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EC NEUROLOGY
Case Report

Toxic Stress and MTBI; An Explosive Combination

Erik J.T. Matser[1]*, Boon AE[2] and Mertens IMEL[3]

[1]*Practice for Clinical Neuropsychology, Helmond, The Netherlands*
[2]*Department of Neurology, St Anna Hospital Geldrop, The Netherlands*
[3]*Psychology Practice 'Dialoog', Weelde, Belgium*

***Corresponding Author**: Erik J.T. Matser, Practice for Clinical Neuropsychology, Helmond, The Netherlands.

Received: September 01, 2017; **Published:** October 07, 2017

Abstract

When treating patients with Mild Traumatic Brain Injury, neurologists often encounter discrepancies, in that complaint patterns do not correlate directly with medically established signs of brain damage or the lack thereof. For many of these patients, complaints are progressive, suggesting either an unlikely progressive damage to the brain, or a vicious circle. We hypothesize that 'toxic stress' may be one of the factors causing an increased symptom load and leads to persistence, increased severity, and often progression of the posttraumatic syndrome in those MTBI-cases, even in the context of theoretically minor structural brain damage. At the same time, this implies a good prognosis when managed adequately.

Keywords: *Toxic Stress; MTBI; Emotional*

Introduction

Traumatic brain injury can have longterm or lifelong physical, cognitive, behavioral and emotional consequences [1]. Even mild TBI, can cause long-term cognitive problems that affect a persons ability to perform daily activities and return to work [2-4].

In the 80's it became clearer that MTBI causes persistent complaints of the cognitive domains of attention/concentration/speed of information processing/planning and memory, the so-called frontal and temporal brain functions [5]. These patients also have limited energy and often experience changes in the emotional status. Countless examples can be found in sports and epidemiological research from the nineties to prove that performance in neuropsychological testing is inversely related to number of concussions incurred and blows tot he head [7]. Even sub-concussive blows can have the same debelitating effect as our research showed in the late eighties and nineties [6-8]. This research data was repeatedly reproduced by others such as the Einstein College in New York. Both research lines showed crippling lifelong consequences, resulting in the person/ athlete being pushed out of his social activities and his paid employment [9-11]. MTBI can therefore be placed high on the list of most debilitating injuries. As a direct result of this research from that period [8], changes were made to the rules of youth football forbidding heading in several countries. In the USA a billion dollar class action concussion injury settlement against the NFL has become final and effective on the 7th of January 2017.

Besides the persistent complaints, the number of people affected by MTBI is alarming. A huge amount of people is affected bij brain injury. In the United States alone, about 5.3 million Americans, approximately 2% of the population has suffered long-term or lifelong TBI-related complaints that have resulted in hospitalization. In the UK an estimated 1 million people attend hospital A&E each year following head injury. Of these around 135,000 people are admitted to hospital each year. Across the UK there are an estimated 500,000 people (aged 16 - 74) living with long term disabilities as a result of traumatic brain injury. Approximately 85% of traumatic brain injuries are classified as minor, 10% as moderate and 5% as severe. Around 1 in 3 injury-related deaths involve a TBI. Men are two to three times more likely to have a traumatic brain injury than women. This increases to five times more likely in the 15 - 29 age range. Similar statistics

apply to Europe. Life expectancy for brain injury survivors is normal, so over time, what may seem like a low volume problem becomes a high volume one [12]. In addition, the amount that remains untreated is unknown. The true number of persons living with TBI-related disability is likely to be much higher. To compare: the percentage of injury-related productivity loss attributed to MTBI is 14 times greater than that associated with spinal cord injury. We are being presented with an immense problem and a crucial issue, a silent epidemic [13].

MTBI and risk factors for persistance and accumulation of complaints

Diminished cognitive reserve

Even when two individuals have an equal volume of damaged brain tissue, the symptoms of the brain injury may differ entirely. The first person will still function normally, whilst the second shows signs of brain injury. Therefore there is no synchronous relationship between the actual injury to the brain after acquired brain impairment and the symptoms a person displays. In other words there are inherent differences in the vulnerability to the effects of aging or brain lesions and perhaps also in their capacity to adapt or compensate for such processes [14]. Within the context of brain injury, we use the term cognitive reserve to describe the ability of our brain to compensate and apply strategies in order to retain normal function. Having a certain amount of cognitive reserve points to the amount of resilience one possesses in the wake of brain injury.

