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Depression and Post-Traumatic Brain Injury: Clinical and Neuropsychological Characteristics

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Abstract

Major depression disorder (MDD) is reported to be the most frequent psychiatric complication after traumatic brain injury (TBI), with a prevalence of 14-77%. The aim of this study was to evaluate the psychiatric consequences of TBI, and to identify the neuropsychological and psychopathological correlates of post-TBI MDD in order to highlight their differences from those of primary MDD. This was a retrospective case-control study. Sixteen patients with closed brain injury, and a lesion revealed by computed tomography (CT), were recruited and were evaluated one (T1), three (T3) and six (T6) months after discharge from Neurosurgery Department; the control group consisted of six patients with MDD. Psychiatric picture was evaluated by using the rating scales BPRS, HRSD, BDI, HRSA. GAF and IADL were also administered. Neuropsychological profiles were assessed by using neuropsychological tests, focused on memory and frontal-executive functioning. At T1, MDD was observed in 10 cases (62.5%) and anxiety disorders in 6.25%. At T3 and T6, MDD was diagnosed in respectively 8 (50%) and 7 cases (44%). Post TBI MDD had less severe depressive symptoms "stricto sensu", showed greater social isolation and hostility and more cognitive deficits in comparison with the control group. MDD seem to be a frequent TBI complication. Patients with post-TBI MDD have a specific psychopathological profile characterised by a less severe depressive symptomatology and a neuropsychological pattern that is significantly associated with greater deficits in cognitive functions than those with primary MDD.

Keywords: Traumatic brain injury; Major depression; Anxiety; Neuropsychological profile

Introduction

Psychiatric disorders seem to be a major cause of disability after traumatic brain injury (TBI) [1-3]. The prevalence of post-TBI psychiatric sequelae ranges from 34% to 50%, depending on the severity of the trauma [4,5]. Major depression disorder (MDD) is the most widely studied psychiatric disorder after TBI. The published rates of axis I disorders in patients with TBI are 14-77% for MDD [6-9], 2-14% for dysthymia [7-9], 2-17% for bipolar disorder [8,10,11], 3-28% for generalised anxiety disorder [6-10], 4-17% for panic disorder [6,8-10], 1-10% for phobic disorders [6,8,10], 2-15% for obsessive-compulsive disorder [6,8,10], 3-27% for post-traumatic stress disorder (PTSD) [6,8,10-12], 5-28% for substance abuse or dependence [6,8-10], and 1% for schizophrenia [6,13].

On the other hand patients are at high risk of developing depression not only during the acute phase, but also for decades after the TBI [14]. Jorge et al. [15] investigated the effects of TBI in 66 patients, who were followed up for more than one year. Using the DSM III-R diagnostic criteria, 42.4% of the patients were diagnosed as having MDD, and this finding was supported by a large-scale study conducted by Kreutzer et al. [16]. Who found that 41.9% of 722 patients had MDD on the basis of the DSM IV criteria. Levin at al. [17] studied a cohort of 125 adults with mild TBI and, reviewing their own earlier work in which they cited a 17% incidence of MDD in subjects with mild TBI one-year after injury, they noted an increased incidence of depression by age, and that this increased by a factor of 7 if there were abnormal cumputed tomography (CT) findings.

Mild TBI has also been found to be a risk factor for MDD and generally increased levels of depressive symptoms have been observed in long-term follow-up studies [17]. Koponen et al. [14] evaluated the frequency of Axis I and Axis II disorders in a retrospective 30-year follow-up study of 60 patients who had been treated for TBI. These patients were particularly vulnerable to developing depressive disorders, and showed a lifetime prevalence of MDD of 26.7% [14]. Patients experiencing major depressive episodes following a mild TBI have increased levels of anxiety disorder, cognitive deficits and disability in comparison with those who do not develop depression [2,4]. Jorge et al. [4] found MDD in 33% of 91 patients who had sustained a TBI, comorbid anxiety in 76.7% and aggressive behaviour in 56.7%. Forty of their patients had sustained a mild TBI, whereas the rest had moderate-severe TBI.

