Clinical Cases in Medicine

ISSN: 2770-2359

Case Report

Interesting Case of Traumatic Brain Injury - Neuropsychological Assessment

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Abstract

Craniocerebral damage due to Traumatic Brain Injury (TBI) mediated by multiple molecular cascades can be expressed through neuropsychological complications, involving cognitive deficits, post-traumatic epilepsy, personality change, as well as severe and chronic psychosis. The purpose of this study was to investigate and identify potential patterns associated with the neuropsychological manifestations following TBI by examining bibliographic case reports through a systematic review, and to describe a clinical case of Psychotic Disorder Following Traumatic Brain Injury (PDFTBI) in the right temporal lobe with concomitant cognitive defects and post-traumatic epilepsy. The time within the first year and over 5 years following TBI as well as male gender stood for risk factors for developing PDFTBI. The incidence of misidentification syndromes and epilepsy was significantly higher compared to other psychotic disorders. Negative symptoms of schizophrenia were less pronounced in contrast to positive symptoms. The pattern in which physical violence was expressed also differentiated. A positive correlation was disclosed with concurrent cognitive impairments most commonly in memory and executive functions. Association of the symptomatology with frontal and temporal pathology was disclosed.

Keywords: Neuropsychology; Psychotic disorder following traumatic brain injury; Craniocerebral trauma; Epilepsy; Temporal lobe; Neurotrauma; Neurocognitive; Cognition

Introduction

Traumatic Brain Injury (TBI)

Traumatic Brain Injuries (TBI) can be penetrating or closed, depending on whether the cranium and dura mater are breached. The Central Nervous System (CNS) injuries can be classified into primary or secondary. Craniocerebral lesions due to direct tissue impairment from the impact forces are primary CNS injuries and they can be either localized (laceration of the brain parenchyma) or diffuse (as in the diffuse axonal injury). Secondary injuries are developed as tissue response to the primary injuries or systemic events (involving inflammation, ischemia, lack of blood flow auto regulation, and glial proliferation) [1-4]. The mechanism of closed TBI can be explained by cytotoxic processes such as dysregulation of calcium (Ca^{2+}) and magnesium ions (Mg^{2+}), neurotransmitter excitotoxicity, free radical-induced injury, and diffuse axonal injury [5,6]. Post-TBI residual effects vary in each patient. The majority of patients who suffer moderate and severe traumatic brain injuries as well as a minority of patients with mild craniocerebral injuries are faced with complications due to long-term neurodegeneration processes involving neuropsychiatric disorders, such as cognitive deficits, post-traumatic epilepsy, personality alterations, as well as severe and chronic psychosis/schizophreniform disorder. Acute changes in neurotransmitters, involving acetylcholine, norepinephrine, dopamine and serotonin levels, are implicated for post-TBI psychiatric manifestations (involving a decrease in dopamine levels, abnormal levels of lumbar Cerebrospinal Fluid (CSF) 5-Hydroxylindoleacetic Acid (5-HIAA), as well as an acute increase in cholinergic transmission after TBI followed by chronic reductions in neurotransmitter function and cholinergic afferents) [5-9].

Traumatic Brain Injury (TBI) is one of the major public health problems at a global level and has been described as a "silent epidemic," reflecting the common underestimation of its actual incidence and impact [1,4,10]. In the United States, each year more than 1.4 million TBI incidents occur, among which approximately 50,000 are fatal, 235,000 are hospitalized, and 1.1 million are discharged from emergency departments after receiving medical care. In the United States, approximately 5.3 million people live with long-term disabilities as a result of TBI, while direct and indirect annual costs are estimated at more than $ 56 billion. In Europe, an annual incidence of 235 TBI cases per 100,000 individuals is estimated based on studies from different countries, while 6.3 million people live with some level of disability related to TBI. In northern Europe, the main causes of TBI are falls, mainly related to alcohol use, while in southern Europe TBI incidents are mainly due to traffic accidents. Assault injuries and gunshot wounds are also frequent TBI causes [11]. People from all age groups are affected, with causes varying by age group: fall-related injuries are more prevalent among children and older people, while injuries related to traffic accidents and violence are more common in adolescents and young adults [1,12,13].

Although some degree of independence may be managed to be regained by some patients with regard to their self-care, deficits for critical thinking and decision-making processes may be still evident with inability to continue working/educate, provide for the needs of their families, or engage in social activities. TBI complications can sadly lead to difficulties in family relationships as well as poor quality of life for patients and their caregivers [5,7]. Sadly, the age range of TBI survivors has been estimated at 15-24 years following trauma [14].

Citation: Antonis T, Maria S, Kostas F, John N. Interesting Case of Traumatic Brain Injury - Neuropsychological Assessment. Clin Cases Med. 2020;1(1):1001.

Publisher Name: Medtext Publications LLC

Manuscript compiled: April 10th, 2020

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Methodology

The authors describe a case of severe traumatic brain injury and craniotomy of the right temporal lobe with concomitant cognitive defects, post-traumatic epilepsy, and psychotic disorder after a car crash. The following case study is written in compliance with the Helsinki Declaration of 1975, as revised in 1983, and the complete anonymity of the patient has been assured. Therefore, a systematic review was carried out on neuropsychiatric complications in traumatic brain injury incidents (case reports) described throughout international literature by searching the electronic data bases of PubMed, Google search, Google Scholar, Heal Link, EMBASE, Scopus and Cochrane Library. No language restriction was applied. The search terms were: "traumatic brain injury," "craniocerebral injury," "psychotic disorder following traumatic brain injury," "post-TBI psychosis," "temporal lobe epilepsy," "interictal psychosis," "postictal psychosis," "psychosis after craniotomy," "craniocerebral trauma," "deficits after traumatic brain injury," "cognition," "complications after traumatic brain injury," "temporal lobe injury," "post-traumatic epilepsy," "post-traumatic seizures," "neurocognitive impairment," "neurodegeneration." No language restriction was applied. A descriptive review of the literature was also conducted in order to study and discuss the findings in comparison to the existing knowledge. Overall, 141 articles and books deriving from various disciplines concerning traumatic brain injury and its complications including 65 case studies dating from 1971 to November 2019 were thoroughly studied. All 141 articles were reviewed and evaluated by the authors. Meta-analytic observations were made on the available PDFTBI cases. In addition, a random sample of 115 hospitalized patients in the Adult Psychiatry of the "George Papanikolaou" General Hospital of Thessaloniki was studied and was utilized as a comparison group to this study. Data were analyzed by SPSS (Statistical Package for the Social Sciences). (Z-Score = 13.3588. p-value = 0.00001. The result is significant at $p<0.01$)

