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Case Study: Psychoneuroendocrinology of Mild Traumatic Brain Injury Recovery

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BACKGROUND: The correlation between the endocrine system and cognitive functioning has been increasingly discussed in the literature in recent years, as a growing number of studies in this field emerge. Despite this growth in interest in this correlation, however, the topic still remains heavily under-explored especially in the case of female athletes who have sustained traumatic brain injuries. There exist many obstacles in acquiring relevant data to enrich this field of research, including, but not limited to, current medical approaches, difficulty in isolating neurological and psychological symptoms stemming from mild traumatic brain injury (mTBI), the dismissal of multidisciplinary and holistic approaches, as well as limited resources such as time and funding. Although interest has increased and been popularized in the last decade, limited research has been conducted and/or published to specifically explore, clarify, and connect mTBI recovery with endocrine (dys)function.
METHODS: The current case study contributes to this topic and offers empirical data gathered through work with an mTBI participant with preexisting hormonal dysfunction. It describes the hormonal changes that precede and follow mTBI recovery in a female athlete, as well as her atypical recovery and long-term post-concussion symptoms. Data gathered includes hormonal charts, neurocognitive assessments, and quantitative electroencephalography (qEEG) assessments administered over a period of six years.
RESULTS: Possible interaction of the hormonal changes and their importance in mTBI recovery are theorized in this study, as well as the possible impact that mTBI can have on endocrine functioning.
CONCLUSION: The current report suggests a need for further research in the area of hormone function in females who have sustained a traumatic brain injury, even if mild in nature. On a case-by-case basis, there is clinical validity in assessing women who fail to recover from concussion in a timely manner via comprehensive hormonal evaluation and treatment combined with psychological, nutritional, and exercise interventions.

INTRODUCTION

Concussions are a common type of injury among athletes. According to the National Ambulatory Care Reporting System (NACRS) in 2016 and 2017, the time of the initial onset of this study, hospital emergency departments reported diagnosing 46, 000 concussions in children aged 5-19 years old.[1] NACRS has also reported that 26,000 of the diagnosed concussions were male patients, while 20,000 were female. Sports and recreation were the reasons listed as a cause for concussion in 54% of the male patients, while in the female patients, 45% listed sports as a reason for their concussion. The Canadian Institute for Health Information provides recent data from the NACRS, noting that hospitalizations for sport-related brain injuries increased from 1600 to 1700 between 2022–2023 and 2023–2024, and concussions accounted for 30% of sport-related brain injury hospitalizations.[2]

The Public Health Agency of Canada estimates that 21,200 hospitalizations from head injury occur each year in Canada, with concussion accounting for 11%.[3] Sixty-three percent of all cases were males, and males accounted for the majority of cases across most age groups. For youth aged 5-19, 30% of cases were attributable to sports-related injury.

Despite the large number of female athletes, as well as the increasing popularity of women's' involvement in contact sports, little research has been done on recognizing the differences between the concussion recovery process between male and female athletes. Note that throughout the current

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paper, when discussing differences in sex or gender with respect to male and female athletes, we are referring to a distinct group of biological traits that are connected to gene expression, hormone function, and chromosomes. The existing body of literature on this topic indicates that differences between genders can be pinpointed and that there is an imminent need for developing gender-specific treatment protocols. Musko and Demetriades noted that most sports-related protocols are mainly informed by the 6th International Conference on Concussion in Sport, which does not stress the importance of sex differences.[4] However, systematic reviews indicate that female athletes tend to be more susceptible to concussion and have more prolonged symptoms after a concussion than male athletes.[5] McGroarty et al and Musko and Demetriades identify possible factors that play a role in the gender-differentiated post-concussion symptoms and recovery processes to be biomechanical differences and hormonal differences.[4,5] McGroarty found that somatic symptoms tend to be more prevalent in female athletes than in males, such as headaches, migraines, and sleep disturbances, and that they take longer to recover after suffering a concussion.[5] Sicard et al. also found support for their hypothesis with the results of their research, which involved 196 student athletes, that indicated sex differences in executive functioning, finding that female athletes responded significantly more slowly and more inaccurately than male athletes on a measure of executive functions (N-back Task).[6] Their results align with other research findings that show the presence of subtle, but long-term alterations of executive functions in female sports-related concussions that are in greater magnitude compared with their male counterparts.[4,5]