Emotional disturbances are perhaps the most socially and vocationally disruptive sequelae of severe TBI. Patients may experience significant personality changes, becoming childish and dependent, prone to sudden violent outbursts, anxious, or severely depressed. These changes may influence their social relationships and ability to retain employment, and place a great burden on their family members. In particular, aggressive behaviour is one of the most socially and vocationally disruptive consequences of these neuropsychiatric disorders [18]. MDD has also been associated with poorer social functioning at 6- and 12-month follow-up visits, as well as with significantly reduced volumes of left prefrontal grey matter, particularly the ventrolateral and dorsolateral regions [19].

The aims of this prospective study were to investigate the prevalence of psychiatric disorders in patients with TBI, to characterise the severity of clinical symptoms and neuropsychological deficits in patients with post-TBI MDD and to reveal clinical and neuropsychological differences between post-TBI MDD and primary MDD.

Methods

Study population

This retrospective case-control study results by a preliminary longitudinal study by Mauri et al. [20]. The study included patients aged 18-65 years admitted to the Department of Neurosurgery, IRCCS Ospedale Maggiore Policlinico of Milan, Italy, from 2011 to 2013 with a closed head injury and a lesion revealed by computed tomography (CT). The protocol received agreement by our Ethics Committee and the patients or their relatives, acknowledged about the details of the study, provided their written informed consent.

The inclusion criteria were loss of consciousness for at least one minute, the presence of post-traumatic amnesia for at least 30 min and neuro-radiological evidence suggesting TBI. Subjects affected by past unstable neurological conditions (coma, stupor, epilepsy, acute meningoencephalitis, metabolic encephalopathy), pathological conditions of the cardiorespiratory system (cardiac or respiratory failure, cardiogenic shock, pneumothorax), patients with a past psychiatric diagnosis on Axis I or on Axis II and patients with comorbid substance abuse were excluded from the study.

The subjects without a CT-detectable lesion were also excluded because they could develop post-concussive disorders, a complex syndrome characterised by an association of somatic symptoms that distinguish it from the psychiatric disorders that are the subject of this study. The control group, recruited in the same period of TBI subjects, consisted of age and gender matched patients with primary recurrent MDD attending the Department of Neuropsychopharmacology, IRCCS Ospedale Maggiore Policlinico of Milan. The diagnosis was formulated at admission by expert clinicians using the Structured Clinical Interview for Axis I Disorders (SCID-I) [21] and the Structured Clinical Interview for Axis II Disorders (SCID-II) [22] based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) [23].

The patients with TBI were evaluated one month after being discharged from the Neurosurgery Department (T1), and were followed up three (T2) and six months (T3) after the trauma: they underwent CT to monitor the evolution of any parenchymal brain lesions, as well as a diagnostic psychopathological and neuropsychological evaluation. The control group was also evaluated at the time of enrolment and followed up after one, three and six months.

TBI severity

The severity of the TBI was assessed using the 24 h Glasgow Coma Scale (GCS) [24]: scores of 13-15 were defined as mild head injury, scores of 9-12 as moderate head injury, and scores of 3-8 as severe head injury. Patients with a GCS score of 12-15 who underwent intracranial surgery or presented focal lesions greater than 15 mm were considered as having moderate head injury.

Neuroimaging

All of the patients with TBI underwent CT immediately after the trauma as part of the standard clinical evaluation in our Department of Neurosurgery. The nature, extent, and location of the traumatic lesions were classified on the basis of the Traumatic Coma Data Bank criteria [25]. All of the structural neuroimaging scans were interpreted by a trained neurologist, who was blinded to the results of the psychiatric examination.

