PSYCHIATRIC ASPECTS OF POST-TRAUMATIC EPILEPSY: A STILL UNEXPLORED AREA

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Abstract

Traumatic brain injury (TBI) represents one of the most common causes of death and disability in young people and post-traumatic epilepsy (PTE) accounts for 10% to 20% of all symptomatic epilepsies. However, PTE is still a relatively underappreciated condition. This paper is aimed at reviewing current knowledge about psychiatric comorbidities of PTE, looking in particular at the nature of the relationship between traumatic brain injury, psychiatric problems and epilepsy, at the phenomenology of psychiatric disorders in PTE and how to manage them. Data on psychiatric comorbidities of PTE are almost non-existing and this is a paradox considering that TBI itself is burdened by a number of cognitive and psychiatric sequalae which can profoundly affect the everyday life of these patients. Preliminary data seem to suggest that the bidirectional relationship between epilepsy and psychiatric disorders is maintained in TBI and people with a psychiatric condition at the time of the TBI, or as a consequence of it, are at increased risk of developing PTE and vice versa. However, a number of questions are still unanswered concerning the genetic and environmental contributors, the phenomenology of psychiatric disorders in PTE and how to prevent and address them properly. Further research in this area is urgently needed in order to provide the best possible care to people with PTE.

Key words: traumatic brain injury, post-traumatic epilepsy, depression, agitation, antidepressants, antiepileptic drugs

1. Introduction

Psychiatric disorders represent a frequent comorbidity in epilepsy with a lifetime history identified in one every three patients [1]. During the last 10 years, research in this area has progressed with good epidemiological studies as well as new data on the role of psychiatric comorbidities on the long-term prognosis of the epilepsy [2]. In fact, it is now established that patients with epilepsy and psychiatric disorders do not only have low quality of life but they are also less likely to be seizure free[3][4] and they present with increased morbidity and mortality[5].

Despite post-traumatic epilepsy (PTE) accounts for 10% to 20% of symptomatic epilepsies and 5% of all epilepsies [6], it is still an unappreciated condition. This is probably due to the lack of evidence for the effectiveness of drug treatments for the prevention of seizures in people with traumatic brain injury (TBI) [7,8]. TBI is one of the most frequent causes of disability among young adults, with devastating neurological, cognitive and psychiatric consequences. Epidemiological studies report 1.4 million cases each year in the United States [9] with a total of 5.3 million people suffering from long-term disabilities due to a TBI and total annual costs are in the region of 56 billion dollars [10].

It is well-known that TBI is associated with a number of psychiatric disorders and behavioural changes. The famous case of Phineas Gage (**Fig. 1**), a construction worker who, in 1848, survived a severe frontal lobe damage, is probably the first detailed description of the behavioural consequences of TBI [11]. Phineas Gage developed PTE 12 years later with his first seizure in February 1860. His physical and mental state significantly deteriorated after that as "he continued to work in various places but he could not do much" [12]. On the 20th May 1860, he suffered a cluster of seizures and he then developed status epilepticus and died on the subsequent day.

Despite interest of the scientific community on the case of Phineas Gage, a systematic approach to psychiatric problems in TBI comes later on with Adolf Meyer and the concept of "traumatic insanities" [13]. Nowadays, it is established that people with TBI can develop a variety of psychiatric problems including mania, depression, aggressive behaviour, dyscontrol disorders, psychosis, obsessive compulsive behaviour, post-traumatic stress disorder, apathy [14]. The prevalence of these conditions varies according to epidemiological studies and this is probably linked to the site of the injury, the severity of the TBI, the presence and severity of concomitant cognitive problems and associated comorbidity [15].