Although clinical data indicates differences in the occurrence, reporting, and consequences of sports-related concussions (SRCs) between sexes, female athletes have not been given enough specific attention in research, leading to the absence of treatment guidelines specific to female athletes after injury.[7] Duffy et al. recognize the lack of inclusion of female participants in the existing research samples, and in their research indicate that sports-related brain injuries (SRBI) in females cause a neurochemical response that affects specific parts of the brain, such as the hypothalamus and the pituitary gland.[7] Although they note that research regarding the role of the pituitary gland and the hypothalamus in SRBI is rare, the initial evidence suggests that these parts of the brain regulate the production of sex hormones and when impacted by a blow to the head, result in deficiency of progesterone and estrogen, triggering neuroendocrine dysfunction that further affects an individual's cognitive functioning and recovery.

Endocrine System and Cognitive Functioning

As Duffy et al. noted, concussions can affect the parts of the brain that are responsible for the production of estrogen and progesterone, and as such, cause neuroendocrine dysfunction.[7] Estrogen and progesterone are known to have a neuroprotective role in the human body. Their increased concentration in the bloodstream is related to decreased severity of cognitive symptoms in the acute phase of concussion recovery.[8] Estrogen and progesterone are known to be neurosteroids and play multiple roles in the development, maintenance and overall function of the brain.[9] It is believed that they work together to improve the function of neurons by forming and reducing synapses, enhancing synaptic transmission, and providing neuroprotective effects.[10,12] Gurvich et al. indicated that estrogen and progesterone receptors can be found in important brain regions, such as the hypothalamus, thalamus, hippocampus, amygdala, and cerebellum, as well as the prefrontal brain region, suggesting the importance of these hormones in higher order cognitive functioning and spatial cognitive performance.[9]

CASE REPORT

History of Research Participant

Descriptive Data

The subject was born in 1990, is a biological Caucasian female, and was 26 years old and single at the onset of the present study. The participant holds a university degree and a graduate certificate in the field of Biochemistry and is reportedly of mid-to-high socioeconomic status; her parents were both college-educated and self-employed.

Relevant History

The subject was initially interviewed on February 14, 2017, and reported the presence of positive social and work relationships; however, she also provided self-report of a high level of stress in her daily life. The subject reported that she played various sports throughout her lifespan, namely house league and recreational soccer and baseball, wherein she sustained a diagnosed

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concussion/whiplash injury, noting that she also sustained multiple blows to the head (which did not result in a concussion diagnosis or treatment) beginning around age 12. She indicated having an above-average interest and involvement in health, fitness, and nutrition. She advised that she had the presence of pre-concussion hormonal dysfunction and subsequent hair loss. The subject was not on any medications at the onset of the study, although trialed Nortriptyline three months post first diagnosed concussion for a period of three months and Gabaentin ten months post same concussion for two months, reporting no positive impact on symptoms, thus it was discontinued.

Environmental Factors

The subject is employed within the field she is educated in and reported positive work relationships and environment. As noted in Descriptive Data, the subject reported high daily stress and positive social relationships in her life, and at the onset of the current study, was not in a romantic partnership. The subject indicated infrequent alcohol consumption (0-1 drinks per month) post-concussion, and no other use of substances.

Protective Factors and Lifestyle Dynamics

Protective factors in this context refer to factors, actions, or efforts a person can take to reduce the negative impact of issues relating to physical and mental health. Health, social, and psychological protective factors in the subject's life that should be considered include the following: she is university educated, has a history of regular physical activity, she continued exercising after injury, is a self-reported hard worker and rule follower, and has positive relationships in her life. The subject reported no prior history of eating disorders; She was a normal body mass index (BMI) of 24.1 at the onset of the study, did not report any food allergies, noted a vegetarian and dairy-free diet, exercised five days per week, approximately 30 minutes per session, through high intensity interval training.

Presenting Problem

Self-Reported Data

The subject reported ongoing post-concussion symptoms, including headaches (ongoing), dizziness (prior, has subsided), sensitivity to sound/loud environments, low-blood pressure (some fainting), minor short term memory issues, difficulty concentrating (ongoing, however, some improvement), feeling confused when senses were overstimulated (ongoing, usually at work), loses train of thought (daily), difficulty sustaining long conversations (daily), anxious distress and depressed mood relating to symptoms, indicating that initially post-concussion, her general degree of anxious distress was reported at an 8/10 on a scale of 0-10, with 0 representing no distress and 10 representing the worst distress she could imagine; she additionally reported depressed mood at 5/10 post-concussion, but by the initial interview of the current study, she reported that after engaging in self-work on these symptoms, her depressed mood was rated at approximately 2-3/10 (no formal assessment or diagnosis, based on subjective self-report).

