39
TMT B	107.1 (74.0)	153.5 (74.8)	2.55	132.95 (81.97)	162.50 (107.36)	0.42	137.24 (82.06)	133.13 (103.51)	−0.12
SDMT	43.63 (14.1)	29.44 (15.2)	3.64*	36.40 (16.87)	33.20 (14.94)	0.68	35.37 (16.73)	40.14 (16.18)	0.71
Fine motor speed									
Pegboard right	84.6 (37.1)	88.5 (22.8)	0.75	87.85 (40.38)	110.50 (83.57)	0.54	89.32 (41.02)	96.75 (73.96)	0.41
Pegboard left	90.0 (56.3)	95.67 (22.8)	1.06	93.79 (39.98)	86.00 (23.86)	0.64	90.52 (26.14)	104.56 (75.71)	0.99
Global outcome									
GOS[a]	1.12 (0.5)	1.63 (0.7)	10.2**	1 [1, 2]	1 [1.5, 2]	−0.57	1 [1, 2]	1 [1, 2]	−0.02
Neuroimaging									
Ventricular Score	60.61 (10.1)	58.98 (9.7)	0.49	63.31 (12.59)	65.08 (16.62)	0.40	59.71 (12.49)	67.41 (14.80)	1.57
Evans Index	0.28 (0.04)	0.27 (0.04)	2.01	0.277 (0.042)	0.280 (0.046)	0.89	0.275 (0.042)	0.291 (0.036)	0.98
III Ventricle Index	0.039 (0.016)	0.032 (0.01)	5.65**	0.038 (0.019)	0.040 (0.020)	0.88	0.039 (0.019)	0.038 (0.020)	−0.04
Cella Media Index	0.147 (0.045)	0.162 (0.048)	0.53	0.146 (0.050)	0.154 (0.036)	0.72	0.151 (0.050)	0.166 (0.036)	0.81

	Hemoglobin < 12 g/dL			*Hematocrit < 30%*			*SBP < 80 mm Hg*		
	Absent	*Present*	*t/Z*	*Absent*	*Present*	*t/Z*	*Absent*	*Present*	*t/Z*
Memory									
Sum recall	40.60 (12.81)	41.86 (13.12)	0.35	42.30 (12.03)	40.89 (14.00)	−0.40	42.62 (12.22)	28.50 (16.44)	−1.68
Delayed free recall	5.80 (3.10)	6.64 (3.90)	0.82	6.67 (3.45)	6.07 (3.82)	−0.61	6.72 (3.48)	2.00 (2.44)	−2.65**
Figure 3-min recall	16.40 (8.14)	19.54 (7.50)	1.36	17.81 (7.42)	19.37 (8.28)	0.70	18.85 (7.68)	14.50 (3.48)	−1.07
Frontal functions									
FAS	27.60 (10.26)	29.64 (9.75)	0.73	29.13 (10.30)	29.19 (9.80)	0.02	29.51 (9.90)	24.50 (11.26)	−0.96
TMT A	110.74 (92.44)	66.26 (37.52)	−2.00	94.00 (79.43)	66.84 (40.59)	−1.54	81.90 (67.82)	75.50 (13.69)	−0.18
TMT B	161.06 (102.63)	130.58 (75.43)	−1.05	143.58 (87.05)	133.71 (85.06)	−0.40	135.33 (84.95)	179.25 (91.72)	0.92
SDMT	33.88 (21.53)	36.26 (13.46)	0.41	35.93 (18.50)	35.50 (14.23)	−0.08	36.42 (16.95)	28.00 (9.05)	−0.97
Fine motor speed									
Pegboard right	103.83 (61.37)	86.71 (40.16)	−1.06	96.64 (50.37)	87.56 (46.26)	−0.68	91.43 (49.06)	103.75 (40.20)	0.57
Pegboard left	113.74 (71.33)	87.65 (23.82)	−1.54	106.72 (59.56)	85.16 (23.49)	−1.69	97.28 (49.02)	90.00 (16.97)	−0.29
Global outcome									
GOS[a]	1 [1, 2]	1 [1, 2]	−0.03	1 [1, 2]	1 [1, 2]	−0.37	1 [1, 3]	1 [1, 2]	−1.11
Neuroimaging									
Ventricular Score	61.48 (12.98)	61.22 (13.42)	−0.06	60.57 (13.27)	61.81 (13.10)	0.35	60.56 (13.26)	68.67 (8.42)	1.19
Evans Index	0.283 (0.043)	0.276 (0.041)	−0.58	0.278 (0.036)	0.278 (0.048)	−0.03	0.276 (0.041)	0.30 (0.035)	1.08
III Ventricle Index	0.037 (0.019)	0.040 (0.020)	0.43	0.039 (0.020)	0.039 (0.019)	−0.11	0.039 (0.019)	0.042 (0.021)	0.28
Cella Media Index	0.160 (0.055)	0.152 (0.045)	−0.58	0.153 (0.055)	0.156 (0.041)	0.17	0.152 (0.050)	0.180 (0.027)	1.06

