

Age effects on long-term neuropsychological outcome in paediatric traumatic brain injury

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In order to investigate the relationship between age at injury and long-term neuropsychological impairment, 29 children and adolescents who sustained traumatic brain injury (TBI) were studied at least 6 years post-trauma. Tests of intellectual, memory, visuospatial and frontal lobe functions were administered to patients and 29 normal matched control subjects. Correlations between performance on neuropsychological tests and age showed the following direction: the younger the child when TBI was sustained, the worse the cognitive outcome. After controlling for injury severity, visuospatial functions remained related to age. Patients' performance differed significantly from that of controls in half of the neuropsychological variables analysed. To further investigate the effects of age at injury, the sample was divided in two groups (TBI before and after age of 8) and then compared with their respective controls. Patients damaged earlier presented impaired intellectual and visuospatial functions. The results suggest that neuropsychological sequelae remain after at least 6 years of evolution, and that there is an age at injury effect.

Introduction

The so called 'Kennard principle' supports the idea that behavioural effects of brain damage may be less deleterious if sustained early in life. This principle is not Kennard's original idea, other precedent investigators mentioned that the effect of lesions in the immature brain produce less consequences than adult lesions. Kennard reported only limited lesion effects in the infant monkey with the entire hemisphere removed and found that monkeys given motor and pre-motor cortical lesions early in development presented a better recovery of motor function measures than monkeys injured later. However, she recognized from her own work that the infant sparing effect was not universal or absolute and also noted that some symptoms could worsen or become manifest with maturation of the passage of time (see [1] for review).

The existence of a great brain plasticity in infantile lesions was supported by studies that stressed the good acquisition of language in children with hemiplegia or good recovery after hemispherectomy performed at early age [2–4]. Moreover, the

rapid resolution of acquired aphasia from several aetiologies in young children supported the principle [5, 6]. More recent papers [7–9] found that childhood closed head injury compromised patient language competence, not only when children but also when adults.

Animal studies conducted by Goldman and co-workers [10, 11] demonstrated that recovery of function following cortical resections depended on age, localization of the lesion, and preservation of a residual area functionally related to the damaged cortex that may subsume its functions. In humans, the consequences of brain damage can be observed later in development; after infantile frontal lobe lesions, for example, subjects may appear symptom-free early in life, but their situation may change with continuing maturation. Lesion-related deficits may emerge even after 20 years of age [12, 13].

After several studies of TBI, Levin and co-workers [14–17] concluded that adolescents have a better prognosis than children. Children with TBI share common characteristics with adults; the most frequent neuropsychological sequelae are memory, attention, and frontal lobe dysfunctions [14–20]. The main differential sequelae were seen in general intellectual functioning. Children with TBI present lower intellectual quotients than controls, but this finding has not been observed in adults who sustain TBI [21]. Language is another function more affected in children than in adolescents following closed-head injury [22].

After severe head trauma, several patients cannot return to school. In a follow-up study from the Traumatic Coma Data Bank, Ruff *et al.* [23] found that, at 6 months post-injury, 38% of children with severe TBI were not back to school. At 12 months, 66% of the former students had returned. The three most potent predictors for the reincorporation were intactness of the patient's verbal intellectual ability, speed of information processing, and age.

Two years post-injury, a group of adult patients with moderate-to-severe head injuries had psychosocial functioning problems as being unable to work, support themselves financially or live independently [24]. Olver *et al.* [25] found a slightly higher incidence of cognitive, behavioural and emotional changes reported at 5 years post-injury than at 2 years in a sample of patients from 11–69 at age of injury. Thirty-two per cent of those working at 2 years were not employed at 5 years and many students had also become unemployed.

Previous investigations in paediatric TBI have examined patients using short injury-test intervals [14–17, 26, 27]. Klonoff *et al.* [28] carried out a longitudinal study with an initial sample composed of 231 subjects with a 5 year follow-up and concluded that recovery of neuropsychological functions was good in both groups, those impaired after 9 years old and those impaired before this age. However, the study paid little attention to memory and prefrontal functions.

Cattelani *et al.* [29] reported data from 20 adults who suffered TBI at an age between 8–14 years. Subjects who suffered a severe head injury presented a higher pre-injury incidence of character disturbances than the normal population, and injury-related difficulties to socialise which persisted long-term. Intellectual and functional sequelae were frequent. Social maladjustment and poor quality of life were present several years after injury.

Five or more years after a severe brain injury, children 7 years or younger at the time of injury suffered severe disability, as measured by the GOS scores, more often than did the older groups, and they were less often capable of independent employment than the children injured between the ages of 8–16 [30].