Case Presentation

Background

A 49-year-old female patient of Albanian origin, residing permanently in Greece with her two children and legal spouse with whom she is under marital separation, was hospitalized voluntarily in the adult psychiatric ward of AHEPA University General Hospital of Thessaloniki following an involuntary two-week hospitalization at the place of residence under a public prosecutor's order due to behavioral disorganization and delusional ideation on the grounds of post-traumatic epilepsy. The onset of symptomatology was reported to have occurred at the age of 31 years when the patient suffered craniocerebral injury in a traffic accident (subdural hematoma in the right temporal lobe, followed by craniotomy after four years at the age of 35 years). The patient had a free medical history before the traffic accident. Four years post-traumatically the patient experienced episodes of loss of consciousness with concomitant falls and urine leakage despite receiving antiepileptic treatment. Afterwards, the patient experienced epileptic seizures, mixed anxiety-depressive symptoms, outbursts of anger and impulsive behavior. Her overall postaccident functionality was reported to be very poor. During the last two years and after the self-discontinuation of her medication, the patient experienced worsening of her symptomatology, while she started experiencing delusional ideas of persecution, acoustic and visual hallucinations, aggression, lack of empathy and non-compliance with therapeutic instructions. Her behavioral disorganization eventually escalated to the point of setting fire to her estranged spouse's clothes leading her to the aforementioned involuntary psychiatric hospitalization (until then she had only been hospitalized in the neurological ward). She was diagnosed with schizophreniform delusional disorder due to another medical condition (DSM-V code 293.81/ICD-10 code F06.2) and was administered the following medication with partial improvement: (a.) olanzapine 405 mg long-acting intramuscular injection monthly; and per OS administration of (b.) tb haloperidol l 20 mg daily; (c.) tb biperiden hydrochloride 4 mg daily; (c.) tb diazepam 30 mg daily; (d.) tb oxcarbazepine 900 mg daily; (e.) tb folic acid 5 mg daily.

Neuropsychological assessment

The patient's cognitive functionality was assessed through the following battery of examinations used in the Neuropsychological Laboratory of AHEPA University General Hospital Psychiatric Department. The main objective of the patient's neuropsychological assessment was to investigate her cognitive deficits with the basic battery of trials of the Neuropsychological Laboratory of the 3rd Psychiatric Clinic of Aristotle University of Thessaloniki, which examines major aspects of cognitive behavior and performance. Specific areas evaluated: attention and concentration levels, visual perception, learning ability, memory parameters (verbal, visual, working, long term), verbal functions and academic skills, visuospatial and visual constructive ability, abstract thinking, speed of information processing, ability to conceptualize, and executive functions. From the subject's history, there was no initial need to go beyond the basic battery of cognitive abilities and to add specialized trials. Neuropsychological examination included trials for evaluating memory function (episodic memory, reverse recall, fluency test), attention (stroop, straight number recall, Trail Making Test A), and executive functions (Trail Making Test B, Cube test, Visuospatial ability test). Her scores on both direct and long-term memory tests (episodic memory, reverse recall, fluency test) appeared deficient for her age and cognitive level. With regard to long-term memory at the time of assessment, difficulties were encountered in trials involving the conceptual organization of the events to be memorized (episodic memory). The recollection of mnemonic traces of general knowledge (explicit memory) varied to normal levels. The subject's attention span was very low, as indicated by the slow execution of the first part of the Trail Making Test, and by her performance in the Stroop interference condition as well. In general, the subject's performance in Information Processing Speed (IPS), learning, memory, and executive function ranged below the normal limits considering her age and level of education at that time. In particular, the patient's performance in individual neuropsychological trials included in the battery was indicative of reduced precision and speed of shifting visual attention to a different kind of reaction, difficulty in abstract thinking and parallel processing of information. The patient had a significant difficulty in the category fluency test (Fluency Index) (6 responses in 60" in the "ANIMAL" category and 9 responses in 60" in the "FRUIT" category). Particular deficits in vigilance (capability of readiness for response) as well as alertness (involving the general receptivity to stimuli and preparedness for response) were generally identified. Deficits in both short and long-term memory were characteristic. The patient was shown to maintain a normal level of ability to perform activities of daily living as well as to assess and control reality.

Evaluation

According to the results of the tests at the given time, the patient presented with characteristic cognitive dysfunction involving deficits

in ability of alternating attention, encoding and speed of information processing, learning, working memory and executive function. More specifically, deficits in memory were present in trials requiring free recall, interference, and working memory, whereas impaired attention was directly associated with difficulty focusing on a task. Delusional persecution ideas as well as depressive affect were reported by the patient as well.

Results

The sample of incidents presenting with Psychotic Disorder Following Traumatic Brain Injury (PDFTBI). As aforementioned, random PDFTBI patients having been described throughout literature by various authors comprised the examined sample. The male predominance in the group sample (four-fold) was statistically significant (M:F ratio; 4:1) (Z-Score = 8.4853. p-value = 0.00001) (absolute figures: 80 and 20 respectively), and this finding was also consistent with previous studies [15]. The mean age of the sample was at 36.4 years (age range from 14 to 75 years. Variance = 202.92359. Standard Deviation = 14.24512), while the average time having elapsed between the realization of the brain injury and the onset of the psychotic disorder was estimated at 5.26 years (range from 0 to 20 years. Variance = 34.20053. Standard Deviation = 5.84812). A bimodal distribution of time between TBI and onset of psychosis was noted. 44.10% developed a psychotic disorder within the first year after sustaining a TBI, whereas 38.24% developed a psychotic disorder in the period following 5 years (a finding also consistent with previous studies) [15]. With respect to the causative factors, the vast majority of the craniocerebral injuries were severe (31%) followed by mild (11%) followed by moderate traumatic brain injuries (6%) ($p<0.01$). Traffic accidents were the most frequent cause of injury, followed by accidental falls, followed in turn by assault ($p<0.01$). The frequency of psychotic disorder following TBI due to experienced domestic violence was higher among females (M:F ratio; 1:4) (Z-Score = -1.5309. p-value = 0.06301). Furthermore, the investigated sample was quite heterogeneous in regard both to the reported symptomatology and localization of lesions. (Table 2 and 3) Long-term cognitive deficits were described in 44% of the cases. Affective symptoms were present in 26% of the sample with a significant female predominance (M:F ratio; 1:2) (Z-Score = -2.1658. p-value = 0.015). Auditory hallucinations were the most experienced disorder of perception followed by visual hallucinations and in turn followed by gustatory, tactile and olfactory hallucinations ($p<0.01$). Erotomanic delusions were expressed in 2% of the sample and only by female patients (Z-Score = -2.8571. p-value = 0.00212). Co-morbidity with epilepsy was noted in 16% of the subjects, with a higher frequency in females as well (M:F ratio; 1:2.4) (Z-Score = -1.9094. p-value = 0.02807). Regarding expressed violence, hetero-destructive behaviors were far more frequent in comparison to deliberate self-harm (2.7:1) (p-value = 0.00587). Perinatal factors were not correlated with the onset of the psychotic disorder following TBI ($p<0.01$).

