Retrospective Observation

Pain Management in Mild Traumatic Brain Injury: Central Sensitization as a Multispecialty Challenge

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Background: Several studies indicate that approximately two-thirds of individuals with mild traumatic brain injury (mTBI) will develop chronic pain, which is often debilitating and a primary factor in long-term disability. Patients with mTBI can suffer concurrently from multiple pain types, such as chronic neuropathic (central or peripheral), nociceptive, or nociplastic pain; however, the prevailing pain types in mTBI patients remain undetermined. This knowledge void limits the formulation of effective therapies for mTBI-related pain.

Objective: We aimed to identify the predominant pain mechanism in patients who had developed persistent post-concussive syndrome (PPCS) after the onset of their mTBI.

Study Design: We conducted a retrospective observational study following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. Our study focused on a cohort of mTBI patients with PPCS and chronic pain.

Setting: This study was conducted at an outpatient neurology clinic from January 2020 to December 2023.

Methods: The study included patients who met the criteria for post-mTBI PPCS. Exclusion criteria consisted of a history of chronic pain before the injury, being in the acute/subacute stage (fewer than 90 days after receiving the injury), or the presence of any other neurological comorbidities. We employed a range of diagnostic instruments, including a clinical research tool to measure the degree of central sensitization. Since patients with mTBI often show normal structural imaging, we used several neurophysiological techniques, including evoked potentials, videonystagmography, and quantitative electroencephalography, to confirm the presence of brain pathology objectively. The severity of the post-concussive symptoms was measured using the Rivermead Post-Concussion Symptoms Questionnaire. Central sensitization was assessed using the Widespread Pain Index and the Symptom Severity Index. The correlation between concussion severity and widespread pain was analyzed statistically.

Results: Out of 223 initial mTBI patients, 67 met the study criteria. The main reasons for exclusions included pre-existing chronic pain or other neurological diagnoses. Among the patients, 39 (58%) were male, averaging 45.7 years of age (range: 20-72). Ethnicity distribution was as follows: 26 (39%) Hispanic, 22 (33%) White, 12 (18%) Black or African American, and 7 (10%) Asian or Pacific Islander. We found that patients with PPCS exhibited high levels of central sensitization, highlighting its critical role in the pathophysiology of chronic pain post-mTBI. We observed a significant correlation between the extent of central sensitization and the presence of non-painful symptoms, suggesting shared neuropathological processes between chronic pain and other PPCS manifestations.

Limitations: This project was a retrospective study, which made it subject to limitations. Also, the measures used to assess some variables were self-reported, subjecting the data to recall bias.

Conclusion: We showed that high levels of central sensitization were universally present in the cohort studied and should be considered the primary therapeutic target in managing chronic post-

mTBI pain. Therefore, chronic pain in this population is likely driven by central nervous system pathology that contributes to both the pain experience and other post-concussive symptomatology. A significant clinical implication of our study is that patients displaying high levels of central sensitization often report severe pain in discrete body parts, leading clinicians to mistakenly focus on treating the issue with antinociceptive therapies or interventional procedures that are frequently ineffective.

Key words: Mild traumatic brain injury, concussion, chronic pain, central sensitization, nociplastic pain, persistent post-concussion syndrome, fibromyalgia, pain management

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Traumatic brain injuries (TBIs) are a predominant cause of death and disability for individuals aged 1-44, underlining a significant public health concern not only in the United States but globally (1). The Centers for Disease Control and Prevention reports that TBIs affect approximately 2.5 million individuals annually (1). This issue results in 1.4 million emergency department visits and culminates in 50,000 deaths per year. Every year, 80,000-90,000 individuals become affected by lifelong disabilities caused by TBIs (1).

A significant proportion of these TBIs (approximately 75-90%) are classified as mild TBI (mTBI) (2). This "mild" designation can be misleading, since the condition leads to serious and lasting impairments in a subpopulation of patients. Commonly held criteria include a loss of consciousness lasting 30 minutes or less and/or a brief period of confusion or disorientation (3). A lower threshold characterized by a transient alteration of consciousness (i.e., confusion) is an acceptable criterion in most expert classifications. The terms "concussion" and "mTBI" are often used interchangeably, with a consensus favoring the latter in nonsport settings (3).