Psychopathological assessment

The severity of depressive and anxiety symptoms was assessed using the Hamilton Rating Scale for Depression (HRSD) [26], the Beck Depression Inventory Scale (BDI) [27] and the Hamilton Rating Scale for Anxiety (HRSA) [28]. The patients' global functioning was evaluated using the Global Assessment of Functioning (GAF) [29] and Instrumental Activity of Daily Living (IADL) [30] scales, and the severity of their psychopathological condition was evaluated using the Brief Psychiatric Rating Scale (BPRS) [31].

Neuropsychological evaluation

The participants underwent neuropsychological assessment by an experienced neuropsychologist (DM) at T1, T2 and T3, and the analyses included in this article focused especially on memory and frontal-executive functioning. The neuropsychological tests consisted of Raven's Coloured Matrices (PM48) [32] to evaluate logical operativity, Prose Memory [33], Digit Span [34] and Corsi's Span [34] to evaluate memory, Verbal Fluency [35], Semantic Fluency [35] and Token Test [36].

To evaluate language ability, Trail Making Test (a, b, and b-a, taken as a measure of the speed of information processing and mental flexibility) [37], Attentive Matrices [38], the Wisconsin Card Sorting Test (WCST) [39], scoring the number of categories achieved and the number of perseverative errors, and the Tower of London (ToL) test [40] (including the mean number of moves above the minimum possible, and the mean number of problems solved within one minute) to evaluate attention-executive ability.

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Statistical analysis

The data were statistically analysed using descriptive methods, analysis of variance (ANOVA), the chi-squared test, multifactor analysis of variance (Tukey's test), the Mann-Whitney test and regression analysis (simple regression). The analyses were made using the Statgraphic Centurion program, version XV (2005 Statpoint, Inc. USA, www.statgraphics.com).

Results

Sample

Eighty-five subjects experienced TBI were evaluated for the study. Sixty-five did not satisfy the inclusion criteria: 31 were excluded because of their age, 9 because of problems in language comprehension, 8 patients were moved to other hospitals upon discharge, 2 had a psychiatric diagnosis before the TBI, 4 had a history of comorbid substance abuse, and 15 refused to take part in the study. Sixteen patients were including into the study (M=10, F=6): 13 injured in a motor vehicle collision, 1 by an accidental fall, 1 by an assault and 1 by a working accident. On the basis of their baseline GCS scores and CT data, 6 patients (37.5%) had mild TBI, 6 (37.5%) moderate TBI, and 4 (25%) severe TBI. The mean GCS score was 10,56 (+ 4.4). On the basis of the Traumatic Coma Data Bank Classification [24], 8 patients (50%) had diffuse lesions and 8 (50%) focal lesions.

The cranial injury patterns included acute epidural hematoma (22%), acute subdural hematoma (42%), traumatic subarachnoid haemorrhage (29%), contusion (80%), skull fractures (22%), skull-base fracture (34%), and contusion of the brain stem (18%). Regarding the control group, 20 patients with diagnoses of MDD were recruited. Six patients were excluded because they have a history of comorbid substance abuse, 5 subjects because had a comorbid diagnoses on Axis-II, 2 patients because refused to take part in the study, 1 because had a comorbid vascular disease. So the final control group consisted of 6 patients (3=M, 3=F) with a diagnosis of MDD. There were no significant differences between the cases and controls in terms of age, gender, and years of schooling or premorbid intelligence quotient (IQ) (Table 1).

Frequency of mood disorders in TBI patients

One month after discharge (T1), MDD was diagnosed in 10 patients (62.5%), and an anxiety disorder, a post-traumatic stress disorder (PTSD) in 1 patients (6.25%). Among the patients with MDD, 4 (40%) had mild MDD and 6 (60%) severe MDD. At the subsequent assessments three (T2) and six months (T3) after discharge, MDD was diagnosed in respectively 8 (50%) and 7 cases (43.75%) (Table 2). At T1 the total GAF score (p=0.034) and trauma severity was significantly higher in the patients with a psychiatric diagnosis (p=0.016). Total BPRS score and total BDI score were significantly related to trauma severity (p=0.019).