Neuroimaging and electroencephalographic examinations were available in 39% of the patients (41% CT, 44% MRI, 46% EEG, 13% SPECT) (Table 3), among which, patients having detectable pathological findings (92.3%) were twelve-fold compared to PDFTBI patients without pathological findings ($p<0.01$). The most common sites of localization of traumatic craniocerebral lesions were in both the frontal and temporal lobes equally at a 1:1 ratio, while parietal lesions were 3.8 times less frequent ($p<0.01$) and no occipital localization was reported apart from a finding in the temporo-parieto-occipital junction (2.56%). Bilateral and lateral frontal pathologies were almost

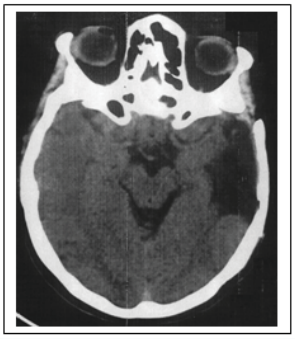

Figure 1: Computed tomography scan disclosing the patient's right temporal lobe deficit.

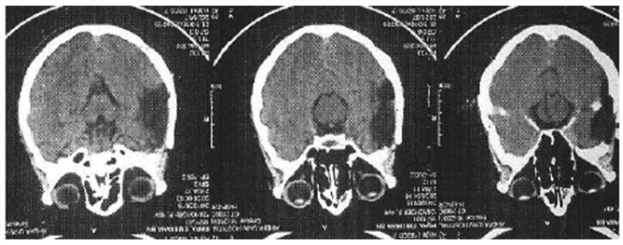

Figure 2: More sections on the computed tomography scan disclosing the patient's right temporal lobe deficit.

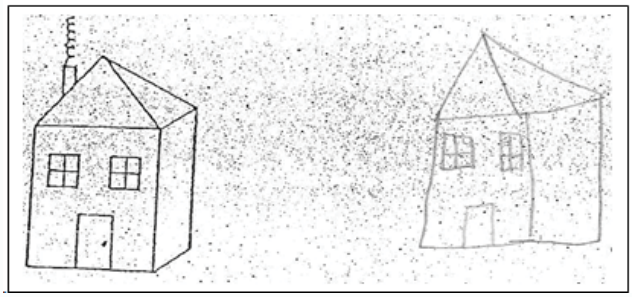

Figure 3: Copy of a figure by the reported patient.

equally frequent. A higher lateral temporal localization of lesions was noted (2.8:1) compared to bilateral or hippocampal localization (p-value = 0.0006). Furthermore, in regard to localization in the parietal lobes (although less frequent), lateral lesions were far more probable in comparison to bilateral (p-value = 0.00027). In addition, a higher correlation was noted for the left hemisphere pathology: left-sided lateral frontal lesions were eight-fold in comparison to the right lateral frontal lesions (p-value = 0.0044), a moderate difference in frequency was noted between left and right-sided lateral temporal lesions ($0.05< p\text{-value}<0.10$), and left lateral parietal lesions were fivefold more frequent compared to the right-sided (p-value = 0.01044).

Regarding the described symptomatology in association with the localization of the aforementioned findings, the following results were noted. Delusional thought content as a symptom was inversely correlated with parietal lesions ($p<0.05$), but was mainly correlated with temporal, especially lateral ($p<0.01$), and frontal pathology, especially bifrontal ($p<0.05$). (The difference in the frequency

between temporal and frontal localization of the findings was not statistically significant.) In addition, delusional thought content as a symptom was moderately correlated with left hemisphere pathology (0.05< p-value<0.10). Auditory hallucinations as a symptom were correlated with temporal pathology (p = 0.05), especially lateral (p<0.01), and negatively correlated with parietal pathology (p<0.05). In this case, although right temporal lesions were the most frequent, no predominant pattern of left or right hemisphere pathology could apply. In addition, greater hippocampal involvement was observed in comparison to other symptoms. On the contrary, visual hallucinations were associated with fronto-parieto-temporal lesions almost equally dispersed without any specific correlations. Misidentification and reduplicative phenomena were associated with fronto-temporal lesions without significant differences, but were negatively correlated with parietal pathology (p<0.05).

Personality change, as a symptom, was associated with fronto-temporal lesions equally at a 1:1 ratio and was also inversely correlated with parietal lesions (p<0.05). Equilibrium of left and right hemisphere pathologies was noted.

Affective symptomatology was associated with fronto-parieto-temporal lesions (all three lobes) (greater involvement of the parietal lobes), but correlated with lateral localization (frontal 0.05< p-value<0.10; temporal and parietal p<0.01) and left hemisphere pathology (temporal p<0.05; frontal and parietal 0.05< p-value<0.10).

Epilepsy and cognitive deficits were associated with fronto-parieto-temporal lesions almost equally dispersed. (Cognitive deficits were slightly more frequent in temporal lobe pathology but p-value was marginally above 0.10.) Bifrontal and lateral frontal pathologies were equal at a 1:1 ratio. In temporal and parietal lobes, lateral localization of lesions was noted, as well as equilibrium of left and right hemisphere pathologies. The abovementioned findings were also consistent with previous studies [15].