Research indicates that a staggering two-thirds of mTBI patients are also affected by chronic pain (4-7). In a large meta-analytical study, the prevalence of chronic pain was surprisingly greater in patients with mild TBI (75.3%) than in those with moderate or severe TBI (32.1%) (4). Pain is one of the most challenging issues in managing these patients (8-12). Pain hampers rehabilitation (13) and prevents patients from achieving a desirable level of functioning (14-16). In patients with mTBI, chronic pain is frequently inadequately managed, reflecting the dearth of research outlining the specific mechanisms underlying the type of pain, i.e., whether it is central neuropathic, nociceptive, or nociplastic. This lack of understanding hinders development and implementation of appropriate therapies.

Therefore, the aim of this study was to assess the main features of pain associated with mTBI. Clinical characteristics of pain affecting patients with mTBI initially appeared to be central sensitization and the main mechanism involved. We thus used a diagnostic instrument for pain centralization developed for use in clinical research to further evaluate these patients (17).

Several major terms used throughout this manuscript are often subject to variable definitions in peer-reviewed literature. Therefore, to ensure clarity, we defined the present investigation key terms below:

- Persistent Post-Concussion Syndrome: This term describes a condition in which concussion symptoms, such as headaches, dizziness, cognitive deficits, chronic pain, and more, persist beyond 3 months after the initial mTBI or concussion. PPCS can be associated with disability, hindering instrumental activities of daily living. Although "PPCS" is a term most often used in the setting of mTBI, it is sometimes found in the peer-reviewed literature to refer to the post-TBI syndrome that occurs after moderate and severe TBIs.
- Chronic postsurgical or posttraumatic pain (CPPP): Recently defined by the International Academy for the Study of Pain (IASP) for inclusion in the ICD-11, CPPP is persistent pain that appears or worsens after tissue injury and outlasts the healing process (lasting for over 3 months) (18). CPPP was not considered in the ICD-10 classification.
- Central sensitization: This phenomenon, defined by the International Association for the Study of Pain, involves the increased responsiveness of nociceptive neurons in the central nervous system, leading to pain hypersensitivity. Central sensitization represents a range of severity levels and can coexist with other types of chronic pain, contributing to mixed pain types. Central sensitization results from molecular and structural modifications of neurons in the central nervous system.

Methods

Study Design and Patients

We retrospectively analyzed the medical records of patients evaluated in an outpatient neurology clinic from January 2020 to December 2023. Patients who had been diagnosed with mTBIs and chronic pain were

initially selected and later screened for the presence of persistent-post concussive syndrome. The study was approved by an investigational review board (Advarra, Austin, TX) and followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations for the reporting of observational cohort studies (19).

Diagnosis of mTBI

The diagnosis of mTBI is variable across expert criteria. Our diagnostic approach aligns with the Department of Veterans Affairs/Department of Defense criteria (3). Specifically, our criteria are as follows: evidence of a traumatically induced physiological disruption of brain function resulting from an external force; a score of 13-15 on the Glasgow Coma Scale; momentary loss of consciousness (LOC) lasting up to 30 minutes, a momentary alteration of consciousness/mental state (AOC) lasting up to 24 hours; the presence of post-traumatic amnesia for fewer than 24 hours or of transient (or potentially persistent) post-traumatic neurological deficits; an absence of abnormalities identified in standard structural imaging.

The diagnostic parameters above also meet the criteria guidelines provided by the following expert groups:

A. The Ontario Neurotrauma Foundation (20).
B. The Mayo Clinic's criteria for symptomatic TBI (21).
C. The 5th International Conference on Concussion in Sport (22).

To increase diagnostic specificity beyond these criteria, we have integrated guidelines from the American Congress of Rehabilitation Medicine into our routine practice (23). In these guidelines, emphasis is placed on objective neurophysiological data rather than solely subjective symptoms. Our diagnostic protocol consequently includes the assessment of cognitive functions with embedded validity indicators, tests of oculomotor function, quantitative EEG, and dynamic posturography.