Clinical Perspective and Considerations

The subject has had multiple, persistent post-concussion symptoms lasting two years post-injury. It is noteworthy that she did not experience any loss of consciousness with her head injuries. Her age of menarche was 13, reported hormonal and menstrual dysfunction pre-and post-concussion, diagnosis of secondary amenorrhea and ongoing mismenorrhea, and hypothalamic hypogonadotropic hypogonadism are all factors that are of clinical relevance. It is also of importance to consider that there exists post-injury neurocognitive deficit in comparison to the subject's self-report of prior functioning. The subject reported that her symptoms were limiting her hours of work per week at the beginning of this study. The role of a life-long history of physical activity is also an important consideration. Post-concussion, the subject also engaged in a variety of treatments including, physiotherapy, chiropractic, massage therapy, electroencephalography (EEG) neurofeedback, Power Coaching with Mind Kinetics (online mental health resources), as well as a prescriptive exercise program and nutritional modifications.

METHODS

Materials

NeuroGuide™ is a tool set to help connect symptoms and behavior to brain functional networks.[13] One of the tools is EEG neuroimaging, which can be used statically or in real-time to assess Brodmann Areas and nodes and connections of brain functional networks that are likely linked to symptoms. The NeuroGuide™ program was used to analyze the raw EEG data as well as to

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statistically interpret the quantitative electro-encephalography (qEEG) studies. Default montages of Z Scored Absolute Power were used to analyze the statistical differences between the initial qEEG and the subsequent re-tests, using T-test analysis. The tool has confirmed high reliability index exceeding 0.95 as well as good validity coefficients and gained FDA 510(k) clearance.[14,16]

CNS Vital Signs NeuroScreener is a tool that objectively assesses neurocognitive function using computerized neuro-psychological screening tests that assist in the evaluation and management of neurodegenerative, neuropsychiatric, and neurodevelopmental disorders, aid the monitoring and management of their progression, measure the response to treatment and help identify domains needing additional or full neuropsychological evaluations.[17] This tool has demonstrated good psychometric characteristics in clinical and non-clinical samples, with coefficients ranging from 0.65 to 0.89 for test-retest reliability and exceeding 0.70 for Cronbach's alpha for internal consistency.[18] Validity coefficients ranged from r=0.50-0.80 concurrent validity, regression R^2~0.60 for construct validity, and Cohen's d >0.80 for discriminant validity.[18,20]

Hormonal analysis refers to blood tests performed in a laboratory, referred by a physician.

Procedure

Retests were performed approximately every 6 months.

Spider model is a technique utilized in this study as a means of viewing, mapping, and making connections between various systems (Appendix 3).

RESULTS

Hormonal Test Results

- November 3, 2015: pre-concussion, all within normal ranges
- January 2017: Low Triiodothyronine Free (Free T3) , Thyroid Function; Low
- June 20, 2017: Low Free T3; Low Beta Estradiol; Low Creatinine
- June 24, 2017: Low Triiodothyronine Free (Free T3) – Thyroid Function; Low Estradiol – Reproductive & Gonadal (menstrual cycle stopped)
- September 8, 2017: on bioidentical hormones - menstrual cycle resumed- all within normal ranges
- July 30, 2018: on bioidentical hormones, menstrual cycle resumed- all within normal ranges
- May 2020: all within normal range

Saliva Hormone Test (February 15, 2018): Progesterone: high end of range; Testosterone- low end of range; noon Cortisol- above normal range;

Microbiome Test Report: February 11, 2020: Lack of microbiome diversity

Blood Work: October 30, 2017: low estrogen levels; on hormone therapy; irregular cycles; high progesterone; missing cycle

CNS Vital Signs

- Feb 2017: NCI=102
- Jul 2017: NCI=103
- Aug 2018: NCI=114
- May 2019: NCI=112
- July 2020: NCI=112

Hormone Analysis

- Low estrogen and low range progesterone before her 2015 concussion
- Low estrogen, progesterone and T3 2 months after the 2015 Concussion
- Low estrogen and T3 7 months after the 2015 Concussion
- Started Bioidentical Hormone Replacement Therapy (BHRT) a year and a half after the concussion, leading to hormone increase, with one exception- low estrogen in October 2017, a few months after starting BHRT- which then increased again and normalized.
- After her second concussion, no change in hormone levels (perhaps because she was on bioidentical hormones; there was also no decrease in her NeuroCognitive Index; but there were unusual changes in her qEEG- sudden decrease in Alpha, Beta and Gama waves which previously tended to increase).