The aim of the present paper is to examine the relationship between age at injury and performance on cognitive outcome measures at least 6 years post-trauma, in the belief that the use of a long-term neuropsychological evaluation may clarify the sequelae of TBI.

Method

Subjects

Twenty-nine subjects (24 boys and five girls) who sustained severe TBI in childhood were selected from the archives of two paediatric neurosurgery services at Hospital de la Santa Creu i Sant Pau and at Hospital Vall d'Hebron, both in Barcelona, Spain. Criteria for selection included age at injury of less than 16 years, minimum of 6 years since injury, and a Glasgow Coma Scale score [31] of 8 or less, except for patients with higher GCS scores who had focal brain lesions detected by computed tomography during their hospitalization. Exclusion criteria were (1) psychiatric or neurologic antecedents; (2) history of mental retardation or developmental disorders; and (3) insufficient language and sensorimotor ability to successfully perform the neuropsychological battery selected. The patients were divided into groups according to age at the time of injury (0–8 years, 9–16 years). Clinical characteristics of the sample are presented in table 1. In two patients, GCS was not obtained because of their age, but they were included in the study, as one case presented signs of decerebration and the other suffered an intraventricular haemorrhage. The cause of injury was car accident in 12 cases, motorbike in four, fall in seven, and pedestrian–automobile crash in six. Nine patients presented focal lesions: one right temporo-parietal, two left temporo-parietal, seven pre-frontal, and four in basal ganglia.

The control group consisted of 29 subjects matched to patients according to sex, age, years of education, and socio-economic status. Controls were relatives, friends, or neighbours. Exclusion criteria were psychiatric, neurological or developmental disorders. All the subjects or their parents gave informed consent.

Table 1. Demographic and clinical features of patient groups

Variables	Total (<i>n</i> = 29)			Age ≤ 8 years (<i>n</i> = 14)			Age > 8 years (<i>n</i> = 15)		
	Mean	SD	Range	Mean	SD	Range	Mean	SD	Range
Age at injury (years)	8.21	4.20	0.17–16	4.58	1.96	0.17–7	11.60	2.50	9–16
Injury–test interval (years)	9.07	1.85	6–12	9.93	1.64	7–12	8.27	1.71	6–11
Age at test (years)	17.34	3.88	7–23	14.5	3.03	7–18	20.0	2.45	15–23
GCS score	6.78	3.11	3–15	6.0	1.60	4–9	7.40	3.87	3–15
Length of coma (days)	10.01	10.50	0.13–41.63	11.18	10.83	1.50–41.63	8.83	10.51	0.13–37
Lesion volume (cm ²)	10.32	33.38	0.00–166.48	15.60	45.84	0.00–166.48	5.42	15.32	0.00–57.68

Measures

A battery of intellectual, memory, visuospatial/visuo-perceptive/visuoconstructive and frontal lobe tests was administered to patients and control subjects. Intellectual function was assessed using the Wechsler Intelligence Scale for Children-Revised (WISC-R) [32] or the Wechsler Adults' Intelligence Scale (WAIS) [33] depending on age. Memory performance was based on a version of the Rey Auditory Verbal Learning Test where the subject learned a list of 15 common nouns in five repetitions and recalled the words after a 20 minute delay. The learning variable was calculated subtracting the number of words recalled in the first repetition from the words recalled in the fifth repetition. The percentage of forgotten words (from the fifth to the sixth trial) was used as a measure of forgetting. Visual memory was examined using recall of the Rey's Complex Figure (RCF) [34]. Visuospatial functions were assessed by copying the RCF and by using Benton's Line Orientation Test [35]. For frontal lobe function assessment, the Trail Making Test forms A and B [36], Stroop Test [37], and the Wisconsin Card Sorting Test (WCST) [38] were used. The Stroop test consisted of three tasks, first to say the colour name of 20 colours, second to read 20 colour names printed in black, and third to say the ink colour of 20 colour names (for instance the word *green* in red ink). The maximal time allowed for every task was 45 seconds and number of hits was registered. The variable considered was the Stroop effect, computed as the number of correct responses in the first task minus the number of correct responses in the third task.