Diagnosis of PPCS

PPCS diagnosis has also been marked by inconsistencies across various expert definitions (24). Many peer-reviewed studies have transitioned from the diagnostic symptomatology found in the ICD-10 or DSM-IV, favoring the Rivermead Post-Concussion Questionnaire for symptom selection (25). Typically, patients are diagnosed with post-concussion syndrome when they exhibit at least of the following 3 symptoms: headaches, dizziness, fatigue, irritability, impaired memory, impaired concentration, and insomnia. However, the methods of classification show variability, and an ongoing debate exists regarding the inclusion of symptom severity in the diagnostic criteria.

In our practice, we have established the presence of at least 4 symptoms from the previous list to enhance diagnostic specificity. Additionally, we require a diagnosis of a mild neurocognitive disorder attributable to TBI, as defined in the DSM-5 criteria and objective abnormalities on neurophysiological tests (26). This disorder must manifest immediately after the TBI or upon the return of consciousness and persist beyond the acute post-injury phase. Our approach is closely aligned with the DSM-5 criteria.

For the selection of medical records, the present investigation utilized the following inclusion and exclusion criteria:

Inclusion Criteria:

1. Patients met the criteria for mTBI.
2. Patients met the diagnostic criteria for PPCS (symptoms that had persisted beyond 3 months).

Exclusion Criteria:

1. Patients had a diagnosis of chronic pain preceding the diagnosis of mTBI.
2. Patients had abnormalities identified in the brain MRIs that would place them in a higher TBI category (e.g., brain contusion).
3. Patients were in the acute/subacute stage (fewer than 90 days post-injury).
4. Patients had neurological comorbidities that might have contaminated the objective findings (stroke, epilepsy, etc.).

All identifiable information was removed or de-identified before analysis.

Measuring Severity of PPCS

The severity of PPCS was measured using the Rivermead Post-Concussion Symptoms Questionnaire (RPQ) (27). The RPQ-16 encompasses the most common symptoms associated with post-concussion syndrome. This questionnaire ranks symptom severity on a 0-4 scale, with 0 implying no symptoms and 4 indicating severe difficulties. The maximum cumulative score on the RPQ-16 is 64. Eyres and colleagues refined the RPQ, partitioning it into RPQ-3 and RPQ-13 (28). The RPQ-3 focuses on early symptom clusters of post-concussive syndrome, whereas the RPQ-13 targets later clusters. This symp-

tom stratification improved test-retest reliability and established stronger positive correlations, with higher RPQ-13 scores signifying a more pronounced impact on function. We collected and analyzed both RPQ-3 and RPQ-13 data for the present study.

Objective Assessment of mTBI Using Videonystagmography (VNG) and Quantitative Electroencephalography (qEEG)

We employed VNG and qEEG techniques to supplement our clinical assessments. Although we do not use these techniques in isolation for the diagnoses of TBIs, they add objective evidence that substantiates the presence of a brain injury and assists specialists in guiding neurorehabilitation strategies.

VNG is a technique recognized for efficacy in detecting eye-movement abnormalities and vestibular pathology. This method proves especially relevant in TBI scenarios, given the susceptibility to injury of certain brain regions that control eye movements. Acquired data are processed and analyzed using computer algorithms to delineate potential vestibular or brain-related pathologies post-trauma (29).

Meanwhile, qEEG uses computer-based mathematical algorithms to numerically assess wave frequencies, amplitudes, and connectivity. The qEEG technique offers a refined evaluation of EEG data. Although it cannot be employed as a standalone diagnostic tool due to its poor specificity, qEEG aids in identifying objective anomalies, increasing confidence in diagnosing PPCS for therapeutic planning. Aberrations such as slow-wave changes, alterations in delta power, and discrepancies in specific wave frequency ratios have been noted in mTBI contexts (30). This method compares patient-specific data against a normalized database to pinpoint deviations from normalcy (31-33).