Cognitive reserve is linked to level of educational attainment, intellectuality, occupation and reading skills. It should be noted, that it is cognitive reserve that keeps the brain in good condition, but when a certain threshold is crossed, the brain loses all ability to compensate. Up until this point, normal function has been sustained as long as was possible [15-17]. This is often the case with those engaging in combat sports. After several knockouts, they present with mild but persistent complaints. After a subsequent knockout, they quickly develop a progressive onset of dementia (dementia pugilistica). It seems that the cognitive reserve is then completely drained.

Visual disturbances

The nature of the visual complaints which occur, is as we know, largely dependent on the location of the injury in the brain. Visual tasks require a vast neuronal network, which is spread throughout the brain. Visual symptoms occur in many patients, the most common of which are accommodative disorders, convergence insufficiency and saccadic dysfunction. Posttraumatic disturbed saccadic eye movements may imply cortical and subcortical deficits and are asscociated with more complaints. Even at 30 days postinjury and despite being clinically asymptomatic, advanced techniques are able to detect subtle lingering alterations in the concussed brain [18]. Therefore, progressive neuroimaging techniques such as fMRI in conjunction with assessment of oculomotor performance may be beneficial in clinical management of concussion. Visual symptoms often remain unnoticed or inadequately diagnosed and impair function of MTBI patients significantly [19,20].

Inflammation

There has been a significant amount of research done on the role of inflammation in perpetuating the secondary injury response following traumatic brain injury (TBI) over the past two decades. This is clearly an important contribution to exacerbation of neuronal injury. The neuroinflammatory response following traumatic brain injury (TBI) is known to be a key secondary injury factor that can drive ongoing neuronal injury [21]. Data present striking evidence of persistent inflammation and ongoing white matter degeneration for many years after just a single traumatic brain injury in humans [22]. Repetitive head trauma may also cause inflammatory lesions with p-tau accumulation, neurotoxicity, and progressive neurodegeneration. However, the association of p-tau and concussion is still to be determined [23].

Apoe4 genotype

Risk factors for chronic neurobehavioral impairment include concussion exposure and/or multiple concussions and APOE e4 genotype [24]. Meta-analysis research from 2008 indicates that the presence of the APOE4 allele is not associated with the initial severity of brain injury following TBI but is associated with increased risk of poor long-term outcome at 6 months after injury [25].

Concussion history

Studies of repetitive head impacts (sometimes called "subconcussive" impacts) suggest that there are changes in brain white matter following repetitive head impacts. The most commonly observed neurocognitive impairments have been in the areas of memory and processing speed. Symptom load (i.e. the number and severity of concussion symptoms) has been found to be increased in athletes with a history of two or more concussions. Athletes with a history of concussion may have more severe subsequent concussions and may take longer to recover. The number of concussions an individual has sustained and the time interval between concussions may be an important factor in the risk for and the severity of subsequent concussions and symptom load. There is also evidence of a positive association between the number of concussions an individual has sustained and risk for depression [26].

In summary: risk factors for repeat concussion injury include history of multiple concussions. Particularly within 10 days after initial concussion there is a risk for post concussion impairments [1,2].

New diagnostic techniques

New diagnostic techniques give us an increasingly clearer picture of the changes which take place in the brain after the acquired brain injury. To highlight, there are some developments currently surrounding diffusion tensor imaging, highly sensitive to the detection of white matter lesions that correlate with depression and behavioral disturbances [3].

Diffusion tensor imaging (DTI) is a method of assessing axonal integrity in vivo and reduced n-acetyl aspartate – (N-acetyl-aspartate (NAA)) measured by proton nuclear magnetic resonance spectroscopy (1H-NMR) has been used as a marker of neuronal injury in many cerebral pathologies) - on MR-spectroscopy, Ct-perfusion, MR-perfusion and SPECT-defects as a measure of reduced blood-flow [4].

Summary

Many of the above mentioned issues may cause persistence. However none seem a clear and significant marker and there are great inherent differences between clients. These all seem to contribute towards explaining of some of the complaints after MTBI, but do not offer an explanation for the strong causal relation with persistence of physical, functional, mental and emotional complaints. Therefore, it may be the case that perhaps other regions, disturbed functions, or non-neurological factors are more relevant to duration and severity of posttraumatic dysfunction and likelihood of complete recovery. Based on our clinical experience there appears to be a non-neurological explanation for persistence which applies to a certain category of MTBI patients: the combination of MTBI and Toxic Stress.

