Case Report

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Trauma & Acute Care

2016
Vol.1 No.3:24

Mild Traumatic Brain Injury and Posttraumatic Stress Disorder Responding to Vortioxetine Treatment: A Case Report

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Received date: October 20, 2016; **Accepted date:** November 8, 2016; **Published date:** November 20, 2016

Citation: Khouzam HR (2016) Mild Traumatic Brain Injury and Posttraumatic Stress Disorder Responding to Vortioxetine Treatment: A Case Report. Trauma and Acute Care 1: 24.

Abstract

Although sport-related concussion or mild traumatic brain injury are common, they are infrequently associated with posttraumatic stress disorder (PTSD). This report describes the case of a 17-year-old male high school football player who sustained a sport-related concussion complicated by the development of PTSD. The association between PTSD and mild traumatic brain injury is briefly reviewed. The diagnosis and resolution of his PTSD symptoms in response to the treatment with the antidepressant vortioxetine and its mechanism of action are summarized.

Keywords: Concussion; Post-concussive symptoms; PTSD; Athletes; Vortioxetine

Introduction

Mild traumatic brain injury (MTBI) or concussions are becoming common contact sports injuries and have emerged as major health care concerns in the United States and Worldwide [1–5]. The incidence of sports-related concussions is estimated to be 1.6 to 3.8 million annually [4-9]. The danger associated with premature return to play and emerging evidence of long-term consequences of MTBI has led to the institution of state and national legislations to regulate youth athletics [10]. These legislations also prompted youth athletics' administrators to propose new guidelines that expanded the use of emergency assessment with emphasis on neuropsychological testing, and requiring high school football coaches to attend courses on concussion management [11]. Despite these significant changes in the identification and management of concussions, in many instances MTBI can be difficult to recognize due in part to an absence of a unified and universal definition [12]. Research of high school football players has shown that even without clinically observed symptoms of concussion, blows to the head can lead to demonstrated measurable neurocognitive, physiological and psychological impairments [13]. Among the various scholastic sports, football has the highest MTBI concussion rate [14]. Furthermore, there is a lack of well-documented studies that delineate the differences between the cognitively and psychologically based symptoms resulting from MTBI versus the primary psychologically based symptoms that are a consequence of developing PTSD during and after the course of a concussion event [15]. There is also limited empiric prospective data to guide the different treatments for MTBI and its complications including PTSD [9,16]. Consequently the separation of the PTSD cognitively and psychologically based symptoms from the MTBI induced symptoms can be difficult and clinically challenging.

This case illustrates the difficulties in delineating MTBI concussion induced symptoms from PTSD based symptoms. The MTBI, cognitive difficulties which were attributed to the patient's concussion, were consistent with PTSD psychological symptoms which improved with vortioxetine treatment. Further research would be needed to confirm the effectiveness of vortioxetine in treating the cognitive and psychological symptoms related to PTSD in the context of a concussion event and MTBI.

Case Report

A.M. was 16 years old when he sustained head to head collision during one of his high school football team practice sessions. He had a brief episode of unconsciousness and was immediately evaluated through the local emergency room hospital where he undergone an uneventful medical evaluation including a normal head CT scan. A neuropsychological assessment was conducted and it showed a mild degree of deficits in attention, planning skills verbal and visual memory. He was diagnosed with concussion and MTBI. The players and the coach who witnessed the incident confirmed that prior to his brief episode of loss of consciousness, he was arguing with another player who reportedly threatened to beat him up on his way back home. A.M's last recollection before he lost consciousness is that he felt scared and worried that the threats of being beaten up were real. The player that made these threats was physically stronger and was known to be a bully. A.M. could not remember how he was hit, and began to

experience episodes of intense anxiety because he was not able to focus or complete his school works. He was always an A's student and never failed any subject. His constant complaints of increased difficulties with remembering in addition to getting angry and irritable alarmed his parents and they decided to seek a comprehensive medical and psychological evaluation of their son condition. His prior medical history was unremarkable and there were no prior or current use of alcohol, illicit drugs, caffeine or nicotine and no family history of psychiatric or medical conditions. Physical examination and routine laboratory tests were all normal. A.M. was not taking any prescribed or over the counter medications, any vitamins or food supplements. The neuropsychological evaluation established a link between the onset of his current symptoms and the day of his concussion thus confirming that he had MTBI. The executive functioning, attention, working memory, visual construction, verbal learning and memory were intact. In contrast psychomotor and processing speeds were impaired. The neuropsychologist determined that the mental abilities in the areas that are usually impaired as result of concussion such as attention, and working memory were not affected [9], and informed the parents that processing speed deficiencies which could occur after a head concussion, are not usually a complication of MTBI but they can be a manifestation of co-occurring psychiatric conditions such as depression, anxiety and PTSD [17-19].