CNS Vital Signs NeuroScreener

- Most affected: Motor Speed domain (staying in Low Average during the recovery, average at the end)
- Least affected: Processing Speed and Psychomotor Speed domains (staying Above Average during recovery)
- Gradual, steady recovery in general, with minor fluctuations in certain domains.

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qEEG Analysis

qEEG analysis demonstrated a consistent pattern characterized by the following:

- Increased Delta activity in prefrontal and frontal regions
- Increased Theta activity in left-prefrontal region
- Decreased Alpha activity in temporal, parietal, and occipital regions
- Increased High Beta activity in right-temporal region.

T-Test Analysis (see Appendix 1)

Neuro Guide uses a large normative EEG database of healthy individuals (matched by age, sex, etc.) and applies t-tests to compare a subject's brain activity—such as power, coherence, and phase—to the norms in order to determine if their measurements significantly differ, with z-scores derived from the normative means and standard deviations that correspond to statistical significance. T-tests are also employed to assess differences in functional connectivity patterns across brain regions. T-tests were applied to z-scores of absolute power in delta (0.5 - 4 Hz), theta (4 - 8 Hz), alpha (8 -12 Hz), SMR (~12-15), and beta (12 - 30 Hz) frequency bands at each electrode site between each re-test to follow recovery and changes.

- Decreasing activity after both concussions-activity decreases, then tends to go up**
- Least changes between 2nd and 3rd retest (January-August 2018); she was on bioidentical hormones with normal hormone levels, as well as being in active recovery, before her 2nd concussion
- Most statistically significant changes are noted in the frontal and prefrontal regions, within the Delta and Theta (4-6 Hz) bands .
- Statistically significant changes in the temporal/parietal lobes within the Beta wave were noted after the first concussion until August 2018. Beta wave normalized after, possibly due to starting BHRT July 30, 2018.

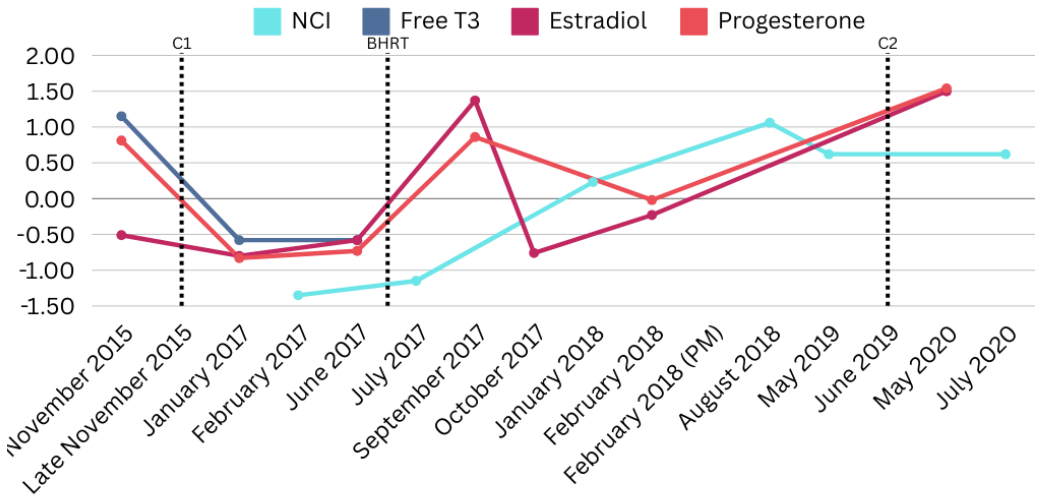

Figure 1. Z-score representation of the hormones that demonstrate significant fluctuations