At T2, total BPRS score was significantly higher in women (mean 43.83 ± 3.54 *vs.* 36.2 ± 6.84) (p< 0.05). During the 6 months of the study, the scales for evaluating global functioning (GAF and IADL) and BPRS significantly improved (p<0.001). In terms of neuropsychological performance, there were significant differences between the patients with mild and severe TBI at Trail Making Test-a (p=0.028), Verbal Span (p=0.041), the Token Test and the number of WCST categories completed (p=0.027). There was also a trend towards significance in relation to the Attentive Matrices, WCST and the memory tests (Corsi's Span and Prose Memory). There were no differences between the patients with moderate or severe TBI.

Post-TBI MDD versus primary MDD patients

The age, education, psychopathological characteristics and cognitive performance of the patients with primary and post-TBI MDD were compared at T1 (Table 3). No significant differences were reported for age and education of patients. There were no statistically significant between-group differences in the total GAF score or severity of psychiatric symptoms (total BPRS score), but the subjects with TBI had many problems in instrumental activities (assessed using the IADL).

Although total BPRS scores were substantially equivalent, the comparison of symptom clusters showed that the patients with TBI presented a more severe symptomatology regarding 'thinking disorders cluster' (items: conceptual disorganization, grandiosity, hallucinatory behaviour, unusual thought content) and 'hostility/suspiciousness' cluster (items: hostility, suspiciousness, uncooperativeness), whereas the controls were characterised by more severe symptoms in 'anxiety/depression cluster' (items: somatic concern, anxiety, guilt feelings, depressive mood).

There was a statistically significant between-group difference in the total BDI and HRS-D scores (p<0.05), which were higher in the controls (primary MDD patients) (Table 3), but no significant difference in total HRS-A scores. The post-TBI MDD patients showed significantly greater deficits in neurocognitive functions, particularly at the Trial Making Test-a (p<0.05), Digit Span (p<0.05), Corsi's Span (p<0.05), Verbal fluency (p<0.01), and the Token Test (p<0.05).

Table 1: Sociodemographic data. Not significant differences between the two groups (TBI patients and primary MDD patients) were observed.

	TBI patients n=16 (mean ± SD)	Control group n=6 (mean ± SD)
Age	40.44 (± 14.0)	45.14 (± 12.86)
Sex (male)	10 (62.5%)	3 (50%)
Education (years)	12.63 (± 3.88)	14.43 (± 3.78)
Premorbid IQ	107.98 (± 13.58)	116.7 (± 12.02)

TBI patients with and without MDD

At T1, the two TBI groups were homogeneous in terms of age, years of schooling and pre-traumatic IQ, and there was no statistically significant difference in trauma severity, although the depressed patients had higher GCS scores (2.3 ± 0.9 *vs.* 1.4 ±

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0.7). They also had significantly higher total BPRS score (p<0.01), BDI score (p<0.01) and HRSD score (p<0.01). The same patients performed significantly worse at Raven's Coloured Matrices (p<0.01), Trail Making (both sections) (p<0.05), Digit Span (p<0.01), Corsi's Span (p<0.01) and the Token Test (p<0.05). There was a trend towards a significant difference in the verbal fluency scores, which were lower in the depressed patients (15.0 ± 8.1 *vs*. 23.9 ± 9.8).

The Attentive Matrices and Tower of London test scores were similar in the two groups. The total WCST scores were deficient in both groups, although lower in the depressed (77.3 ± 15.6 *vs*. 90.1 ± 24). Table 4 shows the clinical and neuropsychological data in the two groups.

Neuromorphological data

75% of the patients had a pattern of frontal focal lesions, and 25% had diffused lesions. Eight of the depressed patients (80%) had frontal lesions, and 2 (20%) bilateral frontal lesions. A left frontal lesion was observed in 3 of the 10 subjects with MDD, 4 had a right frontal lesion and 1 a bilateral frontal lesion (Table 5). Moreover, frontal involvement showed significantly higher HRSD scores (p=0.044), the HRSD anxiety cluster (p=0.049) and the BPRS hostility/suspiciousness cluster (p=0.048). The side of the lesion was significantly related to WCST performance (p=0.040) and concentration capacity (p=0.036).