Measurement of Central Sensitization

Central sensitization was measured using the survey version of the instrument developed by Wolfe and adapted by Clauw for clinical research. This tool encompasses the Michigan Body Map, meant to evaluate the Widespread Pain Index (WPI), and a Symptom Severity Index (SSI), meant to evaluate for commonly occurring symptoms in central sensitization (34). The WPI is scored on a scale from 0-19, with each marking on the body map corresponding to one point. The SSI is scored on a scale from 0-12 with questions regarding fatigue, cognitive difficulty, and morning sleepiness over the past 7 days. Each symptom follows a scale of 0-3, with 0 corresponding to no symptoms and 3 meaning severe problems with the respective symptom. Additionally, patients can answer whether they have experienced abdominal pain or cramps, depression, or headaches in the past 6 months. The presence of these symptoms adds one to the total score. Due to the overlap in symptoms seen in the SSI and RPQ-16, the WPI was scored and analyzed separately from the SSI and compared to both the RPQ-13 and RPQ-3.

Statistical Methods

The statistical methods described above were implemented to elucidate underlying relationships among various outcomes in the context of PPCS. The primary outcome was to determine if there existed a correlative interaction between the degree of central sensitization and the extent of PPCS symptoms. We employed multiple regression analyses to determine if confounding variables might influence our scoring. One-way ANOVA was used to determine if gender or ethnicity influenced the patients' WPI, RPQ-3, or RPQ-13 scores. Simple linear regression analysis was used to investigate the influence of age on WPI, RPQ-3, or RPQ-13 scores.

We used simple linear regression to examine correlations between central sensitization and PPCS. The WPI was selected as a surrogate score for the severity of central sensitization and the RPQ scores for PPCS. Because items on the SSI of the CPI overlapped with the RPQ-13 cluster of the Rivermead questionnaire (which could introduce bias), multivariate analysis was focused on the correlation between the WPI or Michigan Body Map and Rivermead questionnaire components. All statistical analysis was conducted in JMP.

This multifaceted statistical approach provided a robust perspective on existing correlations within the instruments used, contributing to a more nuanced understanding of the factors influencing pain associated with PPCS. Those results allowed us to gain insight into the relationships between the level of central sensitization, as represented by CPI scores, and the severity of non-painful PPCS symptoms, as measured by the Rivermead scores.

Data-Sharing Statement

The data from this study are available upon request to the first author (CJF).

Results

Baseline Characteristics of the Population

The present investigation included an initial cohort

of 223 patients diagnosed with mTBI. Eighty-six of the original 223 patients were in the acute/subacute stage of PPCS (< 90 days between assessment and injury) or did not meet the inclusion or exclusion criteria and were excluded. Five patients were removed for being under the age of 18. Six patients were removed for having histories of seizures or epilepsy diagnoses. Five patients were removed for having a history of strokes, exhibiting cognitive decline, or having received cognitive-enhancing medication (Donepezil, supplements, etc.). Lastly, 3 patients were removed for having received previous diagnoses of chronic pain. A total of 67 patients were pursued for further analysis. A summary is shown in Fig. 1.

The demographic distribution of our selected patients consisted of 39 (58%) men and 28 (42%) women, with an average age of 45.7 years of age (range: 20-72 years). Ethnicity was divided into 26 (39%) Hispanic, 22 (33%) White, 12 (18%) Black or African American, and 7 (10%) Asian.

Correlation Between Central Sensitization and PPCS

A significant positive correlation was observed between WPI scores and SSI scores, at an $r^2 = 0.249$ ($P = < 0.0001$). As mentioned, the multivariate analysis focused on the WPI and the Rivermead components to prevent potential bias from overlapping symptoms between the SSI and the RPQ-13.

WPI scores exhibited a significant positive correlation with the RPQ-16 scores (Fig. 2), at an r^2 value of 0.093 ($P = 0.0122$). When the RPQ-3 and RPQ-13 subscales were considered, a significant positive correlation was found between WPI scores and both RPQ-3 and RPQ-13 (Fig. 3 and Fig. 4). Specifically, for RPQ-3, adjusted $r^2 = 0.123$ ($P = 0.0036$) and for RPQ-13, adjusted $r^2 = 0.066$ ($P = 0.0357$).