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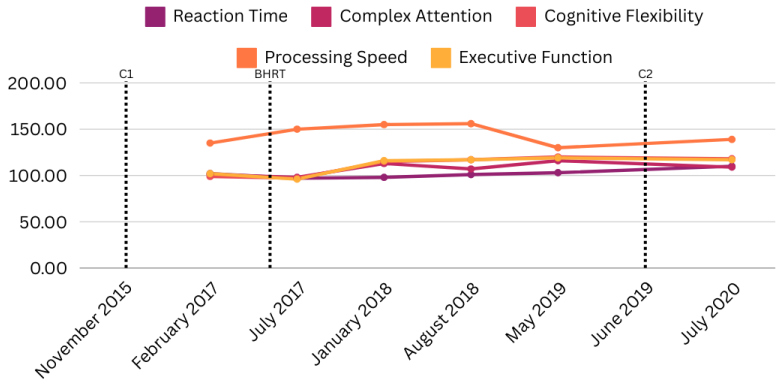

Figure 2. Graphic representation of CNS Vital Signs Scores and subtests

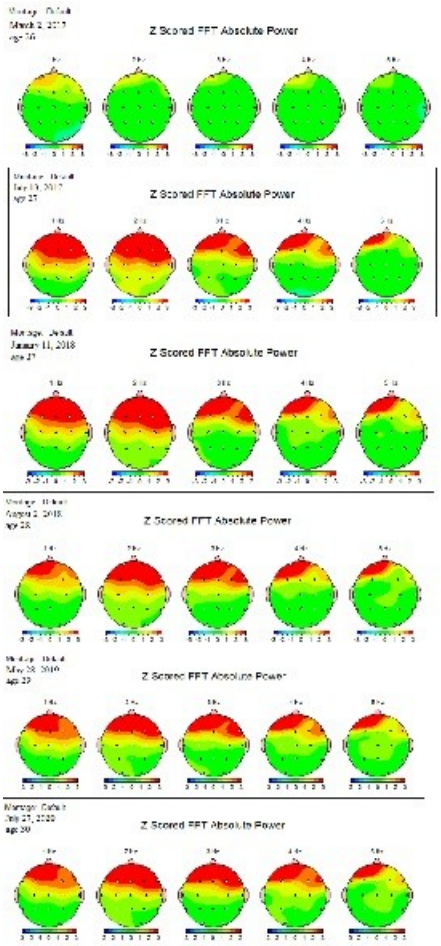

Figure 3. Changes in the frontal and prefrontal lobes within Beta waves

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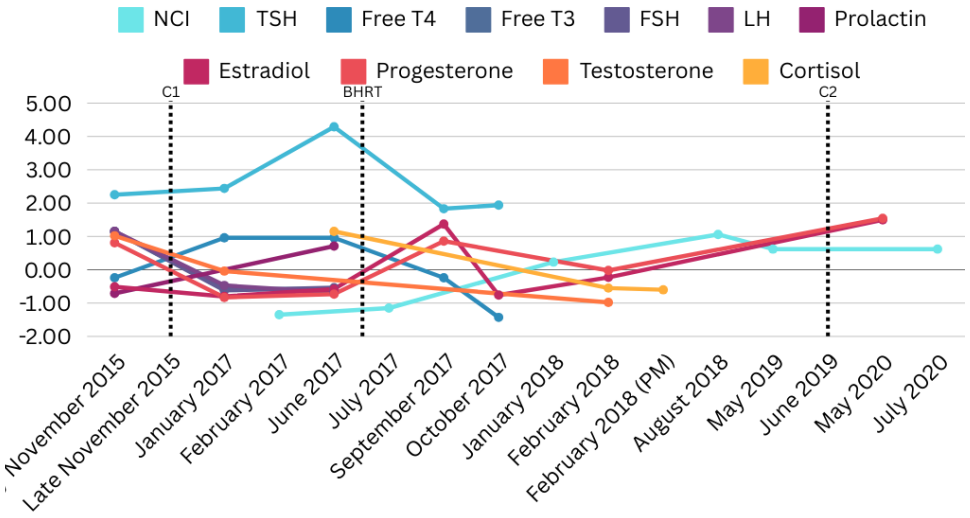

Table 4. Z-scores comparison of fluctuations of all hormones and NCI

DISCUSSION

In review of the subject's history, it can be observed that her hormonal concerns began before her first officially diagnosed concussion at age 25, in 2015. However, she has reported experiencing multiple blows to the head beginning around the age of 12 which were associated with playing soccer and heading the ball. She also reported a hit to the head on a swing pole at age 12, in addition to another blow to the head at age 14 when she was run over by a snowboarder while skiing. The subject's age of menarche was 13 years of age, her onset of amenorrhea was at the age of 23, and she was subsequently diagnosed with secondary amenorrhea which was reported to be associated with the use of Finasteride, a medication for hair loss; the presence of issues relating to hair loss suggests a likelihood of underlying hormone issues.