[a]Values expressed as median and interquartile range.

**$p < 0.01$.

SBP, systolic blood pressure.

Hypoxia. There was no significant association between the neuropsychological and neuroimaging results of patients without any recorded episode of hypoxia during the first three days and those whose arterial Po_2 (Pao_2) was below 60 mm Hg. The degree of Pao_2 showed a tendency to correlate to visual memory.

Hypercapnia. There were no significant differences in any neuropsychological or neuroimaging variables between patients with and without hypercapnia. The degree of $Paco_2$ did not correlate with any variable.

Anemia. There were no significant differences between groups of patients with and without anemia, measured with hematocrit or hemoglobin. Correlational analysis was also negative.

Hypotension. Patients with hypotension scored significantly worse on verbal memory performance (delayed free recall) than patients without. The minimum systolic blood pressure showed a tendency towards correlation with fine motor performance (pegboard, right hand). In the neuroimaging analysis, patients with hypotension showed a tendency toward IIIrd ventricle enlargement than patients without hypotension.

Severity of Injury and Neurological Insults

Pupillary light reflex. The pupillary non-reactive group showed significantly worse outcome than the pupillary reactive group, as assessed by the GOS (Table 3). There was no significant association between the neuropsychological results of patients with and without pupillary reactivity. The neuroimaging analysis showed the III ventricle significantly larger in the non-reactive pupil group. The greater number of non-reactive eyes correlated significantly with poorer outcome as assessed by the GOS and showed a tendency to correlate to greater III ventricle index. Patients with anisocoria scored significantly better on the GOS and on attention and mental flexibility (TMT B and SDMT) than patients without. The neuroimaging analysis was negative.

Glasgow Coma Scale. There was no significant difference between the neuropsychological and neuroimaging results of patients with moderate ($n = 18$) and severe head injury ($n = 39$). Patients with poor motor response in the GCS tended to show worse global outcome than patients with good motor response. The neuroimaging analysis was negative.

Coma duration. Patients with long coma duration had a significantly worse global outcome, as assessed by the GOS, and significantly poorer performance in verbal memory (sum recall and delayed free recall), attention and mental flexibility (TMT A and SDMT) and fine motor speed (pegboard, left hand) than patients with shorter coma duration. In the neuroimaging analysis, longer coma duration showed a tendency towards an association with a larger Evans and III Ventricle Index (Table 4).

Intracranial pressure. There were no significant differences between patients with increased ICP and those without. Correlational analysis showed a tendency towards an association between maximum values of ICP and poor verbal memory. The neuroimaging analysis was negative.

Cerebral perfusion pressure. There was no statistical difference between patients with cerebral perfusion pressure below 60 mm Hg and those above this figure in any neuropsychological and neuroimage measure (Tables 5 and 6).

DISCUSSION

The aim of this study was to examine the relationship between systemic complications and neuropsychological performance and CT data in patients with moderate and severe head injury. Our results show that secondary extraneurological insults, such as pre-hospital hypoxia and hypotension, are related to neuropsychological outcome and long-term ventricular enlargement in patients with head injury, regardless of the severity. However, we failed to find any significant relationships between neuropsychological and neuroimaging data and hypoxia, hypercapnia or anemia. Furthermore, other measures of head injury severity and neurological insults such as GCS scores, coma length, brain-stem reflexes and intracranial hypertension were also related to neuropsychological outcome and ventricular enlargement.