A.M. did not report or show any symptoms of depression and his anxiety and worries were all linked to the fears of being beaten by the stronger player on his football team who threatened to harm him just prior to experiencing the concussion. On self-report measures of psychological functioning, A.M. endorsed symptoms of being directly hit in the head when his helmet collided with the other player helmet and that he keeps reliving this head collision over and over again. He reported experiencing intrusive thoughts, heightened startle reflex, nightmares, increased irritability and social detachment, as well as feelings of shame and guilt related to being scared to be beaten.

The parents were informed that their son symptoms suggest the possibility of PTSD and a suggestion was made for individual therapy to help him cope with the aftermath of his concussion and he agreed to do so.

While in therapy, A.M. experienced a lessening of his fears and was able to improve on his school performance however one day during a therapy session he began to uncontrollably sob and to hide his face between his hands while bending toward his knees. He reported that one night he was lying in bed when he experienced his initial intrusion. He reported that he pictured himself in the school football field and saw himself being thrown against the scoring board and then being constantly hit by the player who threatened him. A.M. described this scene in vivid details and reported that he was intensely distressed. He also related that this terrible scene would sometime come out of nowhere while he was sitting in the classroom. He continued to experience this intrusion several times a day for the past two months. After the onset of the intrusions, he reported increased fears and worries and he avoided going near the football field and that he asked his parents to be transferred to a school that does not have a football team.

The therapist called the parents because A.M. began to sob again, and the parents did confirm his desire to go to another school although he had many loyal close friends that would be devastated if he left the school. The parents also reported that he has stopped watching college and professional football games which was one of his favourite activities he shared with his dad and two older siblings. He also developed avoidance and startling reactions when topics and events related to football were mentioned around the dinner table and at time he would become angry and irritable. The therapist then informed A.M's parents that he most probably has developed PTSD not necessarily due to the MTBI concussion, but as a consequence of being threatened to be beaten by the other player. The therapist also emphasized that A.M. symptoms of diminished interest or participation in significant activities and his feelings of detachment from his friends, the startling responses, the avoidance, the angry behaviours and the irritability would require a trial of medications to which they reluctantly agreed.

A.M. older brother who was majoring in psychology adamantly and persistently persuaded his parents no to consider any of the medications that have been approved for PTSD treatment and belonged to the class of the selective serotonin reuptake inhibitors (SSRIs) because he was convinced that they will lead his brother to commit suicide. Despite the paediatrician efforts to clarify the relative safety of the SSRIs and their beneficial PTSD treatment effects, the parents refused to consent to that treatment option and a referral was made to a child and adolescent psychiatrist who subsequently spent a substantial amount of time explaining the potential beneficial and adverse effects of the various types of medications that have been used for the treatment of PTSD. The parents asked if they could conduct their own search of various medications and a week later and for no apparent reason they requested if A.M. could try the antidepressant vortioxetine which is marketed as Brintellix® or Trintellix®.

Although the antidepressant vortioxetine is considered a partial SSRI, and is not approved for PTSD treatment, A.M's parents and his older brother consented to its use. Before the initiation of vortioxetine treatment A.M. was administered the revised version of Impact of Event Scale (IES-R), which is illustrated in Table 1. He scored 49 with 27 on the Intrusion scale and 22 on the Avoidance scale [20,21]. These scores reflected significant levels of psychological trauma that are consistent with PTSD as being the primary contributor to the psychological and cognitive symptoms and disqualified his cognitive impairments from being the clinical manifestation presentation of MTBI [22,23].

Vortioxetine was initiated at the dose of 5 mg daily, for 2 weeks and then titrated to 10 mg daily. A.M. tolerated the medication without any reported or observed adverse effects. At 6 weeks' follow-up, an IES-R showed a total score of 4, with 2 points on the Intrusion scale and 2 points on the Avoidance scale, thus confirming a significant clinical improvement [20-23].

It has been 7 months since AM began vortioxetine treatment; he had concluded individual therapy sessions due to the remission of his cognitive and psychological difficulties. At this time he is getting ready to celebrate his 17th Birthday and although he has not resumed playing football. He attributed that to a shift in his interests in playing and not to fears of being hit by the player who threatened him when he experienced the head to head collision. He is has not experienced any recurrence of PTSD or MTBI symptoms. His parents are seriously considering the discontinuation of vortioxetine to which he is agreeable.