These results underscore the pronounced dose-response between central sensitization and PPCS symptoms. As the severity of a patient's widespread pain increased, there was a parallel escalation in the intensity of postconcussive symptoms.

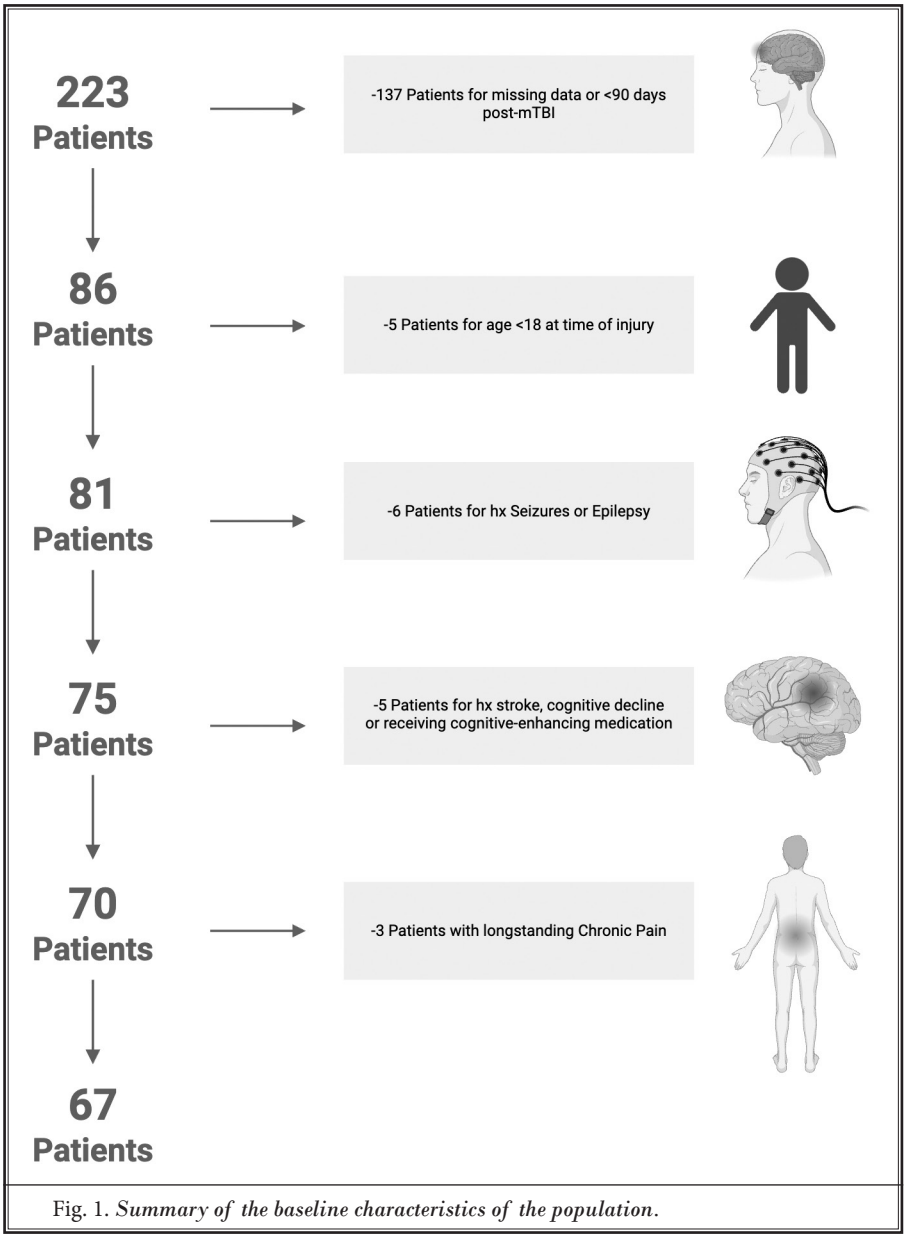

Fig. 1. *Summary of the baseline characteristics of the population.*

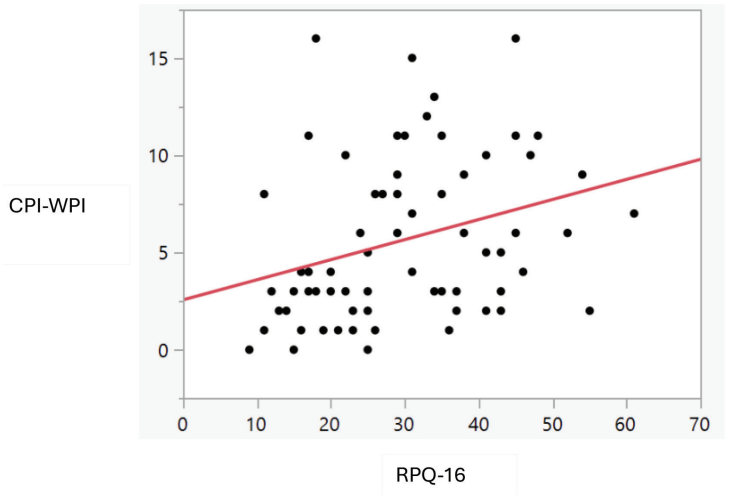

Fig. 2. *WPI vs. RPQ-16: A significant positive correlation between RPQ-16 and the CPI-WPI as shown by bivariate fit analysis (P = 0.0122).*

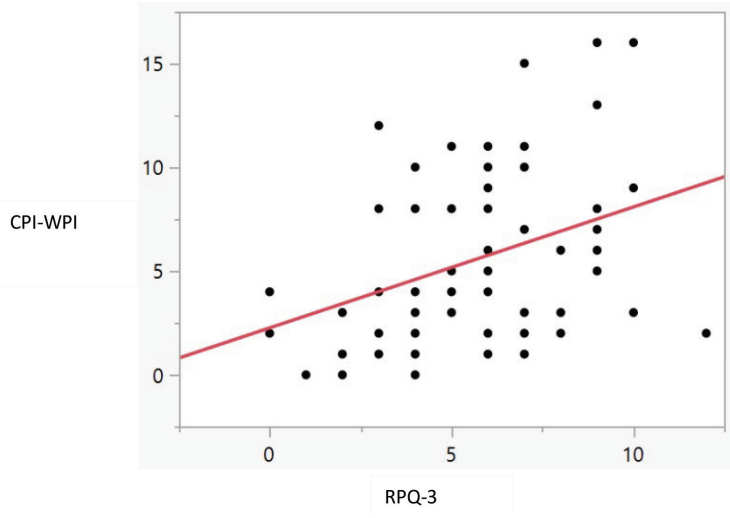

Fig. 3. *WPI vs. RPQ-3: A significant positive correlation between RPQ-3 and the CPI-WPI as shown by bivariate fit analysis (P = 0.0036).*

Influence of Age, Gender, and Ethnicity on CPI Scores by Bivariate Analysis

The mean CPI score across the cohort was 12.8. Thirty-two patients (48%) had scores greater or equal to 13 points, meeting the American College of Rheumatology's consensus criteria score for the diagnosis of fibromyalgia. No significant correlation was found between age and CPI scores (adj. r^2 = 0.018, *P* = 0.28). Similarly, no significant differences in CPI scores were found among gender or ethnicity categories (F = 13.29 vs. M= 12.54, *P* = 0.6349; r^2 = 0.066, *P* = 0.2243).

Influence of Age, Gender, and Ethnicity on RPQ Scores by Bivariate Analysis

The mean Rivermead score (RPQ-16) for patients with PPCS was 29.85, with an RPQ-3 mean of 5.8 and an RPQ-13 mean of 24. No significant correlation appeared between age and either RPQ-3 or RPQ-13 scores. For RPQ-3 versus age, R = 0.017 (*P* = 0.29) and for RPQ-13 versus age, R = 0.0004 (*P* = 0.87).

Nor did significant correlations emerge between gender and either RPQ-3 or RPQ-13 scores. The average RPQ-3 scores were 5.57 for men and 6 for women (*P* = 0.5951). For RPQ-13, the scores were 25.13 for men and 22.43 for women (*P* = 0.3185). Finally, no significant correlation was observed between ethnicity and either RPQ-3 or RPQ-13 scores. The mean square for RPQ-3 was 1.69 (*P* = 0.8533), and for RPQ-13, the mean square was 195.48 (*P* = 0.1725).