Influence of Extraneurological Variables on the Cognitive Outcome and Ventricular Enlargement

Though previous studies have related blood arterial hypotension to outcome (Miller et al., 1981; Levati et al., 1982; Marmarou et al., 1991; Chesnut et al., 1993), the contribution of early hypotension to more specific aspects of long-term neuropsychological functioning in head injury survivors has not been established (Lanoo et al., 1998, 2000). These authors showed that arterial hypotension had a clear adverse effect on mortality, but did not show a relationship with long-term morbidity in terms of neuropsychological functioning in survivors of head injury. Our results do not agree with those of Lanoo et al. (1998, 2000). Even though our sample is small, we

Table 4. Neuropsychological and Neuroimaging Mean and Standard Deviation Scores of TBI in Relation to Severity of Injury

	Pupillary light reflex			*Anisocoria*			*Severity (GCS)*		
	Present	*Absent*	*t/Z*	*Absent*	*Present*	*t/Z*	*Moderate*	*Severe*	*t/Z*
Memory									
Sum recall	43.03 (12.94)	38.50 (14.04)	−0.97	35.45 (15.19)	42.83 (12.42)	−1.67	41.33 (13.30)	41.77 (12.88)	−0.11
Delayed free recall	6.50 (3.62)	5.80 (4.02)	−0.53	4.73 (4.56)	6.74 (3.37)	−1.63	6.39 (3.48)	6.38 (3.71)	0.00
Figure 3-min recall	19.74 (7.58)	17.571 (7.71)	−0.69	14.41 (8.43)	19.88 (7.41)	−1.85	17.36 (9.01)	18.98 (7.26)	−0.67
Frontal functions									
FAS	29.73 (10.29)	32.40 (9.32)	0.74	27.36 (11.49)	30.19 (9.85)	−0.81	30.83 (11.76)	28.38 (9.10)	0.85
TMT A	72.58 (57.79)	100.71 (65.55)	1.16	90.00 (41.72)	79.43 (71.32)	0.40	85.44 (76.68)	79.42 (59.93)	0.31
TMT B	128.74 (87.88)	161.43 (66.40)	0.93	201.50 (86.63)	121.24 (78.06)	2.59**	149.65 (105.04)	133.27 (74.48)	0.57
SDMT	38.68 (17.03)	25.33 (11.36)	−1.84	26.29 (7.11)	38.03 (17.55)	−3.00**	32.93 (17.45)	36.97 (16.25)	−0.78
Fine motor speed									
Pegboard right	92.23 (53.79)	96.29 (27.69)	0.19	90.75 (27.65)	94.71 (53.20)	−0.20	107.06 (72.52)	84.80 (27.47)	1.25
Pegboard left	91.45 (41.19)	98.57 (25.03)	0.44	100.50 (23.73)	97.88 (52.43)	0.13	90.28 (29.39)	99.97 (54.24)	−0.70
Global outcome									
GOS[a]	1 [1, 1]	1 [2, 3]	−2.89**	1 [1, 1]	2 [2, 3]	−4.46**	1 [1, 1.25]	1 [1, 2]	−1.42
Neuroimaging									
Ventricular Score	61.91 (13.09)	63.08 (12.53)	0.25	64.39 (12.87)	60.62 (13.02)	0.86	65.64 (15.60)	59.18 (11.51)	1.72
Evans Index	0.272 (0.034)	0.274 (0.055)	0.06	0.271 (0.049)	0.278 (0.041)	−0.45	0.288 (0.042)	0.273 (0.041)	1.27
III Ventricle Index	0.035 (0.018)	0.054 (0.021)	2.71**	0.048 (0.022)	0.037 (0.018)	1.71	0.045 (0.022)	0.036 (0.018)	1.54
Cella Media Index	0.162 (0.045)	0.157 (0.046)	−0.34	0.163 (0.047)	0.154 (0.047)	0.56	0.156 (0.049)	0.153 (0.049)	0.17

[a]Values expressed as median and interquartile range.

