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Restating traumatic brain injury (TBI) and post-traumatic stress syndrome (PTSS) as a neuroinflammatory process.

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Abstract

Traumatic brain injury, regardless of its cause or degree of intensity, creates changes in the neurochemistry of the brain secondary to neuroinflammation. Neuroinflammation is the secondary insult and the hall-mark of all neurodegenerative processes, arising from microhemorrhage, diffuse axonal injury and dissection, cerebral contusion, and stress all providing the catalyst (NFkB) for the release of immune-based cytokines such as IL-1, IL-1b, IL-6 and TNF-alpha. The interaction of these inflammatory cytokines with the molecular chemistry of the cell membrane, alters cellular functioning leading to neuronal death. As the intracellular content of neurons is released into the surrounding tissues, free radicals are produced raising the level of oxidative stress, thereby furthering disruption of cell signaling and the brain's regulatory systems. Many neural and behavioral functions are affected, including mood, cognitive function, blood pressure regulation, motor coordination, pain, and opioid sensitivity.

Many traumas are of the polytrauma-type, inclusive of peripheral and internal injuries, adding to the rapid production of cytokines that pass through the blood brain barrier to activate microglia. Microglia activation normally provides defensive mechanisms to protect neurons, but with the progression of injury more cytokines, chemokines and leukotrienes are released. At a point in time, the load becomes overwhelming and turns destructive leading to the progressive loss of neurons and thereby, cell-to-cell communication. As more and more of these connections are lost, cognitive and neurobehavioral functionality is eroded leaving the individual with symptomatic-TBI which includes depression, anxiety, obsessive-compulsive behavior, bipolar traits, schizophrenia, Alzheimer's disease, and Parkinsonism.

Identifying and addressing the presence of these secondary insults which are precipitated by varying degrees of neurotrauma, both physical and non-physical, as well as with and without alteration in sensorium, has been the project of the Millennium Health Centers, Inc. since 2004. During this time, we have identified patterns of neurosteroid and neuroactive steroid changes in both sub-concussive and concussive injuries. These patterns are then converted into a treatment approach.

Treatment focuses on two issues, the reduction of inflammation and the temporary replenishment of insufficient or deficient neurosteroids and neuroactive steroids. In addressing the reduction of neuroinflammation, treatment includes a number of nutraceutical products with academically defined abilities to achieve this primary goal, such as Quercetin, DHA, Zn, N-Acetyl Cysteine, and Vitamin D3. When neurosteroids and neuroactive steroids are found to be insufficient, the initial intervention does not use any forms of injectable testosterone. Instead, clomiphene citrate is used to both improve the individual's production of their own steroid hormones as well as to further define the mechanism causing their diminished production. This further helps to maintain the potential for recovery of their own natural production of hormones instead of suppressing it with hormone use.

Introduction: The Issues

The majority of cases of TBI in civilian and combat-related settings are categorized as "mild," a category based primarily on the characteristics of the acute sequelae following the injury. The criteria for the classification of mild can vary, but the DoD/Department of Veterans Affairs March 2009 Clinical Practice Guideline has adopted the following criteria: (1) brief loss of consciousness (<30 min), (2) brief alteration of consciousness (< 24 hours), (3) posttraumatic amnesia for 0 to 1 days, or (4) Glasgow Coma Score of 13 to 15 (15 = normal), and (5) a normal-appearing brain CT-scan [**1**]. Nonetheless, over time, many of these individuals develop symptoms referred to as post-concussion syndrome, symptomatic TBI, or post-traumatic stress disorder. When the symptoms become socially disruptive, the individual might seek help from their primary care provider who refers them out for psychiatric evaluation after having performed basic biochemical and hormonal assessments. If a history of TBI is acknowledged, an MRI is frequently performed with nearly 80% of these studies being read as normal [**2**]. At this point, the presentation is considered 100% neuropsychiatric with medication being offered to control the symptoms of depression, anxiety, insomnia, emotional volatility, lack of libido and cognitive impairment [**3**].