The sample of random psychiatry inpatients (comparison group)

This sample derived from the random recording of the last one hundred fifteen (115) hospitalizations in a random adult psychiatry department (Table 4). It should be further clarified that this group consisted of patients who had experienced psychiatric symptomatology and/or conduct disorders regardless of etiology, were hospitalized in the psychiatric department either by their own will or by a prosecutor's order and had been admitted either directly from the emergency department or as a transfer from other wards and departments of the general hospital due to psychiatric symptomatology manifestation such as patients who were hospitalized due to other medical conditions in any another hospital department while manifesting psychiatric symptomatology and the latter was an aggravating factor in the course and outcome of their hospitalization and their medical

condition due to behavioral disorders (e.g. hetero-destructive behavior; active suicidal ideation; non-compliance with doctors' instructions in the context of delusional ideation; wandering tendencies in the context of psychopathology; neurological/neurosurgical patients with psychiatric symptomatology, delirium after pathological treatment, withdrawal syndrome after pathological treatment, suicide attempts following pathological/surgical/orthopedic treatment, etc.).

In this sample, male and female patients were randomly equal (absolute figures: 58 and 57 respectively), while the mean age was at 42.4 years (age range from 19 to 83 years. Variance = 236.40686. Standard Deviation = 15.37553), which was 6 years older compared to the mean age of the PDFTBI sample. In average, male patients were in their early 40s at the time of hospitalization, while females' mean age was at 44.2 years.

Unsurprisingly, the clear majority of the patients of the recorded cases suffered from mental disorders without any organic association (82.6%), among which, schizophrenia spectrum disorders were identified in 25.3 percent. Neurocognitive disorders, such as delirium, toxicosis, traumatic brain encephalopathy, cerebrovascular disease, dementia, brain tumors, multiple sclerosis, undesirable effects of neurosurgical interventions, and other neurodevelopmental disorders stood for a smaller portion of the sample (14.8%), while mental disorders associated with epilepsy were observed in 2.6% of the cases.

Physical violence (including auto-destructive and hetero-destructive actions towards people or inanimate objects) was expressed by 64.4% of the patient sample, while 37.8% of violent patients engaged in acts of interpersonal violence mainly towards their close family members and care-givers. Mean age for the expression of physical violence was at 41.0 years for both genders (with age range from 19 to 83 years).

A slightly higher propensity for interpersonal violence was disclosed among male subjects in comparison to females (M:F ratio; 1.1:1). No cases of homicide were recorded.

Attempted homicide was recorded in 1.7% of the sample (2.7% of physically violent patients). A higher propensity for homicide attempt was disclosed among male subjects in comparison to females. All of the perpetrators were males suffering from mental disorders without organic association (100%). With respect to fire setting, 1.7% of the sample set fire to their house or one else's property. Acts of serious self-harm and suicide attempts were observed in 27.8% of the sample.

By comparing the sample of patients with psychotic disorder following TBI and the sample of random psychiatric inpatients, different trends appeared. The rates of physical violence (including auto-destructive and hetero-destructive actions towards people or inanimate objects) between PDFTBI and random patients were divergent with a clear predominance in the sample of random psychiatry inpatients (PDFTBI patients: Random patients' ratio for physical violence; 1:2) (Z-Score = -4.732. p-value = 0.00001), while there was also significant divergence in the type of the expressed physical violence between the two groups of patients.

More specifically, the patients comprising the PDFTBI sample tended to engage in significantly less actions of self-harm (PDFTBI patients: Random patients' ratio for auto-destructive actions; 1:3.9) (Z-Score = -3.9526. p-value = 0.0004) (Physically violent PDFTBI patients: Physically violent random patients' ratio for auto-destructive actions; 1:1.9) (Z-Score = -2.0943. p-value = 0.01831). When the samples were viewed as separate categories, a higher incidence of hetero-destructiveness compared to auto-destructiveness was noted among patients in the PDFTBI sample (ratio 1:2.7; p-value = 0.00587), in contrast to the random patient sample that exhibited higher propensity for auto-destructiveness.

In addition, with regard to the intensity of interpersonal violence, it was observed that the patients comprising the PDFTBI sample group tended to express lower levels of homicidal behavior in comparison with the sample group of random psychiatry inpatients (Z-Score =

Figure 4: The patient's clock-drawing test.

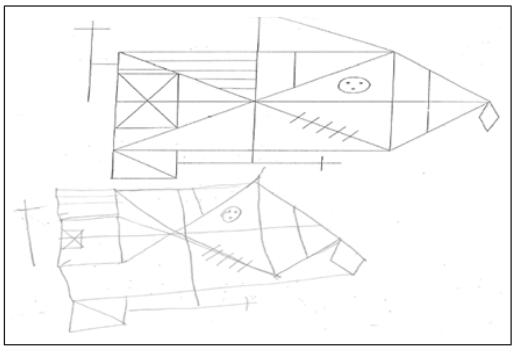

Figure 5: The patient's Rey-Osterrieth Complex Figure test (ROCF) (damaged right temporal lobe).

-1.3249. p-value = 0.9342). Arson or fire-setting was an action rarely exhibited in both sample groups with female predominance in both sample groups as well. The levels of fire-setting incidence were slightly higher among the patients comprising the PDFTBI sample group (PDFTBI patients: Random patients' ratio; 1:1.7) (Physically violent PDFTBI patients: Physically violent random patients' ratio; 1.2:1) (not significant divergence. p-value>0.10).

In regard to epilepsy, a clear predominance was disclosed among PDFTBI patients versus the comparison group with statistical significance (PDFTBI patients: Random patients' ratio; 6.1:1) (Z-Score = 3.4505. p-value = 0.00028). Furthermore, the statistical incidence of misidentification syndromes was significantly higher among PDFTBI patients with a clear positive relationship in relation to the comparison group (PDFTBI patients: Random patients' ratio; 19.5:1) (Z-Score = 4.2594. p-value = 0.00001). Erotomanic delusions as well as gustatory hallucinations were exhibited in fairly low levels in both sample groups with a higher incidence in the PDFTBI group sample (Z-Score = 1.5237. p-value = 0.06426). Oedipism was a symptom exhibited only in the examined group of PDFTBI patients (2%) (Z-Score = 1.5237. p-value = 0.06426).