**$p < 0.01$.

Table 5. Neuropsychological and Neuroimaging Mean and Standard Deviation Scores of TBI in Relation to Intracranial Variables

	Intracranial pressure			*Cerebral perfusion pressure*		
	Absent	*Present*	*t/Z*	*Absent*	*Present*	*t/Z*
Memory						
Sum recall	37.00 (13.68)	42.67 (13.68)	−1.11	36.17 (15.79)	41.33 (12.12)	−1.01
Delayed free recall	5.11 (4.02)	6.17 (3.46)	−0.74	5.42 (3.72)	5.61 (3.92)	−0.13
Figure 3-min recall	18.69 (8.51)	17.00 (7.52)	0.51	17.75 (8.30)	18.25 (8.11)	−0.15
Frontal functions						
FAS	27.89 (11.49)	29.50 (9.61)	−0.40	29.83 (13.61)	27.67 (8.44)	0.49
TMT A	80.50 (40.52)	82.82 (95.53)	−0.07	79.73 (45.10)	82.63 (79.80)	−0.10
TMT B	172.00 (84.36)	117.00 (69.38)	1.72	167.91 (89.93)	138.33 (76.65)	0.90
SDMT	32.13 (11.98)	35.22 (19.58)	−0.49	33.60 (12.46)	33.00 (16.64)	0.09
Fine motor speed						
Pegboard right	85.31 (21.19)	103.18 (69.80)	−0.82	89.45 (24.86)	94.75 (58.41)	−0.28
Pegboard left	90.94 (23.23)	94.82 (32.32)	−0.36	89.82 (19.21)	94.38 (31.42)	−0.42
Global outcome						
GOS[a]	1 [1, 2]	2 [1, 2.25]	−1.26	1 [1, 2]	2 [1, 2]	−0.81
Neuroimaging						
Ventricular Score	64.52 (11.83)	61.03 (14.40)	0.72	65.96 (12.53)	61.23 (12.97)	0.99
Evans Index	0.27 (0.040)	0.29 (0.035)	−1.05	0.284 (0.040)	0.282 (0.039)	0.09
III Ventricle Index	0.045 (0.019)	0.040 (0.024)	0.64	0.045 (0.020)	0.041 (0.022)	0.46
Cella Media Index	0.166 (0.043)	0.140 (0.045)	1.53	0.164 (0.042)	0.150 (0.047)	0.80

[a]Values expressed as median and interquartile range.

found a significant relationship between systolic blood pressure lower than 80 mm Hg and poor memory performance.

Strong relationships between hypoxia and mortality have been reported (Gilchrist and Wilkinson, 1979; Miller et al., 1981; Jane and Rimel, 1982; Levati et al., 1982; Chesnut et el., 1993; Combes et al., 1996). However, little is known about the impact of systemic hypoxia on cognitive outcome (Ruff et al., 1991). The occurrence of an early hypoxic episode is strongly related to the level of consciousness because the protective reflexes are lost when a patient's GCS falls to 8 or below, increasing the risk of airway obstruction and aspiration. We assessed the independent effect of the early hypoxic episode on the outcome, controlling for the severity of injury. The results showed a relationship between early hypoxia and neuropsychological outcome, despite the substantial time interval between this secondary insult and the assessment. Patients who experienced a respiratory insult prior to hospitalization showed not only poor outcome according to the GOS, but also clinically significant neuropsychological impairment. Attention, cognitive flexibility, verbal memory and verbal fluency were impaired in subjects who suffered a hypoxic episode (measured by the presence of at least one of the following signs: abnormal respiration prior to airway control, presence of aspiration, cardiopulmonary arrest, and Pa_{O_2} lower than 60 mm Hg). In other hypoxic conditions such as cardiac arrest and perinatal asphyxia the hippocampus and basal ganglia have been reported to be particularly vulnerable (Fujioka et al., 2000; Mañeru et al., 2001). It is probable that in TBI hypoxia causes additional damage in these areas, and therefore the basal ganglia atrophy may be responsible for the frontal deficits and the hippocampus for the memory deficits.

Long-term ventricular enlargement has been associated with acute measures of injury such as coma duration (Levin et al., 1981; Meyers et al., 1983) or with CT features immediately post-injury (Mataró et al., 2001). The present study showed that a measure of ventricular enlargement such as the third ventricle index is related to extraneurological variables such as hypoxia, regardless of severity of injury. Our results thus suggest that the white matter degeneration around the lateral ventricles induced by the hypoxic-ischemic insults may contribute to ventricular enlargement. However, our neuroimaging study has some limitations. The study was based on CT planimetric quantification of a restricted number of sections through the lateral ventricles. Further studies with volumetric measures from magnetic resonance imaging are required to elucidate the role of the systemic factors in ventricular enlargement.