Neuroinflammation, secondary to neurotrauma (TBI), has been documents to be present 17 years after the initial insult thereby, providing evidence that the process is indolent causing a delayed and progressive presentation of symptomatology in these individuals [**4**]. Once neurotrauma has occurred, there is release of immune-based cytokines specifically IL-1, IL-1b, IL-6 and TNFa all known to be associated with neurodegenerative disorders and to pass freely into the brain [**5**]. The present medical community's strategies for treatment of the sequelae commonly presenting in TBI, does not address these important factors.

Instead, the focus of treatment has been to mask the symptoms with the use of polypharmacy. The consequence of this approach has been several generations of veterans and civilians whose lives have been inextricably altered to the worst. Continued personality issues leading to suicide, persistent depression, isolation, disruption of family, loss of jobs and the incarceration of nearly one-million veterans should be ample enough to acknowledge the fact that we have not provided the best answers [**6]**.

It has been the futility of these accepted modalities of assessment and treatment, that has led the Millennium to look at the science of neuroinflammation and its effects on cognition, mood-disorders, and modulation of neuroinflammation via disruption of the brains molecular chemistry (neurosteroids). We believe that we have a plausible answer:

A Solution

A. The Laboratory (Objective Biomarkers)

Starting in 2004, the Millennium Health Centers, Inc. has developed a simple, cost-effective, reproducible, bio-marker panel that uses standard serum blood tests that address an array of neurohormonal markers [**7**]. These biomarkers look at the brain's regulation of central (neurosteroids) and peripheral hormones (neuroactive steroids) that can be altered after traumatic brain injury [**8,9,10**]. Additionally, the accuracy of the laboratory results is enhanced by the use of laboratory technology such as Mass-spectrometry (LC/MS/MS/MS) to improve the accuracy and reproducibility of testing. Furthermore, a key to the success of the Millennium's program has been the implementation of a paradigm shift in the interpretation of the laboratory results.

Traditionally, the acceptability of any specific laboratory test result is based upon a set of standardized laboratory ranges. Like a ball kicked for a field goal the results must be above the bar and between the poles. Unfortunately, many results are above the bar but to close to either pole instead of being dead center. Laboratory results that come in a few points above the lowest laboratory range are read as "normal", regardless of the patient having symptoms that are characteristic of that deficiency.

In 25 years of practicing Endocrinology and 15 years practicing Neuroendocrinology, the difference between a laboratory result being in the center of the range as opposed to being at the lowest numbers of "normal" are worlds apart in symptomatology. Our greatest outcome results are obtained when the neurosteroids and neuroactive steroids are at their median of the range.

B. Neurosteroids and Neuroactive Steroids

Neurosteroids (NS) are endogenous neuromodulators synthesized in the brain from cholesterol that rapidly alter neuronal excitability (in real-time) by binding to membrane receptors, in addition to the induction of gene expression via intracellular steroid receptors. Neuroactive steroids induce significant antidepressant, anxiolytic, anticonvulsant, analgesic and amnesic effects, mainly through interaction with the gamma-amino-butyric type A (GABAa) receptor. They also exhibit neuroprotective, neurotrophic and antiapoptotic effects along with the ability to diminish free-radical stress all associated with neurodegenerative diseases [**11**].

Neuroactive steroids (NAS) are a group of hormones, derived from Cholesterol, representing the steroidal family that passes through the blood-brain barrier to genetically, epigenetically, and biochemically influence the brains functioning [**12**].

Recognition of the influence of both neurosteroids and neuroactive steroids on brain function and health, has been advancing since the 1980's when Dr. Etienne-Emile Baulieu identified glial cells production of enzymes necessary to metabolize cholesterol down the Pregnenolone cascades to progesterone, cortisol, DHEA, testosterone, DHT, and Estrogens [**13**]. In the past 30 years, the molecular chemistry by which neurosteroids influence and regulate our neuropsychobiology has been increasing at an accelerated rate [**14,15,16**], while acceptance of the science has been slow to occur.