Relationship of Time Span to Injury Occurrence and Score Collection

We investigated whether the time span between the injury occurrence and score collection influenced outcomes. The present investigation found no significant correlations between the time of the Rivermead score collection and the initial injury date. For CPI scores against days between the injury, R = 0.0004 with *P* = 0.88. For RPQ-3, R = 0.003 with *P* = 0.63, and for RPQ-13, R = 0.004 with *P* = 0.60. These results suggest that the timing of the evaluation in relation to the injury was not a critical factor in the given severity of post-concussion symptoms.

qEEG and VNG Analysis

qEEG: All 67 patients underwent qEEG examinations, and all exhibited abnormalities mainly identified as slow-wave changes, increases in theta and/or delta activity, and dysregulations in the frontal and temporal lobes. All patients showed abnormalities of coherence (connectivity). Because we knew different technologies would capture different data, we used

Brain View Neural Scan (Medeia, Inc.) complemented by BrainMasters (BrainMaster Technologies) for capturing the average amplitude of different wave frequencies and Applied Neurosciences (Applied Neurosciences) for analysis of coherence.

Videonystagmography: For the VNG studies, we used automatic equipment and goggles with infrared cameras (Balanceback). Sixty-seven patients underwent VNG examination, which revealed that 65 of those patients had abnormalities associated with central TBI pathology. The most frequent of the deviations identified included abnormal saccades, abnormal smooth pursuits, or abnormal optokinetic nystagmus. Sixty-five out of 67 patients had at least one abnormal finding, including abnormal saccades (49 patients), abnormal smooth pursuits (44 patients), abnormal optokinetic nystagmus (43 patients), Hallpike maneuver abnormalities (12 patients), and abnormal nystagmus of central or peripheral origin (37 patients). Fifty-eight out of 67 patients had a combination of the mentioned abnormalities.

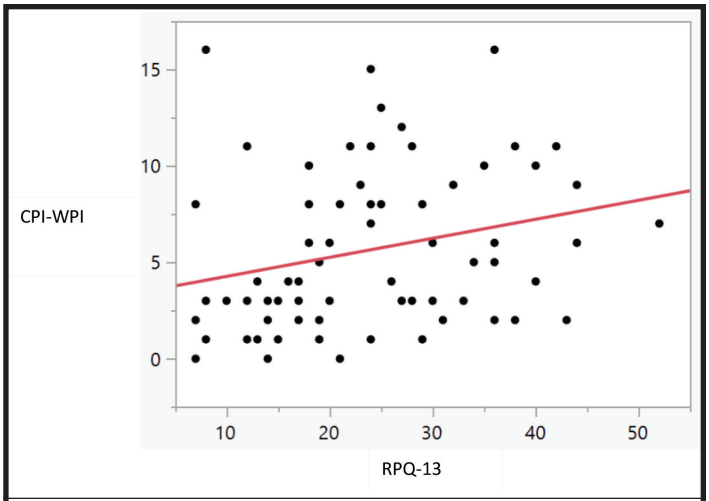

Fig. 4. *WPI vs. RPQ-13: A significant positive correlation between RPQ-13 and the CPI-WPI as shown by bivariate fit analysis ($P = 0.0357$).*

Discussion

Our main objective was to shed light on the mechanism of chronic pain in patients with mTBI. A large subgroup of patients with mTBI develop chronic pain, which is a major cause of disability. Here, we demonstrated that most of those patients exhibited high levels of central sensitization. In this study, we tried to determine if a correlative interaction existed between the degree of central sensitization and the extent of nonpainful PPCS symptoms. Our results showed that not only did patients with PPCS and chronic pain display high scores for central sensitization but, more importantly, that those scores correlated with the severity of non-painful post-concussive symptomatology. Although an association does not prove causation, the data suggest a mechanistic link between PPCS and chronic pain mediated by central sensitization rather than the interpretation that pain results from the activation of peripheral nociceptors.