Drug abuse was significantly less frequent in the examined PDFTBI sample (PDFTBI patients: Random patients' ratio; 1:11.3) (Z-Score = -3.0544. p-value = 0.00114). In addition, no peripartum onset of psychosis was described among the PDFTBI patients' sample in contrast to the random patients' comparison group (Z-Score = -1.3249. p-value = 0.09342).

Discussion

The findings from the foregoing data reinforce the characterization of traumatic brain injury as a "silent epidemic," since, although the majority of causal factors were associated with severe trauma, mild craniocerebral injuries followed second in frequency reaching statistically significant rates [1,4,10].

The mean latency of onset of psychosis was estimated at 5.26 years after TBI, while a bimodal distribution of time between TBI and onset of psychosis was also noted, rendering the onset of a psychotic disorder most probable within the first year, or after 5 years following TBI. These findings are in line with international bibliographic data and findings of previous studies [15,11,16]. Male gender stood for a risk factor for developing PDFTBI and this was a highly robust finding. There was an overrepresentation of men not only in the present PDTBI sample (M:F ratio; 4:1) (Z-Score = 8.4853. p-value = 0.00001), but also in the examined samples of all previous studies. Data were consistent with the previous literature [15,11,16]. On the contrary, family history of schizophrenia was not confirmed as a statistically significant risk factor for developing PDFTBI. Furthermore, another finding that was in line with the respective findings of international literature was that the most common psychotic symptoms associated with PDFTBI were paranoid ideation, delusions and hallucinations, while negativistic symptoms were less pronounced (p-value = 0.00001). More specifically, the most significant symptoms expressed throughout the present sample were: paranoid ideation (68%), delusional ideas (47%), and hallucinations (36%), with misidentification syndromes (17%) and auditory hallucinations (22%) the most common subtypes. A much smaller proportion manifested negative symptoms (10%), which was consistent with the PDFTBI literature reporting a modal presentation of delusions (22% - 80%), hallucinations (47% - 84%) and negative symptoms (15% - 22%) [15,11,16]. Furthermore, the statistical incidence of misidentification syndromes was significantly higher among PDFTBI patients with a clear positive relationship in relation to the comparison group (PDFTBI patients: Random patients' ratio; 19.5:1) (Z-Score = 4.2594. p-value = 0.00001). A clear predominance of epilepsy was disclosed among PDFTBI patients versus (a.) the comparison group of random psychiatry inpatients (six fold higher incidence) (PDFTBI patients: Random patients ratio; 6:1) (Z-Score = 3.4505. p-value = 0.00028); and versus (b.) random TBI patients experiencing epilepsy at a prorated base rate of 7% according to literature (PDFTBI patients: Random TBI patients' ratio; 2.3:1) (Z-Score = 1.9948. p-value = 0.0233; p<0.05) [15].

PDFTBI was found to be associated with concurrent cognitive impairments (44%), most commonly in memory and executive functioning (27.3%). Executive functioning and memory were the impairments most frequently described throughout bibliographic studies, as well, which is a robust finding in the literature. In addition, divergence in the type of the expressed physical violence between PDFTBI and random psychiatry inpatients was disclosed. A higher incidence of hetero-destructiveness compared to auto-destructiveness, but with lower incidence of homicidal behavior, was noted among patients in the PDFTBI sample (p<0.01), in contrast to the random patient sample that exhibited higher propensity for auto-destructiveness. Physical violence is a parameter which, to the authors' knowledge, has not been studied in previous PDFTBI bibliographic research studies. The majority of patients improved with antipsychotic and antiepileptic drugs. As expected from the frequency of the respective symptomatologies within the sample, antipsychotic treatments were used more than antiepileptic drugs (Z-Score = -2.4708. p-value = 0.00676). Clozapine showed the highest efficacy values followed by risperidone and olanzapine. PDFTBI was found

to be associated with lesions to the frontal and temporal areas of the brain as identified by neurological studies, which is an additional finding being strongly consistent with the PDFTBI literature. More specifically, the present study reported 92.3% positive findings in any neuroimaging and electroencephalographic examinations (41% CT, 44% MRI, 46% EEG, 13% SPECT). The most common sites of localization of traumatic craniocerebral lesions were in both the frontal and temporal lobes equally at a 1:1 ratio. In addition, a higher correlation was noted for the left hemisphere pathology. The lateralization that has been observed can be possibly explained by hemispheric dominance. PDFTBI seemed to develop only after a threshold of damage was sustained to key brain areas [15]. Juxtaposed with the aforementioned data, literature on neuroimaging studies of schizophrenia disclosed patterns associated with more global neuropathology, involving global cortical atrophy with enlarged ventricles, but also hippocampal atrophy and hypofrontality, as well as electroencephalographic patterns characterized by generalized slowing. However, bibliographic research on schizophrenia imaging has also indicated positive correlations of both delusions and auditory hallucinations with abnormalities to frontal and temporal-hippocampal areas [15,17,18].

Neuranatomy - the temporal lobes

The bony surface of the medial cranial fossa is an important parameter in the formation of cerebral contusions in the temporal lobe region and mainly in the area of the temporal pole. This is due to the sharp surface of the greater wing of sphenoid bone (pterion) on which the temporal lobe may be injured during a traumatic brain injury (due to inertia). In addition, the hippocampus and structures of the limbic system, responsible for memory as well as the emotional behavior of the individual, are located at the inner surface of the temporal lobe. This region in cases of large hematomas (e.g. epidural) that displace brain structures towards the cerebellar tentorium (incipient brain herniation syndrome) is prone to pressure injuries and micro bleeding [19]. Temporal lobes are involved in understanding and remembering images as well as understanding language and emotions. They are responsible for hearing, complex perception, speech comprehension (in the left hemisphere) as well as behaviors associated with motivation and affect. Damage to the temporal lobe areas is associated with disorders related to face recognition, word comprehension, selective attention, increased or decreased sexuality, as well as aggressive behavior, persistent speech (after damage to the right temporal lobe), olfactory and visual hallucinations, feelings of awe and panic. Concomitant motor phenomena involve perioral stereotypies such as bizarre grimacing and vacuous chewing movements [21,20].