C. Neuroinflammation and Neuropsychiatric Disorders

Neuropsychiatric disorders including conditions such as schizophrenia, major depressive disorder, and bipolar disorder are generally considered to have a multifactorial pathophysiology including both genetic and environmental factors [**17**]. The finding of significantly higher levels of inflammatory markers in patients suffering from neuropsychiatric disorders has laid the foundation for understanding the important role that inflammation has in the pathogenesis of these conditions [**18,19,20,21**]. Patients with depression [**22**], Schizophrenia, Anxiety, symptomatic TBI (PTSD), bi-polar, obsessive disorder [**23**] have been shown to present an increase in serum levels of proinflammatory cytokines, such as IL-1, IL-6, IL-8, IL-12, interferon-c and TNF-a [**24**].

It is the presence of this molecular chemistry, precipitated by neuroinflammation, that is being recognized as the mechanism mediating the onset of a broad range of psychiatric disorders and contributing to non-responsiveness to current therapies [**25**]. This provides a fundamental understanding for why our treatment of depression as well as other forms of neuropsychiatric disorders are met with resistance and the higher risk of suicide. AS long as there is inflammation there cannot be a return to a Neuropermissive

environment that fosters reduction of inflammation, return of normal brain chemistry, and the healing of the brain [**26**].

D. Treatment with Nutraceuticals

Based upon the overwhelming amount of science that already existed, it made sense to approach the treatment of neuroinflammation with a selection of nutraceutical products that have data supporting their ability to modulate inflammation as well as replenish both neurosteroids and neuroactive steroids that were deficient.

Using the results of the biomarker panel, medical and mental health histories, medication response and supplement history, nutrition and exercise history, a treatment protocol was assembled that incorporates nutraceutical products that have a suppressing (down-regulation) effect on NFkB induction and the reduction of inflammatory cytokines. A few of these products are the Tocopherols [**27**], polyphenols [2**8**], N-acetyl cysteine [**29**], and Eicosanoids [3**0**] each nutraceutical has a wealth of peer-reviewed literature supporting their beneficial effects on traumatic brain injury and neuroinflammation.

E. Address the Gut-Brain Relationship/Nutrition

Inflammation arising from the gut under stress, dysbiosis, antibiotic use, or altered immune system functioning generates additional cytokines that readily diffuse into the brain. The use of good nutrition with emphasis on an anti-inflammatory diet can lower the production of these chemicals while the addition of probiotics can help to heal the damaged gut [**31**].

F. Cost-Effectiveness

The Congressional Budget Office, responsible for providing budget and economic information to the Congress, issued a report in February 2012 titled, "The Veterans Health Administration's Treatment of PTSD and Traumatic Brain Injury Among Recent Combat Veterans." The report stated that the average cost per patient (in dollars) for the first year of treatment for all health care provided to overseas contingency operations (OCO) patients by the Veterans Health Administration was $8,300 for PTSD, $11,700 for TBI, and $13,800 for both PTSD and TBI [**32**]. On average, the cost for the first year of the Millennium's assessment and treatment which includes the Millennium's initial bio-marker blood testing, three monitoring blood panels with consults, all physician consultations, and the patient's personalized treatment protocol is $7,500. The Millenniums on average cost in year two and three drops down to $4,750 and $3,500, respectively.

G. Clinical Results

Since 1995, the Millennium has treated patients with hormonal deficiencies noting the improvement in cognitive and mental health. It was not until 2004, when a renaissance in the medical literature suggested that there was a relationship between traumatic brain injury precipitated hormonal deficiencies and the development of neuropsychiatric conditions. Using this triad, we culled from peer-reviewed literature research that offered a solution to the symptomatology associated with TBI based upon the causation; neuroinflammation.

Translational medicine is based upon the application of bench-research into a clinical setting years before it is brought into mainstream medicine [**33,34,35**]. The science supporting the application of each of our nutraceutical products has been sitting waiting to be read and applied.

In 2004, the Millennium began the process of identifying products which were natural and supported by multiple research sources. As the years advanced, the number of articles grew adding to the wealth of information needed to justify their use in a clinical setting for those individuals experiencing symptomatic TBI.