Brain architecture; building a house

Inadequate responders in the living environment of a young child (e.g. physical violence, neglect, but also parents who, due to circumstances beyond their control, are insufficiently emotionally available) strongly inhibits the content of the information flow between the amygdala/hippocampus and prefrontal cortex. A young brain needs a good quality interaction with his environment to fully develop the brain architecture [27,28]. Poverty of the stimulus environment, creates a weak foundation on which the structure is to be built and which is needed for optimal development of the brain tissue. This structure is needed for optimization of learning and adequate handling of emotions. Issues often observed in our treatment cohort are emotional instability, internal unrest, hyperarousal, distorted self-perception and distorted perception of others. In all these situations a great number of our clients have inner alarm bells ringing most of the time. This state of chronic stress also affects increase in experienced pain, increased chance of fear related disorders, depression and the resilience of the immune system.

Toxic Stress

It is difficult to find a neurological explanation for the development of increased symptom load and persistence of complaints after MTBI. Could toxic stress offer the long-awaited explanation for this specific category of MTBI patients, whether with or without neurological symptoms? Many specialists will take notes of the medical history without taking any deep interest in the developmental history

of the person. Pediatrician Nadine Burke Harris opened the eyes of many of her colleagues in Neuroscience in 2015 during a TedMed Talk on the importance of mapping developmental processes which are of vital importance to the development of the brain, in a cognitive as well as an emotional sense [29,30]. It seems that there is a relation between healthy cognitive and emotional development and the level of stress experienced during early childhood. Harvard Medical School compares the proces within cognitive and emotional development to building a house where one first has to build a foundation before building any further [31]. Dr. Nadine Burke Harris proved during her lecture that extreme stress causes moderate to bad development in some parts of the brain. This has negative repercussions for later development in cognitive and emotional sense, a process also known as toxic stress. Her claims are well substantiated by numerous studies.

Stress and cognition

Learning to cope with mild to moderate stress constitutes normal development in children. However when faced with extreme, long-lasting stress combined with the absence of supportive relationships to buffer the effects of a heightened stress response, damage and weakening of body and brain systems can occur. In turn, this can lead to diminished physical and mental health throughout a person's lifetime. Stress immediately increases cortisol levels which can affect certain brain structures such as the hippocampus. The hippocampus becomes one of the regions of the brain that is heavily affected by increased levels of cortisol and other glucocorticoids. In addition, children who have experienced extended periods of extreme stress have smaller brains and have much difficulty in cognitive tasks with the emphasis on memory [32-34]. Cortisol has a known detrimental effect on the cognitive functions such as memory, attention span and self-regulation.

Stress and emotional state

Persistent stress in young children causes the stress regulation mechanisms to deviate from normal coping mechanisms. This in turn results in inefficient stress regulation mechanisms. Children with chronic toxic stress, undergo long term hyperarousal of brain stem activity. This includes increase in heart rate, blood pressure, and arousal states. In addition, these children may experience a change in brain chemistry, leading to hyperactivity and anxiety, later becoming habitual. Overall functioning takes place in a continuous state of fear and cortisol levels are unable to revert to basal ranges after the situation has returned to normal, increasing the risk of various physical and mental illnesses at a later stage in life. It is therefore evident that chronic stress in a young child's life can create significant physical, emotional, psychological, social and behavioral changes [35-38].

These developments have proven to be an eyeopener in our group and, in turn has guided the focus of treatment processes for MTBI patients in general. Two aspects have proved to be essential in allowing for predictions concerning personal perception of the complaints, emotional instability and amount of energy: in-depth enquiry after the uniqueness of each person concerning cognitive and emotional status before the accident and the degree of subjection to toxic stress during early childhood.

The goal of treatment of those suffering from MTBI, is to give an explanation as to why they are suffering from these complaints, how the intensity of these complaints sometimes increase and sometimes decrease and what they themselves can do about it. We invite clients with persistent complaints to take part in intensive treatment programs away from their familiar surroundings. This gives us a comprehensive understanding of the cognitive/emotional development and the living/working environment of the patient. Through the years, it has become increasingly clear that most patients with persistent complaints after MTBI present with specific personality traits. It seems of great apparent significance to not only examine whether the patient experienced internal unrest and had an extreme need to be in control after the accident, but also whether the patient experienced this before. The need for control can be expressed by excessive worrying, being grossly unaware of personal physical limitations, extremely critical of ones own functioning, mentally preparing their conversations with others in great detail and continously scanning the social environment.