Epileptic seizures

Epilepsy is known to be caused by environmental or genetic factors. Subsequently to craniocerebral injuries, for instance, the brain, in an attempt to amend the damage, creates abnormal connections between cells that can cause epilepsy [22].

Epileptic seizures are one of the most common neurological symptoms that occur in human populations [23]. An epileptic seizure arises from predisposing factors for the development of Post-Traumatic Epilepsy (PTE) abnormal electrical activity of the brain [24]. Epileptic seizures are defined as paroxysmal episodes caused by excessive, abnormal neuronal electrical discharges, being either localized in specific areas of the brain or widely distributed. Depending on the characteristics of the seizures as well as their localization, they may or may not have observable clinical manifestations [23]. Abnormal stimulation and synchronization of neurons are key prerequisites for the onset of epileptic seizures and are attributed to mechanisms that disrupt membrane translocation and repolarization, as well as to a defective neural network [25]. Seizures can disrupt many functions of the nervous system, thus causing abnormal motor, aesthetic, autonomic, behavioral and psychiatric phenomena [23,27,26].

As above-mentioned, Post-Traumatic Seizures (PTS) and Post-Traumatic Epilepsy (PTE) are TBI complications. Post-Traumatic Epilepsy (PTE) is a life-long complication of Traumatic Brain Injury (TBI) and refers to recurrent and unprovoked Post-Traumatic Seizures (PTS) manifesting at least one week after traumatization. (Post-traumatic seizures are differentiated from seizures occurring within the first week after TBI, which are considered "provoked," and they are an acute complication due to the craniocerebral injury.) It is estimated that up to 20% of symptomatic epilepsies in the general population are an aftermath of craniocerebral trauma. Seizures begin within the first year among approximately 50% of the cases, following an upward trend and reaching 80% within the first two years. The diagnosis of PTE is assisted by the application of Electroencephalogram (EEG) and neuroimaging. The severity of the craniocerebral injury, the presence of intracranial bleeding (acute intracerebral hematoma; acute subdural hematoma) and the early occurrence of post-traumatic seizures (PTS) constitute rough

Psychotic Disorder following Traumatic Brain Injury (PDFTBI)

Psychotic disorder is characterized as multifactorial as its precipitating cause lies into a combination of underlying components involving predisposing and precipitating factors (involving genetic vulnerability, epigenetic influence through life events, substance use, viral infections) that lead to the onset of psychopathology due to dysregulation of the dopaminergic system [16]. Craniocerebral injury is also a medical condition with an increased incidence of neuropsychiatric complications, including cognitive deficits, post-traumatic epilepsy, changes in personality, affective disorders as well as psychotic/schizophreniform disorder (PDFTBI). The most prominent risk factor for the manifestation of psychiatric complications after craniocerebral injury is the degree of severity and dispersal of the Traumatic Brain Injury (TBI), as well as its localization in the temporal and frontal areas.

Psychosis has been estimated to occur in less than 10% to 20% of the TBI population [5,14]. The clinical presentation of Psychotic Disorder following Traumatic Brain Injury (PDFTBI) is most frequently characterized by a gradual onset with a subacute or chronic course, prominence of delusions (most frequently persecutory, followed by reference, control and grandiosity) and auditory hallucinations (visual hallucinations are less frequent), as well as a lack of negative symptoms. The mean onset is between 4 and 5 years after the injury, while the majority of cases occur within 2 years. Prodrome symptoms may be apparent, including depressed affect, antisocial or inappropriate social behavior, social withdrawal, and deterioration in occupational performance. Impulsive aggression in PDFTBI patients is also frequent (ranging from 20% to 49%) and is associated with damage to the limbic system, orbitofrontal cortex, left anteromedial frontal lobe, and anterior cingulate [1,5,15,16]. Traumatic brain injury can be the primary risk factor for psychosis or contribute to the development of psychosis through secondary seizure disorder (post-traumatic epilepsy). Antipsychotics (especially atypical) are considered to be the most effective treatment for PDFTBI

[1,11,7]. At this point it has to be highlighted that the diagnosis of "psychotic disorder due to traumatic brain injury" which used to be included under the Diagnostic and statistical manual, 4th revision (DSM-IV) is no longer included in the 5th revision (DSM-V), but is incorporated under the umbrella term of "psychotic disorder due to another medical condition." Furthermore, the expression "due to" indicates a direct causal link with the psychotic disorder, whereas psychotic disorder has been repeatedly reported to be multifactorial and the phrase "following" is far more accurate and correct according to evidence-based psychiatry [11,28].

A systematic review of case studies between 1971 and 1994 was carried out by Fujii and Ahmed who examined 39 articles describing a total of 69 PDFTBI cases which matched with the following inclusion criteria: (a.) presence of hallucinations or delusions; (b.) occurring following traumatic brain injury; (c.) not better accounted for by another mental disorder; and (d.) not occurring exclusively during a state of delirium [11]. Loss of consciousness was noted in 89% of cases, while in 75.86 % of the examined PDFTBI cases with detailed data available the head injury was classified as moderate or severe. With respect to the interval between the craniocerebral injury and the onset of psychotic disorder, the mean value was 4.1 years (range 0 to 34 years), in 38% of the cases it was less than or equal to one year and in 50% less than or equal to two years.

Negative symptoms were detected in 14% of the patients (*vs.* schizophrenia rates ranging 25% to 84% according to different studies). The authors detected focal Electroencephalogram (EEG) abnormalities and neuroimaging evidence in the frontal and temporal areas (non-specific findings) in the majority of the examined subjects [11,28].

The relationship between epilepsy and psychosis

Epilepsy and psychosis share a common bond that is not yet fully understood. For decades it has been noted that seizures and psychotic symptomatology may exist concomitantly and share relevant pathophysiological mechanisms [27]. Originally, observations that the onset of epileptic seizures improved the psychotic symptomatology of some patients led to the theory of functional dependence and biological antagonism between schizophreniform and epileptic symptoms (thus leading to the introduction of medication-induced iatrogenic seizures for the treatment of schizophrenia by Meduna) [29]. Afterwards by working with a small number of patients (N=69), rejected previous views, arguing, instead, that there is a positive association between epilepsy and schizophrenia [30]. The current view is that there is a relationship, but in the bond that epilepsy and psychosis seem to have, there may be an antagonism between symptoms of epilepsy and psychosis [31]. (The clinical expression of psychotic disorders is fairly heterogeneous, but there is a common symptomatology (such as auditory hallucinations and blunted affect) as well as an endophenotype (such as P50 suppression and prepulse inhibition deficits) [27].