Table 1: The revised version of Impact of Event Scale (IES-R) and scores interpretation*

Impact of Event Scale - Revised Instructions: Below is a list of difficulties people sometimes have after stressful life events. Please read each item, and then indicate how distressing each difficulty has been for you during the past 7 days with respect to the disaster. How much have you been distressed or bothered by these difficulties?					
	Not at all	A little bit	Moderately	Quite a bit	Extremely
Any reminder brought back feelings about it	0	1	2	3	4
I had trouble staying asleep	0	1	2	3	4
Other things kept making me think about it	0	1	2	3	4
I felt irritable and angry	0	1	2	3	4
I avoided letting myself get upset when I thought about it or was reminded of it	0	1	2	3	4
I thought about it when I didn't mean to	0	1	2	3	4
I felt as if it hadn't happened or wasn't real	0	1	2	3	4
I stayed away from reminders of it.	0	1	2	3	4
Pictures about it popped into my mind.	0	1	2	3	4
I was jumpy and easily startled.	0	1	2	3	4
I tried not to think about it.	0	1	2	3	4
I was aware that I still had a lot of feelings about it, but I didn't deal with them	0	1	2	3	4
My feelings about it were kind of numb	0	1	2	3	4
I found myself acting or feeling like I was back at that time	0	1	2	3	4
I had trouble falling asleep.	0	1	2	3	4
I had waves of strong feelings about it	0	1	2	3	4
I tried to remove it from my memory.	0	1	2	3	4
I had trouble concentrating.	0	1	2	3	4
Reminders of it caused me to have physical reactions, such as sweating, trouble breathing, nausea, or a pounding heart	0	1	2	3	4
I had dreams about it.	0	1	2	3	4
I felt watchful and on-guard.	0	1	2	3	4
I tried not to talk about it.	0	1	2	3	4
*Scoring the IES-R Avoidance Subscale = mean of items 5, 7, 8, 11, 12, 13, 17 and 22 Intrusion Subscale = mean of items 1, 2, 3, 6, 9, 14, 16 and 20 Hyper arousal Subscale = mean of items 4, 10, 15, 18, 19 and 21 Total mean IES-R score = The sum of the means of the three subscale scores The maximum mean score on each of the three subscales is '4', therefore the maximum 'total mean' score is 12. Lower scores are better. A total IES-R score of 33 or over from a theoretical maximum of 88 signifies the likely presence of PTSD.					

Discussion

A proportion of patients experience persistent unspecific cognitive and psychological symptoms following a concussion. These symptoms although frequently reported after a concussion should not prompt clinicians to identify them as a manifestation of MTBI until they are ruled out as components of PTSD which was reclassified in the Fifth edition of the Diagnostic

and Statistical Manual of Mental Disorder (DSM-5)as being a trauma related condition with multiple cognitive and psychological symptoms [24]. The set of non-specific symptoms that could occur following a concussion and MTBI, that persist beyond the expected recovery period may include: irritability, emotional liability sleep disturbance, depression, anxiety and cognitive difficulties especially in tasks that require memory recalls, focused attention and concentration [25,26]. The lack of specificity associated with these constellations of symptoms increases the potential for misdiagnosis and may lead clinicians to attributing the presence of these symptoms to be solely a manifestation MTBI [25,26]. While it is often estimated that 10–20% of patients who sustain an MTBI will experience cognitive dysfunctions, an accurate estimate is difficult to achieve given the lack of specificity in the symptom constellation. Additionally, many individuals who sustain an MTBI or concussion experience a relatively full and uneventful recovery from their injury [22,25,26]. The overlap between the symptoms of MTBI and PTSD are summarized in Table 2.

The psychological, physiological and cognitive components that are associated with PTSD [27] make it a complex mental disorder with some clinicians using it as a diagnosis of exclusion rather than of inclusion especially in patients who sustained an MTBI [28].

Table 2: The overlap between the symptoms of MTBI and PTSD.

MTBI	PTSD
Insomnia	Insomnia
Memory Problems	Memory problems
Poor concentration	Poor concentration
Depression	Depression
Anxiety	Anxiety
Irritability	Irritability
Heahache	Re-experiencing
Dizziness	Avoidance
Fatigue	Emotional numbing
Noise/light intolerance	