Amenorrhea is defined as the absence of menstrual cycles for at least three months caused by dysfunction of the hypothalamus, pituitary, ovaries, uterus or vagina, and if the onset is after the age of 15, it is classified as secondary amenorrhea.[21] The most prevalent causes for developing secondary amenorrhea are hypothalamic and pituitary dysfunction. Pituitary dysfunction can be caused by traumatic brain injury (TBI) and even mild TBI (mTBI) is noted to be a cause for the onset of amenorrhea by disrupted pituitary function, even 12 months after a head injury.[22] Although the head injuries that the participant sustained at ages 12 and 14, as well as multiple mild blows to the head during soccer were not officially assessed or diagnosed, they can still play an important role in the development of long-term symptoms in addition to pituitary and endocrine dysfunction. Even mild and overlooked SR-TBIs may cause pituitary dysfunction that may have distressing consequences in some cases if they remain undiagnosed.[23] Her hormonal dysfunction indicates possible disruption of hypothalamic-pituitary-ovarian (HPG) axis, which can result from the stress of her prior head injuries.[24]

The participant's hormone panel results indicate low estrogen and progesterone even before her first officially diagnosed concussion in 2015, but after the concussion, they decreased even further, maintaining a low concentration of these hormones months after her concussion. The concentration of the sex hormones did not increase during her recovery, despite the participant's active recovery and involvement in multiple treatments such as physiotherapy, chiropractic, massage therapy, EEG neurofeedback, Power Coaching with Mind Kinetics (online mental health resources), as well as a prescriptive exercise program and nutritional

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modifications. Although she did experience subjective improvement and despite her prolonged recovery, she noted being able to return to work after six months of active recovery on modified duties, as well as another six months for her to be able to perform her pre-injury duties. A year and a half after her concussion and continuously low sex hormones, the participant started BHRT, which helped her to increase the concentration of progesterone and estrogen within normal ranges. It is noteworthy to indicate that her sex hormones did not fluctuate after her second concussion in 2017, while she was still on BHRT.

On March 20, 2025, the subject participated in a follow-up interview, which revealed that she is currently experiencing a resurgence of post-concussion symptoms, likely triggered by recent head impacts and compounded by psychosocial stressors including returning to work and caring for a young child (see Appendix 2). Her cognitive functioning—particularly tasks requiring executive function—has declined since an August 2024 whiplash injury, and she reports fatigue, headaches, and nausea when overexerted. Hormonal fluctuations, including the discontinuation of bioidentical hormones, a miscarriage, and the postpartum period, may also be contributing to her symptoms, suggesting that previous hormone therapy may have had neuroprotective effects. Taken together, her experience underscores the complex interrelationship between concussion history, hormonal changes, and psychosocial stress, suggesting a need for integrative approaches in managing long-term recovery and cognitive health.

CNS Vital Signs

The participant's neurocognitive functioning was assessed using the computerized neurocognitive assessment tool, CNS Vital Signs. The results indicated generally steady progress in her recovery with her neurocognitive index (NCI) being as low as 102 (average range) to 112 at the last retest (above average range). The most affected cognitive domain seen in the results is the participant's motor speed, remaining in the low average (9-24th percentile range) during recovery, and reaching the average range at the last retest after the client was placed on BHRT. The least affected cognitive domains were processing speed and psychomotor speed, remaining in the average range throughout her entire recovery. It is important to recognize that there are no significant changes that correlate between the NCI and the hormone fluctuations.

qEEG Analysis

When analyzing the qEEGs, there were noticeable consistent patterns throughout all retests that were characterized by increased delta activity in prefrontal and frontal regions, increased theta activity in the left-prefrontal region, decreased alpha activity in temporal, parietal, and occipital regions and increased high beta activity in the right-temporal region. Ianof and Anghinah (2017) have noted similar qEEG results, although they referred to these changes in the acute phase of the mTBI, 1-10min after the injury. They indicated a noticeable immediate reduction in mean alpha frequency, with increased theta, increased delta, and increased theta: alpha ratio. However, in reference to observed chronic changes after mTBI, the authors confirmed higher power in the delta band and lower power in the alpha bend, which is also seen in the participant qEEGs dating 2 years after the concussion.