Given that both epilepsy and TBI are strongly associated psychiatric problems, it is obvious to hypothesize that psychiatric disorders should represent an important comorbidity in people with PTE. Nonetheless, research in this area is almost non-existing. This paper is aimed at reviewing current knowledge about psychiatric comorbidities of PTE, emphasising gaps in the literature and rise important clinical questions which urgently need clarification. This paper will focus specifically on the nature of the relationship between traumatic brain injury, psychiatric problems and epilepsy, the phenomenology of psychiatric problems in PTE and how to manage them.

2. Search strategy and selection criteria

Articles were identified through searches in PubMed and Embase up to 31st July 2019 using the search terms "post-traumatic epilepsy", "psychiatric disorders", "depression", "anxiety", "psychosis", "seizure", "epilepsy" and "convulsion". No language restrictions were applied. This search generated 388 abstracts. Articles were selected based on originality and relevance to the present topic. Additional articles were identified from the author's own files and from chosen bibliographies.

3. What's the relationship between traumatic brain injury, psychiatric disorders and epilepsy?

The relationship between epilepsy and psychiatric disorders is complex and multifactorial in origin with biological and psychosocial variables implicated. It is now established that many psychiatric conditions, including mood and anxiety disorders or psychoses, have a bidirectional relationship with epilepsy [16], meaning that these conditions are per se associated with an increased risk of seizures and this is due to the involvement of shared brain networks and shared biological mechanisms [17]. But what happens when a third variable strictly linked with the previous two is introduced? In this triangle, many questions can arise in particular: i) Are people with psychiatric disorders, either at the time of the TBI or as a consequence of it, at increased risk of developing PTE?; ii) Are people with PTE at increased risk of developing psychiatric problems as opposed to people with TBI without epilepsy? iii) Are people with PTE at increased risk of developing psychiatric disorders as compared to patients with other epilepsy syndromes?

Regarding psychiatric disorders as an additional risk factors for the development of PTE after a TBI, data from the South Carolina TBI registry showed that a previous history of depression was associated with a 1.85 increased risk of developing PTE at 3 years after a TBI [18]. A cohort Danish study involving more than 200,000 subjects showed that people on SSRIs at the time of the TBI were 5.6 times more likely to develop epilepsy than those who were not on SSRIs [19]. Given that previous studies have shown that SSRIs per se are not associated with an increased risk of seizures [20], it is possible to speculate that to be on SSRI is likely to represent an indicator of a depressive or anxiety disorder severe enough to require pharmacological treatment. These data taken together suggest that the presence of a psychiatric disorder, at the time of the TBI or as a consequence of it, is associated with an increased risk of developing PTE.

Regarding the second question, namely whether people with PTE are more likely to develop psychiatric disorders as compared to people with TBI without epilepsy, a prospective case series of 143 subjects with TBI admitted to a Rehabilitation Unit in Italy, reported psychiatric problems in around 50% of patients who developed PTE against 30% of those who did not [21]. A secondary analysis of a prospective, longitudinal study of moderate to

severe TBI involving almost 2,000 subjects showed a 3.34 increased risk of anxiety symptoms, measured with the GAD-7, at 2 years from the TBI in people with PTE as compared to those who did not develop epilepsy [22]. These preliminary observations clearly suggest that the development of epilepsy seems to be associated with an increased risk of psychiatric problems in people with TBI. However, a number of factors have to be considered. Obviously, the severity of the TBI is an important clinical determinant for PTE [23]. A population-based clinical study from Minnesota showed a five-year cumulative probability of unprovoked seizures of 0.7% in patients with mild TBI, 1.2% for moderate TBI, and 10.0% for severe TBI [24]. Someone could argue that patients with PTE are at increased risk of psychiatric disorders as compared to people with TBI without epilepsy just as a consequence of a more severe TBI. However, this is not necessarily true as psychiatric sequelae of TBI seem to be more evident in people with mild to moderate TBI as compared to those with severe TBI [25]. It is, therefore, tempting to speculate that there may be a genuine "epilepsy-effect" which increases the risk of psychiatric complications in people with TBI. In this context, studies are urgently needed in order to clarify whether the site and laterality of the TBI play a role, whether patients with PTE and psychiatric problems present with limbic damage as a consequence of the TBI, and whether there are genetic predisposing factors. In fact, genetic association studies are now suggesting that there are certain genetic variants which may increase the risk of developing PTE after a TBI [26]. It is, therefore, tempting to speculate that genetic variants linked to the development of PTE may also predispose to the development of psychiatric disorders.