Results

In order to determine if current neuropsychological performance was associated with age at injury, Pearson's product-moment correlations were calculated. In the total group of patients ($n = 29$), significant correlations were found between age at injury and Verbal IQ ($r = 0.39$; $p < 0.05$), Full Scale IQ ($r = 0.40$; $p < 0.05$), Benton's Line Orientation Test ($r = 0.53$; $p < 0.01$), and categories of the Wisconsin Card Sorting Test ($r = 0.37$; $p < 0.05$). All correlations were as expected: the younger the child when TBI was sustained, the worse the neuropsychological performance. After partialling out the Glasgow Coma score as an index of severity, Line Orientation test remained significant ($r = 0.45$; $p = 0.02$). Correlations were as follows; Verbal IQ ($r = 0.33$; $p = 0.09$), Full Scale IQ ($r = 0.32$; $p = 0.10$), and categories of the Wisconsin Card Sorting Test ($r = 0.32$; $p = 0.01$).

The effect of injury test interval was also analysed. No significant correlation was obtained between this factor and neuropsychological variables.

Patients differed from controls on several neuropsychological tests. Statistically significant differences were obtained for VIQ, FSIQ, Rey's Complex Figure, Benton's Line Orientation Test, and Trail Making Test form A (see table 2).

To further investigate age effects, the sample was divided by age at injury (before and after 8 years), and neuropsychological performances were compared with their respective controls. The two subgroups were comparable as they did not differ in terms of clinically relevant variables other than age (age at injury ($t = -8.36$; $p < 0.001$), age at test ($t = -5.39$; $p < 0.001$), such as GCS score ($U = 75.5$; $p = 0.47$), length of coma ($t = 0.54$; $p = 0.596$), and volume of lesion ($t = 0.79$;

Table 2. Means and standard deviations of test scores for patients and controls

Function	Patients ($n = 29$) mean (SD)	Controls ($n = 29$) mean (SD)
Intellectual		
VIQ	91.58 (17.20)*	101.48 (12.36)
PIQ	98.89 (16.87)	106.79 (11.21)
FSIQ	94.37 (17.38)*	104.75 (12.22)
Memory		
RCFT memory	18.72 (5.72)*	22.39 (6.88)
RAVLT trials 1–5	5.13 (2.01)	5.82 (1.77)
RAVLT% forgetting	16.28 (15.02)	16.76 (18.16)
VS/VP/VC		
RCFT copy	28.46 (5.78)*	31.63 (4.16)
Line orientation	21.93 (5.28)*	24.75 (4.65)
Frontal		
Stroop test	24.17 (12.69)	25.96 (10.78)
TMT A (s)	48.93 (22.90)*	37.93 (15.22)
TMT B (s)	106.79 (64.76)	84.37 (35.43)
WCST categories	4.31 (1.83)	4.79 (1.56)
WCST p.e.	16.75 (23.17)	12.34 (14.96)

FSIQ: Full Scale Intellectual Quotient; PIQ: Performance Intellectual Quotient; RAVLT: Rey Auditory Verbal Learning Test; RCFT: Rey Complex Figure Test; TMT: Trail Making Test; VIQ: Verbal Intellectual Quotient; VS/VP/VC: Visuospatial/Visuoperceptive/Visuoconstructive; WCST: Wisconsin Card Sorting Test; WCST p.e.: Wisconsin Card Sorting Test perseverative errors.

* $p < 0.05$.

$p = 0.47$). As current age differed significantly, each subgroup was compared to their respective control (see table 3).

Table 3 demonstrates the different neuropsychological patterns according to the age at injury variable. Patients who suffered the TBI before 8 years old were impaired in VIQ, PIQ, FSIQ, and Benton's Line Orientation. No neuropsychological deficits were observed in the subgroup of patients damaged after the age of 8.

Discussion

According to these results, long-term assessment of neuropsychological functions in children and adolescents who sustained severe TBI revealed effects of age at injury. This variable was related with intellectual and visuospatial performance, i.e. the earlier the occurrence of brain damage, the worse the performance on these functions. This is an important effect because, according to Webb *et al.* [39], many clinicians are guided by the 'Kennard Principle'.

Significant differences in intelligence were seen between the whole of the sample and the control group, but after subdividing the subjects by age at injury the differences remained significant only for the younger group. Thus, lesions in immature brain had adverse effects on the development of general intellectual functioning. In this regard, these results agree with those obtained by Levin *et al.* [15], who found that severe closed head injury produced global intellectual deficits in patients younger than 13 years when injured. The decrease in intellectual

Table 3. Means and standard deviations of test scores for patients divided by age at injury and their respective controls