In 2009, the Millennium evaluated and treated its first active military (JR) who had been exposed to multiple fire-fights, blast trauma, and jarring during his decades in the Green Berets. Using our first neurosteroid/neuroactive steroid assessment panel we provided a treatment protocol that improved his symptoms which allowed him to avoid medical discharge. In 2014, the Millennium began working with Andrew Marr, a medically retired Green Beret, and the co-founder of Warrior Angels Foundation, along with his brother Adam Marr (former Army Aviation Officer). Andrew had been on 13 different medications and used alcohol to "cut the edge" off his emotional lability. Within weeks of his biomarker assessment and treatment, he was no longer on medication or drinking.

Together as the Millennium-Warrior Angels Foundation (MWAF), we recruited other Veterans and Active Military, with symptomatic TBI unchanged or worsened by conventional therapies, into our project. Each participant fills out a 23-paged intake packet, that includes lifetime injuries (civilian and military exposures), subjective behavioral inventory, physical status, nutrition, exercise and drug/medication history before having their biomarker panel performed. Once the results are received, a 4-page report is prepared, and a consult is arranged to review the history, results of labs, and the proposed treatment protocol. The treatment protocol consists of 80-90% nutraceuticals that address inflammation, suppression of cytokine production, and replenishment of important prohormone while 10% - 20% are prescription medications such as thyroid hormones, estrogen, progesterone, and testosterone. All of the hormones are bio-identical and of plant sources.

Since 2009, we have provided full or partial financial grants to cover program expenses for nearly 360 veterans and/or active military. We also have 14 Vietnam war-era Heroes in the population between the ages of 70 and 84 all doing impressively well. Each participant self-monitors their progress with our Monthly Program Questionnaire (MPQ) that looks at psychological, physiologic and physical parameters. Follow-up laboratory testing is performed at 3, 6, and 12 months after starting their treatment protocol. Modification to their initial protocol can be based upon their MPQ responses and/or their laboratory results.

At present, we are tracking 459 individuals who have had an average of 78% improvement in less than 12 months (see the 2019 Summary Report). Most if not all have reintegrated into life, their family, work, higher-education, and are off their prescription medications taking cost-effective and efficient nutraceutical preparations. We have collected both subjective and objective data on over 2800 participants in our program from our offices in Encino California.

H. Prevention

It is clear that we cannot control the exposure of our soldiers' to neurotrauma during training or in battle, but we can influence the outcome. **Biological Resiliency (36)** is that state in which we can improve our protection from stress and neurophysiological challenges through maximizing positive life-style issues pertaining to nutrition, dietary supplementation, sleep, hydration, and alcohol use. There are a number of known nutritional supplements that can help with blast trauma as well as general psychiatric well-being (**37,38,39,40,41,42,43,44,45**). Using these supplements proactively can improve upon the individuals

Biological Resiliency and lead to a faster recovery as we have seen in recovered patients who experience a subsequent trauma.

I. Recommendation

It is the goal of the MWAF to provide a network of facilities around the United States that can emulate and provide the standards of evaluation and treatment that the Millennium has worked on for over 16 years. In regard to our military (veterans and active service personnel), we would like to provide to the DoD/VA the information that we used to develop our program. Ultimately, upon acceptance of the science, a pilot program involving a group of veterans suffering with symptomatic TBI (PTSD/CTE) would be enrolled into the project. Outcome results from this trial population would be used to generate publishable articles to further the acceptance of this paradigm in diagnosis and treatment.

Until such time as the pilot program can be initiated, we would offer our data on patient history, laboratory testing, treatment protocols, and outcomes. We believe that the wealth of documented pre- and post-status reports will allow for the pilot program to move forward.

J. Summary

The continued loss of American life's secondary to depression and suicide is not abating. Conventional medical wisdom elects to treat the symptoms of a condition that has a clear biochemical causation with medication that just masks the symptoms. Laboratory testing is available to identify the alterations in the brain's neurosteroids which can be replenished while providing a non-toxic treatment protocol to drop the inflammatory cytokines initiated by trauma. The Millennium-Warrior Angels Foundation has been providing such assessment and treatment to almost 360 military and over 2800 civilians with an average improvement in life scores of over 78%. It is time now to look closely at the science that has been available for over 30 years and to start the process of fixing the problem and not just masking it.

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