In general, it is estimated that 10% to 30% of patients with epilepsy may experience psychotic symptoms. Patients with chronic psychoses of epilepsy (interictal psychosis) can have ventricular enlargement similar to those seen in patients with schizophrenia [27]. Interestingly it has been also noted that Post-Ictal Psychosis (PIP) lacks negative symptoms (similarly to post-TBI psychoses and differently from schizophrenia) [27]. In post-ictal psychosis, common findings are bilateral temporal seizure foci, and a personal history of traumatic brain injury, encephalitis or low intellectual function (suspected to possibly reflect bilateral cortical compromise) [32]. Electroencephalographic abnormalities were detected among PDFTBI patients at an approximate rate of 70%, especially within the temporal lobe, with seizures occurring in approximately 30% of these patients through an analysis of 69 published cases in the literature. Furthermore, a higher proportion of delusions (95%) was detected among non-seizure patients in comparison to seizure patients (63%) [11,27,33].

The relationship between Temporal Lobe Epilepsy (TLE) and psychosis

Clinical practice and animal experimentation studies have indicated that temporal lobe epilepsy and psychotic disorders may share a common substrate in the hippocampal dysregulation of the dopaminergic system. It is theorized that this phenomenon is driven by the loss of parvalbumin-containing interneurons resulting into the constant hippocampal hyperactivity of the mesolimbic dopaminergic pathway, which renders the system is hyper-responsive to all stimuli even if normally they are unremarkable. Consequently, the individual feels ceaselessly alert to all stimuli which are constantly perceived as threatening without being able to use the distinctive ability to ignore irrelevant events selectively, thus leading to the over-interpretation of benign events and in turn triggering the psychotic symptomatology [34-44]. Furthermore, structural neuroimaging studies comparing the cerebrum of TLE patients with and without psychotic symptomatology disclosed findings of disrupted connectivity in the contralateral hemisphere among positive for psychosis TLE patients, while network metrics were also indicative of an association between the occurrence of psychosis, vulnerability and decreased efficiency in the whole cerebral network [45].

The relationship between Traumatic Brain Injury (TBI) and neurodegeneration

As above mentioned, Traumatic Brain Injury (TBI) is very important to address because apart from its debilitating acute effects, it can initiate long-term neurodegeneration processes leading to pathological alterations (lesions) with especially devastating consequences to cognition and behavior similar to Alzheimer's disease. Furthermore, not only do multiple pathological processes link TBI with neurodegeneration and dementia, but TBI is also considered a major risk factor for Alzheimer's disease. Pathological characteristics that are typically observed in Alzheimer's Disease (AD) have been also detected postmortem in histopathologic brain specimens of TBI (even young acute-phase) and Chronic Traumatic Encephalopathy (CTE) patients, involving increase in hyperphosphorylated tau (P-Tau), amyloid beta (Aβ) and TDP-43 deposits [46-48]. In addition, post-TBI epileptic activity and its consequences as previously reported are also associated, as Alzheimer's disease is a risk factor for epilepsy and psychotic symptoms, while, vice versa, many patients with epilepsy experience cognitive impairments and psychotic symptoms. The relationships between Alzheimer's disease, psychosis and epilepsy suggest an overlap among these nosological entities in the underlying pathophysiology with regard to common pathways in the cerebral structure and neural networks [27,8].

Major deficits as complications of Traumatic Brain Injury (TBI)

All TBIs cause serious effects related to the rehabilitation, functionality and social reintegration of the individual. The person with craniocerebral trauma is expected to develop various cognitive,

psychosocial deficits, as well as speech disorders occurring in different forms and depending on the extent of the damage, the localization of the damage, as well as other idiosyncratic factors. TBI can therefore have a detrimental impact on many areas of the patient's living and deficits may range from mild to very serious and improve or persist over the years and even remain unchanged throughout a person's life [49]. The major deficits that can be identified in a TBI patient are discussed below [5].

Cognitive deficits

Orientation: Orientation relates to one's awareness of four main axes: self, space, time, and situations. People who have undergone TBIs often experience disorientation over time and space. Orientation requires a person's ability to receive, store and retrieve new information occurring after injury. During the recovery of a TBI patient, memory recall of situations precedes the recall of space and time. Time is constantly changing, so information needs to be constantly updated, assuming an increased level of consciousness and awareness [50].

Attention deficits: Attention deficits stand for the most frequent and common consequences of TBI. Attention is a multifaceted cognitive function, which includes alertness, situational awareness, selective attention, sustained and divided attention. Alertness and awareness refer to the state of consciousness in various sensory stimuli and one's perception of the environment. The patient's degree of alertness is measured with Glasgow Coma Score (GCS). Selective (or focused) attention generally refers to one's ability to focus on one among many simultaneous stimuli, as well as the ability to resist distraction. Selective attention is considered to be controlled and directed by connections between the thalamus and the prefrontal cortex. Sustained attention pertains to one's ability to maintain and focus their attention on a stimulus for a long period of time. Divided attention refers to the distribution of limited resources across multiple trials or processes [50]. Consequently, delayed cognitive processing is present in the attention deficits that occur in post-TBI patients, including poor concentration, distraction, and difficulty in multitasking [51]. When the attention problems are severe, the patient may complain of confusion, inability to think clearly, and disorientation.

Memory: Memory deficits, in both short term memory and long-term memory, as well as in Post-Traumatic Amnesia (PTA), are very common in post-TBI patients, but rarely constitute a typical amnesia syndrome. Memory difficulties can be the result of many different factors, rather than the result of a single deficit. According to the reduced hippocampal and white matter volume in post-TBI patients may relate to memory deficits [50]. Consequently, individuals having undergone traumatic brain injuries may experience difficulties not only in short term memory (working memory), which is responsible for the temporary learning of new information, but also in long term memory, which is involved in the recovery and activation of old stored information.

Reaction Time (RT) to stimuli: Slow reaction time and psychomotor retardation is a key component of the clinical picture regarding patients having suffered TBI. According to Brookshire these patients need more time to think before giving an answer [50]. Particularly in cases where the damage is diffuse, the mental speed, memory and attention as well as the general cognitive performance of the patient are greatly impaired [53,52].