Regarding the prevalence of psychiatric disorders in PTE as compared to other epileptic syndromes, no studies have specifically investigated this point and robust epidemiological studies in PTE are non-existing. Data from small cases series seem to suggest prevalence rates up to 50% which would make PTE similar to drug-resistant temporal lobe epilepsy. Studies addressing this point are needed.

4. Is the phenomenology of psychiatric problems in PTE similar to that of patients with epilepsy due to other causes?

The phenomenology of psychiatric disorders in epilepsy has always been matter of intense debate. It is established that some patients develop pattern of symptoms which do not necessarily follow international classificatory systems [27]. Historically, the site and laterality of the epileptic dysfunction were considered relevant for the phenomenology of psychiatric problems rather than the aetiology of the epilepsy itself but no studies have specifically investigated this point.

In the context of TBI, a number of factors have to be considered, including the severity of the TBI, the site of the brain lesion and the presence of cognitive problems affecting major domains such as memory, attention, language and executive functions. All these factors can profoundly affect the phenomenology of any psychiatric condition. In PTE, this is further complicated by the potential effect of antiepileptic drugs and the epileptic activity on

cognitive functions. For all these reasons, the diagnosis and management of psychiatric disorders in PTE can be even more challenging than in other epilepsy syndromes and the lack of data on this subject is quite astonishing.

In terms of basic science studies, only one study investigated the role of epilepsy on behavioural patterns in animal models of TBI [28]. This study showed that rats who developed epilepsy were not different from those who did not, in terms of anxiety-like behaviour in the open field test and depressive–like behaviour in the forced swimming test [28].

Data from a case series of 143 subjects with TBI admitted to a specialist Rehabilitation Unit in Italy, showed that patients who developed PTE were more likely to develop personality changes, like disinhibited and aggressive behaviour, as compared to those who did not [21]. This study has the advantage of a detailed neuropsychological assessment and the authors showed that patients with personality changes did not differ from those without in terms of psychometric testing, suggesting that the personality changes could be linked to the development of the epilepsy itself rather than underlying cognitive problems [21]. This study also showed that the disinhibited behaviour, agitation and irritability correlated with a left-anterior temporal hypoperfusion at SPECT, further confirming the potential role of the epilepsy.

Dyscontrol and impulsivity are relatively common sequelae of TBI and present substantial challenges to recovery and functioning [29]. In epilepsy, dyscontrol has been investigated by a number of authors [30–33]. Early studies reported prevalence rates for aggressive behaviour in unselected samples of patients with epilepsy ranging between 4.3% [34] and 7% [35]. More recently, a multicentre study using an ad-hoc questionnaire, showed that patients with epilepsy have slightly less aggressive responses as compared to the general population [36]. However, when the authors looked at aggressive behaviour in patients with and without comorbid psychiatric disorders, the latter group presented significantly more aggressive behaviour. However, none of these studies specifically investigated the aetiology of the epilepsy and patients with PTE in particular.

In terms of neuroimaging, only one study investigated neuroanatomical correlates of aggressive behaviour in temporal lobe epilepsy, showing reduction in neocortical grey matter in the frontal areas but no association with hippocampal pathology [33].

Further studies are needed in order to clarify whether aggressive behaviour and dyscontrol is specifically linked to PTE as compared to other epilepsy syndromes and whether patients with PTE are at increased risk as compared to those with TIB without epilepsy.