Table 2: Clinical diagnoses of TBI patients.

Clinical data	N°	%
Diagnosis at T1		
None	5	31,25
MDD	10	62,50
Anxiety disorder	1	6,25
Diagnosis at T2		
None	6	37,50
MDD	8	50,00
Anxiety disorder	1	6,25
Mood disorder with manic symptoms (mixed forms)	1	6,25
Diagnosis at T3		
None	8	50,00
MDD	7	43,75
Mood disorder with manic symptoms (mixed forms)	1	6,25

Table 3: Age, years of scholarity (education) and the mean scores of the scales for evaluating psychiatric symptoms and global functioning and the neuropsychological tests in the two groups (primary MDD patients and post TBI MDD patients).

Variable	Primary MDD n=6		Post-TBI MDD n=10		Significativity (p)
	Mean	± SD	Mean	± SD	
Age	45.14	12.86	37.12	15	NS
Education	14.43	3.78	13	2.9	NS
GAF	55.3	4.8	53	7.26	NS
IADL	1.9	0.75	2.9	2.48	NS
BPRS	44.5	5.2	43.1	3.4	NS
BDI	27.4	6.48	20.9	5.2	<0.05
HRSD	22.55	3.26	19.16	1.17	<0.05
HRSA	17.4	2.48	15.33	6.34	NS
RAVEN TEST (CPM)	32.7	2.98	25.1	5.1	NS
TRAIL MAKING TEST					
- section A	35	15.81	76.3	44.9	<0.05
- section B	74.29	22.4	124	77.2	NS
- delta	40.71	20.9	67.9	49.1	NS
PROSE MEMORY TEST	11.36	7.12	8.7	3	NS

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DIGIT SPAN	5.71	1.38	3.5	0.9	<0.05
CORSI'S SPAN	4.57	0.79	3	0.9	<0.05
VERBAL FLUENCY	31.43	6.49	15	8.1	<0.01
SEMANTIC FLUENCY	20.14	3.04	12.2	5.2	NS
TOKEN TEST	34.07	2.21	28.5	3	<0.05
ATTENTIVE MATRICES	47.87	8.7	40	6.5	NS
WCST	91.83	17.88	77.3	15.6	NS
TOL			28.1	3.3	NS
- moves	30.29	2.99	28.9	3.4	NS

Table 4: Clinical and neuropsychological data in depressed and non-depressed TBI patients at T1.

Variable	**Non-depressed TBI patients**		**Depressed TBI patients**		**Sigificativity (p)**
	Mean	**± SD**	**Mean**	**± SD**	
Age	47.5	13	37.12	15	NS
Education	13	4.2	13	2.9	NS
Premorbid IQ	112.1	15.4	103.9	10.9	NS
Trauma Severity	1.4	0.7	2.3	0.9	NS
GAF	1.9	0.8	1.4	0.5	NS
IADL	2.3	1.2	2.1	0.8	NS
BPRS	35	7.1	43.1	3.4	<0.01
BDI	6.8	4.1	20.9	5.2	<0.01
HRSD	9.4	6.7	19.16	1.17	< 0.01
HRSA	8.4	7.8	10.9	3.8	NS
RAVEN (CPM)	31.9	3.8	25.1	5.1	<0.01
TRAIL MAKING TEST:					
- section A	38.6	11.6	76.3	44.9	<0.05
- section B	60.6	29.5	124	77.2	<0.05
- delta	31.8	20.5	67.9	49.1	NS
PROSE MEMORY TEST	13	6.4	8.7	3	NS
DIGIT SPAN	6	2.1	3.5	0.9	<0.01
CORSI'S SPAN	5.5	2.1	3	0.9	<0.01
PHONEMIC FLUENCY	23.9	9.8	15	8.1	NS
SEMANTIC FLUENCY	13.3	6.7	12.2	5.2	NS
TOKEN TEST	32.3	2.5	28.5	3	<0.05
MATRICI ATTENTIVE	43.6	5.9	40	6.5	NS
WCST	90.1	24	77.3	15.6	NS
TOL	29.8	4.5	28.1	3.3	NS

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- moves	31.4	2.7	28.9	3.4	NS

Table 5: Psychiatric diagnoses in relation to the site of lesion (post TBI patients).