Table 6. Correlation Between Neuropsychological, Neuroimaging Data, Extraneurological, Neurological, and Severity of Injury Variables

	Extraneurological			*Neurological severity*				
	PaO_2 min	*$PaCO_2$ max*	*SBP min*	*ICP max*	*CPP min*	*Motor GCS*	*Eyes*	*Coma duration*
Memory								
Sum recall	0.070	−0.059	−0.011	−0.370*	0.072	0.235	−0.102	−0.353**
Delayed free recall	0.125	−0.010	0.043	−0.232	−0.006	0.242	−0.070	−0.312*
Figure 3-min recall	0.307*	−0.169	−0.182	0.054	−0.130	0.025	−0.139	−0.230
Frontal functions								
FAS	−0.012	−0.072	−0.028	−0.138	−0.181	0.094	0.120	−0.272*
TMT A	−0.105	0.007	0.144	0.031	0.023	0.071	0.171	0.399**
TMT B	−0.218	0.132	0.262	0.365	−0.135	−0.163	0.149	0.347*
Symbols	0.208	−0.033	−0.157	−0.199	−0.029	0.108	−0.282	−0.367**
Fine motor speed								
Pegboard right	−0.177	−0.004	0.376**	−0.051	−0.039	0.004	0.025	0.102
Pegboard left	0.095	−0.005	0.197	0.058	0.122	−0.110	0.092	0.634**
Global outcome								
GOS	−0.06	0.00	−0.04	0.35	−0.15	−0.29*	0.42**	0.41**
Neuroimaging								
Ventricular Score	−0.088	0.051	0.175	0.156	−0.085	−0.033	−0.022	0.207
Evans Index	0.008	0.211	0.177	−0.124	0.163	0.028	−0.081	0.276*
III Ventricle Index	−0.024	−0.043	0.288*	0.175	0.007	−0.148	0.300*	0.260*
Cella Media Index	−0.085	−0.088	0.056	0.182	−0.142	0.034	−0.089	0.078

SBP, systolic blood pressure; ICP, intracranial pressure; CPP, cerebral perfusion pressure; eyes, number of non-reactive eyes.
*$p < 0.05$; **$p < 0.01$.

Influence of Severity of Injury and Neurological Insults on Outcome

In agreement with previous studies (Vilki et al., 1988; Levin et al., 1990; Wilson et al., 1991; Ross et al., 1994; Ellenberg et al., 1996), we found significant correlations between several acute severity measures such as length of coma, the absence of brain stem reflexes or lower GCS scores and poor outcome and long-term impaired neuropsychological performance. These data support the hypothesis that severe diffuse axonal injury is an important contributor to neuropsychological sequelae (Vilkki et al., 1988; Ross et al., 1994).

Intracranial hypertension (ICP) has been associated with mortality and morbidity (Miller et al., 1977, 1981; Marmarou et al., 1991). Few data concerning the relationship between ICP and cognition in survivors of severe closed head injury are available. Impairment of memory was related to raised intracranial pressure at 6 months post-injury (Uzzell et al., 1986; Levin et al., 1991), but the same relationship was not found in the neuropsychological assessment at 1 year post-injury (Levin et al., 1991). Our data showed a weak relationship between verbal memory impairment assessed at 6 months post-injury and intracranial hypertension.

Our results should be interpreted with caution in view of the numerous statistical comparisons, which raises the risk that some of the findings may be spurious. In our sample, as expected, the GOS was related to the severity of injury. However, the only secondary insult that affected the GOS was pre-hospital hypoxia. Although we excluded two categories from the GOS (death and vegetative), the scale is a broad measure that may fail to detect important changes within broad outcome categories. It should also be borne in mind that our sample does not represent the full range of head-injured patients, as our subjects were selected with respect to their capacity for neuropsychological examination. Therefore, our results can only be extrapolated to survivors of moderate-to-severe head injuries who recover to a testable level. Occurrence of systemic hypoxia and hypotension are associated with a high mortality and morbidity rate.

To conclude, despite the methodological limitations, our results show that hypotension and particularly hypoxia are related to neuropsychological outcome and long-term ventricular enlargement regardless of the severity of injury. The neuropsychological outcome following severe head injury depends on the extent of primary brain insult sustained at the time of the trauma itself, and the subsequent neurochemical and neurophysiologic pathological changes caused by the injury.

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