As far as depression is concerned, the strong relationship with epilepsy is very well known [37]. As already discussed in the previous section, epidemiological studies seem to suggest that the presence of depression at the time of the TBI, or as a consequence of it, is associated with an increased risk of developing epilepsy. In the TBI literature, depressive symptoms seem to be strictly related to the disruptions of specific cognitive networks [38]. However, there are no studies which specifically investigated the phenomenology of depression in PTE

as compared to that of people with TBI without epilepsy or other epilepsy syndromes. Further studies in this regard would be of great value especially concerning the differential diagnosis between depression and apathy which, in people with TBI, can be sometimes challenging. Apathy is, in fact, another common problem after TBI and it is thought to be related to a dysfunction of executive control of goal-oriented behaviour or the neural substrates of reward-based and emotional learning [39]. In epilepsy, a single study has investigated apathy in an unselected sample of patients as compared to age-gender matched controls and reported no difference [40]. However, data on PTE specifically are not available.

Psychogenic non-epileptic seizures (PNES) represent another frequent psychiatric problem in people with TBI [41]. A retrospective study from the Veterans Affairs Medical Center reported a 57% prevalence of PNES after TBI against a 35% of PTE [42]. TBI in this context is usually mild and a diagnosis of PTSD is strongly associated with the development of PNES [43]. However, there are no specific data about the comorbidity with PNES in patients with PTE. A recent meta-analysis on the prevalence of PNES in people with epilepsy showed a pooled prevalence of 12%, while the prevalence of epilepsy in those with PNES was 22% [44]. Given the strong association between TBI and PNES it is possible to speculate that the comorbidity between PTE and PNES could be substantial. However, it is important to point out that PNES seem to be more common in mild TBI while PTE is probably more common in moderate to severe TBI. Therefore, it may not be necessarily true that patients with PTE present a higher comorbidity with PNES than other epilepsy syndromes. This point needs urgent clarifications.

Psychoses and thought disorders are also strongly linked to both epilepsy and TBI. A number of studies are now pointing out that TBI may be a risk factor for the development of schizophrenia-like disorders and a meta-analysis showed that such a risk is increased by approximately 60% [45]. This seems particularly evident for mild TBI in predisposed individuals such as those with a family history of psychosis [46]. No studies have investigated the prevalence of psychosis in PTE and the potential role of PTE in the development of a thought disorder and this is astonishing considering the strong links between epilepsy and psychoses. A meta-analysis showed a pooled prevalence of 5.6% in unselected samples of patients with epilepsy increasing to 7% in temporal lobe epilepsy[47]. In the context of PTE, it would be also important to clarify the role of post-ictal psychoses and whether people with PTE progress more rapidly from a post-ictal psychoses to a chronic interictal psychosis than patients with other epilepsy syndromes.

5. Is the management of psychiatric disorders in PTE different from that of patients with psychiatric problems in the context of other epilepsy types?

In general terms, the evidence on the management of psychiatric disorders in epilepsy is quite limited. Therefore, it is generally accepted to follow standards of care for psychiatric disorders outside epilepsy, taking into account the specific needs of people with epilepsy such as the risk of interactions and the seizure risk. In the context of PTE, it seems reasonable to apply the same principles. However, it will be important to clarify whether treatment

strategies applied to people with TBI without epilepsy will be as effective in people with PTE.

In terms of psychopharmacological treatments, major drug classes include antidepressants, antipsychotics, psychostimulants and other drugs like beta-blockers or amantadine which are sometimes mentioned in the TBI literature [48].

Regarding antidepressants, data in epilepsy in general are still limited [49]. Current standard of care for depression in the context of a chronic health condition [50] recommends citalopram and sertraline as first-line agents. Available data suggest that this can be a reasonable option in people with epilepsy and depression [49] and it seems to be a reasonable option also in patients with PTE and depression. SSRIs are also considered first-line agents for anxiety disorders, when a pharmacological treatment is needed [51]. As mentioned for depression this seems to be a reasonable option also for patients with PTE.