Significant changes were observed predominantly in the frontal and prefrontal regions of the brain. It is important to note that the qEEGs indicate after both concussions, activity decreases before tending to increase; the activity in many domains tends to decrease after concussion and then slowly starts to increase. A decrease of the brain's activity is normal, since after concussion, brain waves are slower and then normalize; however, this is usual in the first few minutes after concussion and typically normalize after a few hours.[25] The qEEGs for this current study were not administered in such a short timeframe, which suggests one can infer that by the time these qEEGs were administered, the brain waves would have been expected to have normalized.

The most minimal changes on the qEEGs were observed between the second and third retest (January-August 2018), and it is important to note that during this period, the participant was using bioidentical hormones. Her hormones were stable, and more specifically, her progesterone and estrogen levels, which are the neuro-protective hormones, were in average ranges. Numerous studies have confirmed the correlation between sex hormones and cognitive functioning, although this phenomenon has been mainly researched on post-menopausal women, and lacks data on healthy, pre-menopausal, women.[26] Empirical findings discussed by Toffoletto et al. offer preliminary

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evidence of the influence of sex hormones on cortical and subcortical regions of the brain such as the amygdala, anterior cingulate cortex, and inferior frontal gyrus, all of which are involved in emotional and cognitive processing.[11] Progesterone and estrogen have been found to have the ability to stimulate neuron outgrowth, synaptogenesis, and dendritic branching in neuroplasticity.[27] Other estrogen studies have researched the interaction between the HPG axis with the hypothalamic-pituitary-adrenal (HPA) axis, revealing that high-stress levels can alter gonadal hormone function that can impair or enhance memory, depending on the duration and intensity of stress, suggesting that stress is a relevant variable in the HPG feedback loop and production of hormones.[28] Considering the evidence found in the current case that suggests the correlation and importance of sex hormones on cognitive functioning, the changes (and lack of changes) in the qEEGs when the participant had stable hormonal status can be considered as another finding to support the neuroprotective nature of estrogen and progesterone and their important role in TBI recovery.

CONCLUSION

The current case study suggests a need for further research in the area of hormone function in females who have sustained a traumatic brain injury, even if mild in nature. The research participant in this study served as an important representation of the complexity of the interrelationship between the various systems in the human body. It is of particular interest that although the subject had a variety of protective factors present in her life, her injuries still impacted her overall functioning at such a profound level. While there exists some literature surrounding female hormone dysfunction and neurocognitive deficit, it namely surrounds the functioning of menopausal women, thus providing little guidance with respect to women who are at various stages of the lifespan.

Although further research is needed to understand the mechanism, relationship, and appropriate treatment for females who suffer TBI, the present study can strongly inform more robust assessment protocols in a clinical setting. As discussed in this study, employing an interdisciplinary approach to both assessment and treatment will allow for a higher probability of not only understanding, but appropriately diagnosing and treating complex injuries that impact multiple parts of the body, and subsequently, multiple areas of functioning. Additionally, the current study suggests that this interdisciplinary assessment protocol specifically for women should include ongoing assessment of hormone function via a full hormone panel until the injured party has recovered, the use of the "spider model" (Appendix 3) to make connections between various systems, and ongoing consultation between neurology, endocrinology, and psychology when treating women who have sustained a TBI.

This novel case of a female who had experienced hormonal difficulty pre-concussion supports the need for further research and modifications in existing concussion protocols. This case study suggests that on a case-by-case basis, there may be clinical validity in assessing women who fail to recover from concussion in a timely manner via comprehensive hormonal evaluation and treatment combined with psychological, nutritional, and exercise-based interventions. While generalizations cannot made from the single case provided, it is submitted that given the imperative need for assisting women who fail to recover from concussion, appropriate, comprehensive diagnosis and treatment protocols should be considered that include differential approaches that respect this unique and complex hormonal needs of women.

Conflict of Interest Statement
The authors declare no conflicts of interest with the contents of this study.

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