Psychiatric diagnosis	Lesion site	Lateralisation			
		Left	Right	Bilateral	
No diagnosis	frontal	1	0	0	1
	diffuse	2	0	0	2
	Total	3	0	0	3
MDD	frontal	3	4	1	8
	diffuse		2	0	2
	Total	3	6	1	10
Anxiety	frontal	0	1	0	1
	diffuse				
	Total	0	1	0	1
Mixed forms	frontal	0	1	1	2
	diffuse				
	Total	0	1	1	2

Discussion

Traumatic brain injury (TBI) is very common: more than two million people in the United States are reported to be hospitalised each year following non-fatal injuries (National Center for Injury Prevention and Control, Electronic Database) [41]. TBI can be considered the leading cause of trauma-related psychiatric disorders and it is a major public health issue [42,43]. MDD and total mood disorders are significantly more frequent in patients with TBI than in those with similar background characteristics who underwent similar levels of stress (e.g. motor vehicle collisions) without sustain brain injury. This suggests that the neuropathological processes associated with TBI are an important contributing factor to development of mood disorders [4,19].

In our study MDD have demonstrated to be the most frequent psychiatric diagnosis during the six months after TBI, observed in 62.5% of the patients after one month, 50% after three months, and 43.75% after six months. Our findings are in line with earlier reports of high rates of major depression after TBI [6-10,44]. Furthermore, literature data reported that MDD can be observed not only immediately after TBI, but also throughout a 30-year follow-up [14].

Like other Authors [4], we found that the occurrence of MDD was not significantly related to the severity of the brain injury, although there was a significant relationship between trauma severity and the presence of more severe psychiatric symptoms (total BPRS, BDI and GAF scores), thus demonstrating that the severity of TBI may cause a worsening of psychiatric symptomatology and of other neurobehavioral difficulties. On the other hand neuropsychological performances difference between the patients with mild and severe TBI at several tests like the Trail Making Test-a, verbal Span, the Token Test, and the number of WCST categories completed, Attentive Matrices, and the memory tests (Corsi's Span and Prose Memory).

During the six months' follow-up, all of the TBI patients show a progressive improvement in global functioning (evaluated at IADL and GAF), psychiatric symptoms (evaluated at BPRS) and cognitive domains. Nevertheless, a large proportion (57%) was deficient at frontal tests such as Verbal Fluency, Attentive Matrices, TOL and WCST at the end of the study (six months). This would seem to underline that improved clinical conditions correspond to improved psychic symptoms, but not to an improvement in all areas of neurocognitive functioning.

It is not surprising that seems to be an increased risk of psychiatric diagnoses following a TBI because the parts of the brain that are most susceptible to trauma damage are the frontal and parietal lobes, which are also known to be involved in most psychiatric disorders. In particular, the incidence of depression is higher after mild TBI, possibly because of damage to the frontal lobes [45]. In our study, 75% of the subjects had focal frontal lesions and 25% had diffuse lesions; furthermore, 8 patients with a mood disorder (80%) had frontal lesions and 2 (20%) bilateral frontal lesions. There was also a significant correlation between frontal involvement and total HRSD scores, HRSD anxiety cluster scores and BPRS hostility/suspiciousness cluster scores. So our finding seems to demonstrate that abnormalities on CT scan can increase the risk of depression particularly in light of the worse of cognitive and functional outcomes reported when TBI is complicated by intracranial lesions visible on CT scan.