Regarding the risk of seizures with antidepressants, an analysis of data from Phase II–III regulatory trials of antidepressants showed that seizure incidence was not different from that of placebo. The only exception was for clomipramine at high doses (>150 mg) which showed a standardised incidence ratio of 4 [20]. These findings have recently been confirmed in a systematic review [52].

In terms of interactions, antidepressants have a complex metabolism potentially leading to some interactions [53]. All enzyme-inducing antiepileptic drugs seem to reduce the levels of antidepressants by around a quarter. There is no evidence, however, that these changes are clinically relevant and dose adjustments in routine clinical practice are not needed [54]. The only exception is bupropion where the combined treatment with carbamazepine or other inducers can reduce the blood levels of the antidepressant by 90% [53]. Fluoxetine, fluvoxamine and, to a lesser extent, sertraline are inhibitors of CYP2C9 and may potentially increase the levels of phenytoin and, to a lesser extent, valproate [53,54].

As far as antipsychotics are concerned, international guidelines of treatment of first episode psychosis recommend risperidone, olanzapine and quetiapine as first line treatment [55]. These three drugs seem to be well tolerated in epilepsy. Risperidone in particular seems to be associated with the lower risk of seizure worsening and for this reason can be considered a valuable first line option in people with epilepsy [56]. Olanzapine and quetiapine also seem to carry some risk while all other antipsychotics show no difference from placebo [20]. Clozapine is the drug associated with the highest risk with a standardised incident ratio of 9.5 as compared to placebo [20]. The risk of seizures with clozapine is dose- and titration-dependent [54,57] although, in people with epilepsy, seizure aggravation has been reported even at low doses [58].

Atypical antipsychotics are often used in the management of psychiatric sequelae of TBI especially aggressive behaviour [48] but evidence for that is still lacking. A placebo-controlled, double-blind study of risperidone for the management of aggressive behaviour following TBI is currently running [59].

In terms of interactions, all enzyme-inducing drugs reduce antipsychotic levels but the interaction is particularly evident with quetiapine where the combined prescription with carbamazepine leads to undetectable levels even at a dose of 700 mg [54]. There is no evidence that antipsychotics affect the blood levels of epilepsy drugs.

Stimulants are another class of drugs potentially used in the context of TBI especially for attention and concentration problems [60]. A Swedish study involving more than 21,000 children with seizures, showed no evidence of increased risk of seizures from ADHD medications [61]. Preliminary findings in people with epilepsy also suggest that methylphenidate may be an effective and safe option for improving cognition and quality of life [62]. These data suggest that stimulants, methylphenidate in particular, can be safely used in the context of PTE but more studies are needed. Data on potential interactions of methylphenidate are limited to older compounds but there is no evidence of clinically relevant interactions.

Beta-blockers and drugs like amantadine are other drug classes potentially used in the context of TBI to control agitation [63,64]. There are no specific contraindications in the context of epilepsy.

6. Conclusions

PTE accounts for 10% to 20% of all symptomatic epilepsies but data on psychiatric comorbidities are still lacking. This is a paradox considering that TBI itself is burdened by a number of cognitive and psychiatric sequalae which profoundly affect the everyday life of these patients. Preliminary data seem to suggest that the bidirectional relationship between epilepsy and psychiatric disorders in maintained in TBI and people with a psychiatric disorder at the time of the TBI or as a consequence of it are at increased risk of developing PTE and vice versa. However, systematic studies are needed. In addition, several questions are still unanswered concerning the genetic and environmental contributors, the phenomenology of psychiatric disorders in PTE and how to prevent and address psychiatric problems properly.

This paper is part of a special issue celebrating the 20th Anniversary of Epilepsy & Behavior. Historically, Epilepsy & Behavior has played a major role in promoting advances in this area and this paper aimed to show further aspects of neuropsychiatry of epilepsy still unappreciated. I'm sure that this journal will continue to lead on this area contributing to a better quality of life and a better care for our patients.

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