Executive functions: Executive functions comprise a superior brain function that contributes to completing steps to achieve a goal. The wide range of these functions include: inductive and productive reasoning, flexible thinking, task initiation and structuration (organization), planning and prioritizing, problem-solving and strategy-switching, goal-setting, inhibition (impulse control) and emotional control, self-monitoring as well as perseverance in the trial [50,54]. In cases of diffuse brain injury, patients tend to have poor performance in logic problems that need to be mentally solved [55,56]. According to Marshall and Weinstein the impact of the cognitive and executive impairment mentioned above can significantly impede communication [57].

Anosognosia: Post-TBI patients often experience a deficit of self-awareness; they are unaware of their condition or the deficits that they experience, which is referred to as anosognosia. (Mc Glynn and Schacter, 1989)[58] According to research studies, nearly 40% of post-TBI patients experience anosoagnosia, which is a major obstacle to their progress and recovery.

Speech disorders: Except for cognitive deficits, patients who have suffered craniocerebral injuries may often present with speech disorders and speech impediments as well. The most common deficits observed in speech are the following: (a.) disorganized and confused speech, both in oral and written language, with many inaccuracies, repetitions and revisions; (b.) difficulty finding the right words (anomia) and misnaming; (c.) difficulty in listening comprehension; (d.) poor speech with short phrases and limited content; (e.) semantic difficulty (vocabulary), reduced ability to use grammar and syntax correctly (morphosyntactic errors), at the level of both oral and written language; (f.) aphasic syndrome, provided that corresponding focal lesions are present, and especially in cases of severe TBI [51].

Pragmatics and communication: Communication defines the exchange of information and messages between interlocutors (transmitter - recipient). In specific, communication involves the transmission of a message from the transmitter's mind to the recipient's mind. Throughout literature, the "message" is also referred to also as "communicative intention" [59]. Communication can be either verbal or non-verbal (use of gestures and nods). The following communication deficits, however, may occur among post-TBI patients: (a.) difficulty in following a quick conversation; (b.) difficulty in following a conversation in situations where the environment is not quiet and may distract the patient's attention; (c.) limited initiative/reluctance to initiate and continue a conversation; (d.) difficulty in understanding and interpreting non-literal ideas (metaphors); (e.) difficulty in understanding abstract concepts, sarcasm, oblique speech and indirect demands; (f.) socially inappropriate use of language and disinhibition; (g.) difficulty in identifying suitable communication environments and adjusting the speech according to the context of communication; (h.) difficulty in proper inference in all contexts [60]. Therefore, communication may be impeded due to lack of sensible content, lack of sensitivity to the needs and interests of other interlocutors, excessive or meager information on the part of the patient and distorted pragmatics.

Behavioral changes: Behavioral changes following TBI are very common and affect not only the patient himself but also his family members, friends, and social entourage. Conduct disorders range from irritability to disinhibition, behavioral disorganization and physical aggression. The most common problems encountered in such patients may be irritability, aggressive behavior, reduced anger management, impulsivity, lack of self-restraint, decreased social

adaptability, disturbed social perception, affective disorders and anxiety. Depression is a result of the persistent symptomatology that the patient is confronted with. Prevalence estimates for depression are approximately at 35% [61]. Fatigue, anxiety, alteration in the patient's premorbid condition and irritability tend to aggravate and intensify depression, resulting in a vicious cycle that often delays the recovery of the patient to a significant extent. In numerous cases, post-TBI patients try to deal with impairment through negation eventually leading to social withdrawal [62]. Personality changes and behavioral disorders including physical violence in post-TBI patients are more often associated with limited coping skills as well as internal conflicts and frustration arising from the difficulty in processing emotions of bereavement and loss, long-term disability and tension with respect to their relationship with caregivers and significant others coupled with the physical disability itself [5,64,63].

Managing post-TBI patients: Neuroimaging in post-TBI patients can be utilized to detect and visualize ischemia, hemorrhage, encephalomalacia, neuronal loss, and altered cerebral metabolism or perfusion in order to identify the residual effects, approximate prognosis and guide rehabilitation. Strategies for managing post-TBI patients include pharmacotherapy as well as evaluation of neuropsychology, speech and occupational therapy, and development of interdisciplinary team-based rehabilitation strategies, for each patient individually, targeting at functional recovery and reduction of residual symptoms [5].

Preventive treatment with phenytoin for one week is recommended by guidelines for the prevention of Post-Traumatic Seizures (PTS). In addition, levetiracetam is being used more and more for the same purpose and for more extended administration due to a milder side-effect profile [65].

Conclusion

The present study aimed at identifying potential patterns associated with neuropsychiatric manifestations following TBI. A systematic review on the neuropsychiatric complications of traumatic brain injury was conducted by examining bibliographic case reports juxtaposed to a comparison group of random psychiatry inpatients, international bibliographic data and findings of previous studies and analyzed by SPSS. Risk factors for developing PDFTBI were the time within the first year and the time following 5 years post-TBI as well as the male gender. Furthermore, PDFTBI was found to be associated with lesions to the frontal and temporal areas of the brain. The incidence of misidentification syndromes and epilepsy was significantly higher and a differentiation in the type of expressed physical violence was also disclosed compared to other (non-TBI) psychotic disorders. In addition, there was a positive correlation with cognitive impairments and especially deficits in memory and executive functions. In PDFTBI negative symptoms of schizophrenia were less pronounced in contrast to positive symptoms and this has been also observed to apply to psychosis of epilepsy, thus, differentiating these psychoses from other types of psychotic disorders and schizophrenia. The understanding of the underlying mechanisms and molecular cascades behind these neuropsychiatric complications might disclose in which way certain networks and circuits are involved in the manifestation of psychosis [27,8]. Biofluid biomarker studies, coupled with neuroimaging tools in post-TBI longitudinal designs, offer a promising framework to elucidate the latter. In addition, longitudinal study designs in patients integrating neuroimaging data (PET, MRI, CBF, VR-CO2) with biofluid biomarkers (including Aβ, tau, NFL and CVD-associated molecules) are expected to elucidate the contribution of TBI-induced impairment of neurovascular function to neurodegeneration and pathology resembling Alzheimer's disease [8].

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