Perfectionism

The above mentioned aspects are defined as perfectionism. Scientific literature describes perfectionism as a trauma-induced disorder in which achievement of personally demanding and high standards is pursued whilst performing qualitative activities. This causes vulner-

ability because it is almost impossible to meet the high standards that are set. When they are met, the standards are re-evaluated as being insufficiently demanding. This vulnerablility can lead to social isolation, depression and chronic stress. One has to be vigilant constantly. Perfectionism is rooted in early childhood and is a personality trait that develops when children are insufficiently able to learn how to deal adequately with negative emotions. This may be caused by an environment that places great value on achievement, by emotional neglect or physical violence wherein the child reacts bij overachievement in search of approval. Their self-image is thereby built up based on what they achieve, not on who they are. The focus is turned on achievement instead of on the individual. Perfectionism often finds its origin in toxic stress [39-41].

MTBI and Toxic stress; A bad combination!

Alertness, the need for control and perfectionism causes stress levels that are too high and non-adaptive. Body and mind are constantly geared for action and are much less focussed on relaxation. The stress reaction occurs sooner and once reached, it takes longer to break down. After MTBI, this process is amplified. After MTBI, residual complaints cause restrictions which cause loss of control and erosion of self-image. When combined with a non-adaptive stress level, the result is a vicious circle which leads to more stress, more complaints, sub-optimal recovery which in turn leads to even more stress and more restrictions. This situation forces the person to try harder which then leads to physical/emotional/cognitive exhaustion. The vicious circle explains the persistance of the complaints. Perseverence of the activity, in spite of persisting complaints, explains the increase of complaints due to cognitive and emotional exhaustion. Both are added on to the already existing MTBI residual complaints. Persistance and increase after MTBI is a complex process. Residual symptoms of MTBI and insufficient structure in the developmental history can cause a debilitating chain reaction.

Case Study

The client is a 56 year old woman. In primary school, she had no known reading or learning difficulties. There were no noteworthy problems with movement control, nor were there any signs of concentration difficulties and there was normal social interaction in accordance with the developmental milestones. The client describes nervousness, feeling tense and inner unrest since childhood. She grew up in a family in which she was forced to take responsibility for the care of her siblings from an early age. She was never appreciated, mainly criticised. “You are not worth it” is the message she heard from an early age. She doesn’t remember ever being offered any comfort or compliments. She reacted by trying even harder to do her best. At school she remained an outsider and didn’t have any real friends. There was no-one in her environment to whom she could turn for support. She left home at the age of 17. Her parents paid almost no attention to her leaving. Concerned for the welfare of the other children, she bought a cake in an effort to celebrate her departure and turn it into a special occasion. Years later, she continued to feel guilty for abandoning her siblings. On completion of high school and teachers college, she started her working life. She was set on staying in control all the time and worked with extreme precision. Getting to know new people causes her much tension. She struggles to stand up for herself when in contact with acquaintances. Her coping style is passive and she makes use of a variety of avoidance mechanisms. She is seldom calm and at peace.

In 2015 the client made a fall with her bicycle. She turned left, slipped on a frozen puddle and fell hard hitting the left side of her head on the tarmac. The client describes being unconscious for 5 minutes and experiencing a post-traumatic disorientation for approximately 15 minutes. There was also facial injury. The client was transported to the hospital and was kept 1 night for observation. The trauma surgeon diagnosed concussion. On returning home, the client called in sick and consulted her family doctor, who also diagnosed concussion. After the accident, the client spent much time resting. During the first few days, she experienced sensory over stimulation, sluggish speed of thinking and pace of work, was easily irritated, felt extreme fatique, had difficulty with reading and poor concentration. These complaints continued and after six weeks the family doctor referred the client to the Neurologist, who diagnosed a post-concussion syndrome. No abnormalities were found during MRI-cerebrum, opthalmological and neurological examination. The client was then referred to the Ear Nose Throat Specialist. No problems with balance and equilibrium were found. The complaints persisted and after three months the Neurologist referred the client to an Occupational Therapist and a Clinical Neuropsychologist.

During the intake for Neuropsychological examination, the client indicates the following complaints: - pain sensations: regular headaches (pressure pains on temples and eyes); energy: quickly tired, feels unfit, slow recovery after exertion, trouble falling and staying asleep, wakes up feeling tired and needs much time to start up the day, needs an extra hour of bedrest in the afternoon to make it through the day; - thought processes: forgetfulness (amnesia), has difficulty executing multiple tasks at once, difficulty paying attention for any period of time and easily distracted/ over stimulated, a lower speed of thought, more difficulty verbalising her thoughts accurately; - emotional status: irritable more often, feelings of despair because she cannot do the things she would like to be able to do, frustrated by the lengthy duration, fears surrounding the theme: will I ever recover, continuously experiencing inner unrest.