It has been clearly shown that the cognitive effects of TBI become evident after the resolution of post-trauma amnesia [46,47]. The cognitive deficits vary depending on the severity of the injury, but generally involve attention/concentration, memory and executive functioning (problem solving, mental flexibility and imitation), all of which found within the overall picture of widespread brain injury and, in particular, the fronto-temporal damage typical of TBI. Both acute and later cognitive complaints are common even after mild TBI [48]: the prevalence of memory and attention deficits 1-3 months after mild TBI has been reported to be 40-60% [49]. Explosive and violent behaviour has long been associated with focal brain lesions and widespread damage to the central nervous system [50] and agitation may predict longer hospitalisation and decreased cognition [51]. These episodes range in severity from irritability to outbursts that lead to damage to property or assaults on others [48].

Previous studies have consistently found an association between TBI and damage to the prefrontal cortex and basal ganglia, as well as the tracts of white matter connecting these structures [4,7]. This leads to the hypothesis that executive dysfunction and depression may be related to the same

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pathophysiological mechanism (i.e. the disruption of fronto-striatal-thalamic circuits), and the selective volumetric changes in the left prefrontal cortex observed in patients with MDD certainly contribute to their cognitive deficits. However, it is conceivable that a depression-specific mechanism (such as an abnormal aminergic modulation of prefrontal structures) may also impair executive functioning, as observed in our patients.

One of our most important findings is that MDD is a frequent complication of TBI. Our comparison of patients with post-TBI and primary MDD indicate that the former have a specific psychopathological profile, characterized by less severe depressive symptoms (as shown by their HRSD and BDI cluster scores), increased social isolation and hostility, and a neuropsychological pattern that is significantly associated with significantly greater deficits in cognitive functions (revealed by differences in the Trail Making Test-a, Digit Span, Corsi's Span, Verbal Fluency, and the Token Test).

These data are in line with those of previous studies [4,52]. Jorge et al. [4] found that patients with post TBI MDD showed significantly greater impairment in problem solving and cognitive flexibility than their non-depressed counterparts, and that MDD was also associated with poorer social functioning after one, three and six months. Levin [17] observed that patients with MDD following mild TBI showed increased anxiety, cognitive deficits and disability in comparison with those without depression. Furthermore an association between MDD and poor psychosocial functioning following mild TBI has been observed in previous studies [53].

At our knowledge the strength of our study is that it is the first to combine assessments of Axis I psychiatric disorders using structured instruments, cognitive functioning by means of a wide sensitive neuropsychological test battery, and abnormal CT findings.

Furthermore this study is characterized by the combination of patient recruitment limited to those with traumatic brain injury and no premorbid history of psychiatric disorder, neurological disorders, or substance abuse. A potential limitation is that by excluding patients with a history of substance dependence or major psychiatric disorder, our study sample might have been less representative of the general mild-TBI population. Although pre-injury substance abuse has been reported to be related to post injury onset of MDD [44] it has not been confirmed as a risk factor in other studies [4,17]. Moreover, inclusion of patients with intoxication, pre-existing behavioural problems, or baseline functional disability could have complicated the diagnosis of TBI and obscured the impact of trauma on outcome.

However it also has two methodological limitations. The small number of subjects means that our conclusions may not apply to all patients with TBI. Secondly, the follow-up is short compared with that of previous studies. In conclusion, our results suggest that TBI can lead to vulnerability to psychiatric disorders in some subjects, and have a deleterious effect on recovery and psychosocial outcomes. Our data are in agreement with Rapoport [54], who emphasizes how it is important for clinicians to recognize Major Depression following TBI because of its association with poor global and psychosocial outcome, post concussive symptoms and cognitive deficits.

Biological factors such as the involvement of the prefrontal cortex (and probably other limbic and Para limbic structures) may play a significant role in the complex pathophysiology of MDD. A psychiatric evaluation and follow-up should be included in the routine treatment of TBI, considering that neurocognitive disturbances may be difficult to detect and may interfere with compliance to rehabilitation. Further studies are needed to characterise these factors in order to identify patients with TBI at high risk of developing MDD and design appropriate therapeutic interventions.

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