Function	TBI $\leq$ 8 years		TBI > 8 years	
	Patients (<i>n</i> = 14) mean (SD)	Controls (<i>n</i> = 14) mean (SD)	Patients (<i>n</i> = 15) mean (SD)	Controls (<i>n</i> = 15) mean (SD)
Intellectual				
VIQ	83.21 (17.41)*	97.21 (13.41)	99.40 (13.22)	105.46 (10.18)
PIQ	92.71 (14.67)*	105.07 (10.90)	104.66 (17.19)	108.40 (11.45)
FSIQ	86.21 (15.32)*	101.21 (13.53)	102.00 (16.03)	108.06 (10.23)
Memory				
RCFT memory	18.89 (6.99)	23.28 (6.47)	18.56 (4.47)	21.56 (7.36)
RAVLT trials 1–5	5.50 (1.91)	5.92 (1.73)	4.80 (2.11)	5.73 (1.87)
RAVLT% forgetting	15.50 (13.11)	18.20 (10.57)	17.01 (17.04)	15.42 (23.50)
VS/VP/VC				
RCFT copy	26.85 (6.94)	31.32 (5.14)	29.96 (4.14)	31.93 (3.15)
Line orientation	19.42 (5.00)*	24.42 (5.12)	24.26 (4.52)	25.06 (4.31)
Frontal				
Stroop test	28.00 (13.31)	23.42 (11.20)	20.60 (11.36)	28.33 (10.17)
TMT A (s)	55.28 (21.42)	41.35 (19.84)	43.00 (23.34)	34.73 (8.65)
TMT B (s)	112.50 (47.93)	85.85 (37.35)	101.46 (78.69)	83.00 (34.80)
WCST categories	3.92 (1.94)	4.07 (1.73)	4.66 (1.71)	5.46 (1.06)
WCST p.e.	19.35 (29.52)	16.35 (19.17)	14.33 (15.86)	8.60 (8.66)

FSIQ: Full Scale Intellectual Quotient; PIQ: Performance Intellectual Quotient; RAVLT: Rey Auditory Verbal Learning Test; RCFT: Rey Complex Figure Test; TBI $\leq$ 8: Traumatic brain injury at 0–8 years; TBI > 8: Traumatic brain injury at 9–16 years; TMT: Trail Making Test; VIQ: Verbal Intellectual Quotient; VS/VP/VC: Visuospatial/Visuoperceptive/Visuoconstructive; WCST: Wisconsin Card Sorting Test; WCST p.e.: Wisconsin Card Sorting Test perseverative errors.

**p* < 0.05.

functioning may be due to the presence of diffuse brain damage which may be less compensated in young children than in adolescents and adults. A similar pattern has been observed in children treated for lymphoblastic leukaemia [40]. Cerebral white matter damage in children may have developmental consequences for intellectual development which are not observed in adults after diffuse brain damage [21].

In this sample of paediatric TBI, visuoconstructive impairment was found, as assessed by the Rey’s Complex Figure Copy. This test involves visuospatial as well as visuoperceptive and visuoconstructive functions [41]. An age effect was observed for Benton’s Line Orientation Test, which may be considered more specific of visuospatial abilities; unfortunately, though, this test has not been used in previous studies of neuropsychological sequelae of child TBI. In adults, scores on the Benton’s Line Orientation Test are low in patients with basal ganglia degeneration and also in white matter dysfunctions (Parkinson, Huntington, multiple sclerosis) [42].

Chadwick *et al.* [26] reported that TBI children had difficulty performing visuo-perceptual and visuomotor tasks. Memory functions demonstrated no age effects. For the whole sample, patients had lower scores than controls on visual memory, but also for visuoconstructive/visuoperceptive capacities. After dividing the group by age at injury the differences disappeared.

The lack of significant differences between the groups of patients divided by age at injury and their controls on memory and frontal functioning may be due to the small size of the sample when it is divided.

Contrary to the expected results, patients differed from controls in Trail-Making test A, but not in Trail-Making test B. Trail B is considered a test more sensitive to acquired organic impairment. This is difficult to explain. Performance in Trail B tends to significance and the patient group showed a significant wider variance, thus, it is possible that a subgroup of patients were really impaired.

The age taken to compare the groups is arbitrary. Age of 8 was taken as the cut-off because it is well-known that children have already acquired such complex functions as reading, writing, and arithmetic. In addition, it has been found that some frontal tasks, as the Wisconsin Card Sorting Test, can be performed at adult levels at 8 years of age [43].

The long range of age in the group of patients could be a limitation of the study, but a control subject matched by age and years of education was included for every patient, which allows grouping neuropsychological data of this range of age into a single group.

In summary, the findings provide further evidence of the relative plasticity of damage occurred in the immature brain. After long-term evolution, there are evident neuropsychological sequelae in several cognitive domains: intelligence, memory, visuospatial, and frontal lobe functions. Age effects were particularly noticeable in visuospatial abilities and intelligence.

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