After considering the specific cause and nature of the complaints, it was decided that a neuropsychological examination should be performed. The following pattern was observed: variable scores on memory tasks, mild concentration deficits, mild deficits in visual information processing. No deficits in planning, orientation, executive functions, expressive and receptive language functions, no apraxia. Testing showed very mild changes in cogntion. Significant high scores are recorded on taking the Perceived Stress Scale on symptomatic stress, anxiety and feeling extremely restricted in her social role. Testing of personality traits indicate the following characteristics: an aloof, withdrawn personality, reserved when in contact with new people, exacting, perfectionistic, extreme self-discipline, makes and checks a plan of action and subsequently carries it out to the letter, is guarded and focused on details. The client describes herself as a perfectionist. Her partner confirms this.

Diagnostic summary

The cause, duration and persistance of the complaints point towards a post-concussion syndrome. The current cognitive complaints presented by client fit within this framework. This must be added on to the background of a perfectionistic personality, high anxiety perception and continuous, unrelenting high stress levels. The latter is a symptom of toxic stress caused by the emotional neglect during her early childhood and teenage years. The client is unable to execute tasks as well as she would like due to the residual complaints. This results in significant high scores on anxiety and stress perception. These scores were already highly elevated during the course of her life. The client puts emphasis on what she can achieve, not on who she is. When we combine this with the residual complaints limiting her, the result is a clinically increased stress perception which greatly impacts her function.

Treatment

Initial treatment was aimed at helping the client to understand the residual complaints after traumatic brain injury and how to cope. The aim was to prevent overstimulation and exhaustion as well as to give the body sufficient rest to start recovery. This was combined with medical fitness with emphasis on relaxation exercises, yoga and mindfulness training. After several weeks, therapeutic sessions were started to shed light on the development during early childhood and how this caused the development of perfectionism together with the incessant internal unrest. She also gained understanding of how this in turn causes the unceasing tension she experiences.

By making use of these above mentioned methods, the client was given insight into the development of her self image and coping. We emphasized and worked with her to clear the issues surrounding her individual response to stressors to minimize vulnerability and to strengthen resiliency. During the course of the sessions, the client slowly adjusted her self-image and was able to think of herself as a person with inner strength and who, in spite of all her negative experiences, still had turned into a caring individual, regarded by others as friendly and kind. In the course of treatment, the worrying diminished significantly and the client was more at peace. Her coping has also improved: she now positively engages with others, more often than before. She is setting clearer boundaries for others but is kinder towards herself. Her concentration is improving. Slowly she is starting to experience the negative relation between the increase in anxiety and the surge in complaints.

Discussion

Another approach is being called for to treat the consequences of MTB. In view of the enormous number of people with persistant complaints and increased symptom load which often develop in the wake of MTBI, toxic stress appears to play a crucial role in the ability

to cope and greatly affects the prognosis for recovery. When during treatment of MTBI, level of toxic stress is measured and taken into consideration, a whole new level of quality of life can be reached, whereas before, the patient was told to learn to live with it. It is surprising that this combination has not yet received the attention it deserves.

With the growing knowledge of the effects of toxic stress we have to change the leading question in medicine from: what's wrong with the person? To: what has happened to the person? This question is seldom asked in a doctor's examination room. The role of the developmental history not only sheds light on the impact of MTBI on a patients life but is also essential in examination and treatment of a great amount of other disorders and combinations of disorders (chronic fatigue syndrome, chronic pain syndrome, fibromyalgia syndrome, hypertension, diabetes etc). Many MTBI /toxic stress sufferers show dramatic improvements when they are given, or taught how to use, various coping mechanisms, from mindfulness and meditation to biofeedback.

Conclusion

Healthy relationships can help guide stress response, by finding ways to respond actively to stress, and to reduce the stress in a patients life. Being responsive and being attentive are the two key characteristics essential to maintaining a healthy relationship at home as well as at work. These circumstances will support any person to continue to evolve in cognitive and emotional sense. With the above described treatment options in mind, this now also becomes true and within reach for those with residual complaints after MTBI.

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Volume 8 Issue 3 October 2017
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