In general it is intuitive to diagnose PTSD in individuals exposed to single or repeated extreme traumatic events found in war, terrorist attacks, natural or man-caused disasters, and by violent personal assaults and accidents rather than in athletes who experienced a concussion [29]. Concussions and MTBI can occur when the brain is violently rocked back and forth within the skull following a blow to the head or neck as in contact sports [23,29]. A.M.'s description of the head to head collision consisted of momentary loss of consciousness sometimes referred to as post-traumatic amnesia and subsequent cognitive difficulties. He did not report any PTSD symptoms initially but they became later evident during his individual therapy sessions. His medical evaluation confirmed the absence of any underlying physical illness that could contribute to his cognitive difficulties. In most MTBI patients, cognitive symptoms resolve within a relatively short period [30]. It became clear that the threats that he received from the other player significantly contributed to his decline in his school work. While it is certainly possible that the concussion contributed to A.M.'s cognitive dysfunctions, his presenting symptoms were most probably due to PTSD, rather than MTBI reported by many studies that were conducted in veterans who sustained MTBI [31-35]. A.M.'s scores on measures of cognitive and emotional functioning were obtained using the IES-R scale and the scores interpretations are summarized in Table 1[20]. The IES-R scale is a 22-item self-report measure that assesses subjective distress caused by traumatic events [20]. It is a revised version of the 15-item IES original version [21]. The IES-R contains seven additional items related to PTSD startling symptoms, which were not included in the original IES. Respondents are asked to identify a specific stressful life event and then indicate how much they were distressed or bothered during the past seven days by each "difficulty" listed. The Items are rated on a 5-point scale ranging from 0 ("not at all") to 4 ("extremely"). The IES-R yields a total score (ranging from 0 to 88) and subscale scores can also be calculated for the Intrusion, Avoidance, and Hyperarousal subscales [20,21]. In general, the IES-R (and IES) is not used to diagnosis PTSD, however, cut-off scores can be used to monitor patients' improvement and that how it was utilized in A.M's case.

In regard to the medications that are usually used for the treatment of PTSD, the SSRI's are the first line treatment with two agents of this class sertraline and paroxetine being FDA approved for PTSD treatment [36]. A.M's family refused all suggested SSRIs and chose instead vortioxetine an antidepressant which is only FDA approved for the treatment of depression [37]. Vortioxetine has a novel multimodal mechanism of action as an is not first line recommended for PTSD as well as a 5-HT1A full agonist and 5-HT3 receptor antagonist; it also has an inhibitory effect on 5-HT7 and 5-HT1D receptors and partial agonist of 5-HT1B receptors [38]. The downstream effect of this multimodal action is an increase in dopamine, norepinephrine, and acetylcholine activity in the prefrontal cortex [38] these downstream effects are thought to help restore some cognitive deficits associated with depression [39]. A.M. did not report symptoms of depression that could affect his cognitive functions; it is possible that vortioxetine multimodal unique effects could have contributed to the remission of his cognitive dysfunctions [39]. Although the option of using vortioxetine was based on the parents' request, the psychiatrist prescribing it off-label agreed to prescribed based on two main assumptions first it's very mild side effects profile [40] and second its SSRI activity which is beneficial for PTSD treatment. However clinicians reading this case report should be aware that it is not a first line recommended treatment for PTSD and that there have not been any researches or published reports confirming vortioxetine's effectiveness in PTSD to MTBI treatment. Vortioxetine adverse effects (AEs) include nausea, constipation, and vomiting, most commonly occurred in the first week of treatment, with a median duration of 2 weeks with nausea being the most commonly reported AE leading to discontinuation and it appeared to be dose dependent [40]. The recommended vortioxetine starting dosage is 10 mg, administered orally once daily without regard to meals. Dosage

should then be increased to 20 mg daily, as clinically warranted and tolerated [37]. A.M.'s tolerated and to responded well to the lower daily dose of 10 mg which could be attributed to his younger age [41]. As an antidepressants vortioxetine carries the standard black-box warning about the elevated risk of suicide in patients taking an antidepressant and is not approved for patients age <18 and Suicidal ideation was reported in 11.2% of patients taking vortioxetine, compared with 12.5% of those given placebo [42]. Fortunately this did not happen in this case, however clinicians should not interpret this positive outcome as a precedent to use vortioxetine in other young patients with PTSD or MTBI.

A.M.'s presentation suggested that the presence of cognitive symptoms identified as MTBI-related may be a manifestation of PTSD that coincided in its onset with the school football practice events [43]. The accurate diagnosis of PTSD prompted the therapist that was treating him to recommend medications. Although vortioxetine led to a remission of his cognitive and psychological dysfunction, such an outcome could not be generalized without the conduction of more research. It is hoped that this case will provide some insight into the risk associated with the development of concussions, MTBI, and PTSD due to football and other contact sports in young school age athletes.

Conclusion

Despite clinical studies and improved understanding of the medical and psychological risks associated with contact sports in the context of concussions and MTBI, prevention and treatment strategies for young age athletes is still lacking. This case study illustrated the common cognitive and psychological dysfunctions that are associated with MTBI and PTSD. The case also highlighted the importance of accurately diagnosing and treating PTSD in MTBI patients and the favourable prognosis that would result from the initiation of a prompt treatment.

However one case is not sufficient to generalize these findings without further rigorous research on the medical and psychological risks associated with brain injury related to football and other contact sports.

Acknowledgments

The author deeply thanks wife Lynn and children Andrea, Andrew and Adam, sisters Hoda and Hela, brother Hadi for their encouragement and sincerely appreciates Drs. Avak A.Howsepian, David P. Soskin, Oriana P. Vesga-Lopez, William C. Torrey, Alan I. Green and Heba Gad for their support.

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