Central sensitization, or the amplification of neuronal signals for pain within the central nervous system, leads to pain hypersensitivity (35). This process, facilitated by the brain and spinal cord, can lead to severe pain that surpasses the expected level based on nociceptive input or peripheral tissue damage (36). Central sensitization involves altered sensory processing, including temporal summation, and enhanced brain activity in pain-related regions like the insula, anterior cingulate cortex, and prefrontal cortex (37,38). Central sensitization is a primary mechanism underlying nociplastic and central neuropathic pain. The International Association for the Study of Pain (IASP) defines nociplastic pain as pain that arises from altered nociception without clear evidence of tissue damage or a lesion of the somatosensory system (35). In contrast, the IASP defines central neuropathic pain as pain associated with structural abnormalities in the somatosensory regions of the brain, as identified by structural imaging.

It is essential to recognize that patients with PPCS may also experience concomitant chronic pain mediated by peripheral nociceptive mechanisms. These mixed pain states coexist to varying degrees in individuals who have experienced extensive trauma. According to the latest IASP/ICD-11 classification scheme, peripheral nociceptive injuries are categorized under CPPP or chronic pain secondary to musculoskeletal pain (39). Therefore, an accurate assessment of the contributing mechanisms of each individual's pain is paramount, since treatments targeting central (i.e., brain) pain mechanisms differ substantially from those for nociceptive pain.

Wolfe developed a scoring system similar to that used by the American College of Rheumatology for fibromyalgia to gauge central sensitization in various types of pain (36,40,41). Subsequent studies found that the level of central sensitization predicted disability

and pain severity to a better degree than did more objective indicators of illness, such as inflammation or joint destruction (42,43). Furthermore, Brummett et al confirmed that the extent of central sensitization more accurately predicted response to interventions like surgery, spinal injections, or medications than did disease activity or imaging abnormalities (44). These findings highlight the dominant influence of the central nervous system in various types of chronic pain.

Interestingly, based on their CPI scores, 32 patients in our cohort (48%) meet the American College of Rheumatology criteria for the diagnosis of a fibromyalgia-like syndrome. Fibromyalgia is a widespread chronic pain syndrome with a higher prevalence in women than in men. The development of post-traumatic fibromyalgia has been a matter of ongoing debate (45,46). However, our study showed no significant differences in CPI scores between men and women. Despite the higher prevalence of fibromyalgia in women and their generally higher pain ratings, we anticipated observing a distinction in the scores.

PPCS is characterized by a host of coexisting symptoms, including fatigue, mood abnormalities, cognitive issues, and sleep disturbances, in addition to chronic pain (47). The characteristics of chronic pain following mTBI resemble those of chronic central pain from other causes, with painful regions exhibiting allodynia, hyperpathia, and windup (12). Chronic pain is a common complication of TBI, independent of psychological disorders such as PTSD and depression, and is prevalent even among patients with apparently minor injuries to the brain (4). Therefore, recognizing central sensitization as a key driver of pain in most patients with PPCS is a critical step toward understanding pain mechanisms in PPCS and devising more effective treatments for the condition (35,36).

Limitations

Our study has several limitations, one of which is its retrospective design. Also, the measures used to assess the variables were self-reported, subjecting the data to response and recall bias. Many of our patients with chronic symptomatology presented to the clinic were also involved in litigation, which might have influenced the results. Although the diagnosis of mTBI is primarily clinical, the presence of objective VNG and qEEG abnormalities mitigated this latter issue.

Conclusion

In conclusion, the present investigation underscores a pivotal clinical insight: central sensitization is an important mechanism underpinning chronic pain in patients with PPCS. Importantly, patients with pronounced central sensitization frequently describe intense pain in discrete body sites (e.g., spine, or joints). This factor can inadvertently lead health care specialists to concentrate on addressing these localized pain areas through antinociceptive treatments (e.g., nonsteroidal anti-inflammatory drugs or interventions), which are often ineffective. Recognizing central sensitization (often referred to as "central pain" or "brain pain") and differentiating it from nociceptive pain is essential for tailoring effective pain management strategies for these patients.

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