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THE PREVALENCE OF LYME DISEASE AND ASSOCIATED CO-INFECTIONS IN PEOPLE WITH A CHRONIC POST-CONCUSSIVE SYNDROME

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SUMMARY

Introduction: *There is increasing awareness that Lyme borreliosis (LB) and traumatic brain injury (TBI) may cause mental health symptoms. TBI and Lyme disease compromise the health and activities of millions of patients per year. The chronic symptoms and disability of TBI and Lyme disease share a similar clinical presentation. We have identified an alarming number of individuals suffering from post-concussion syndrome (PCS) that are refractory to care and that have serologically tested positive for Lyme disease.*

Subject and methods: *A single-center retrospective review of patient charts that were symptomatic a minimum of one year after a TBI that were tested for Lyme disease to ascertain if there was a relationship.*

Results: *217 PCS patient records (93 females with a mean age of 34 years, 120 males with a mean age of 40 years and 4 individuals with unknown gender) were included in the review. 38% had a positive Western Blot Igenex IgM. There was a statistically significant relationship of a positive Western Blot Igenex IGM predicting chronic PCS Pearson* $\chi^2(1)=6.8866$, $P=0.009$, *Fisher's exact score* $p=0.015$ *and* $\phi=0.2813$ *representing a moderate effect size.*

Conclusions: *Long term PCS over one year's duration is associated with undiagnosed Lyme disease. There was statistical and substantive significance between individuals with chronic PCS having a positive Western Blot Igenex IgM. Males were more likely to have a positive Western Blot Igenex IgM than females.*

Key words: *Lyme disease - traumatic brain injury - post-concussion syndrome - mental illness*

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INTRODUCTION

Traumatic brain injuries (TBI) and Lyme disease compromise the health and activities of millions of patients per year. The chronic symptoms and disability of TBI and Lyme disease share a similar clinical presentation. Lyme disease causes immune and metabolic effects that result in a gradually developing spectrum of neuropsychiatric symptoms, usually presenting with significant comorbidity which may include developmental disorders, autism spectrum disorders, schizoaffective disorders, bipolar disorder, depression, anxiety disorders (panic disorder, social anxiety disorder, generalized anxiety disorder, posttraumatic stress disorder, intrusive symptoms), eating disorders, decreased libido, sleep disorders, addiction, opioid addiction, cognitive impairments, dementia, seizure disorders, suicide, violence, depersonalization, dissociative episodes, derealization and other impairments (Bransfield 2018).

Moreover, current evidence suggests a link between sports-related concussion and depression symptoms in elite athletes (Rice et al. 2018) and students who experience a concussion may be at increased risk for poor mental health outcomes, including suicide attempts (Yang et al. 2019). Our specialist TBI clinic has appreciated an alarming incidence of Lyme disease in patients suffering from a post-concussion syndrome (PCS) secondary to TBI. Furthermore, we have witnessed a dramatic improvement in function and reduction in disability following treatment of these patients. TBI, according to the World Health Organization, will surpass many diseases as the major cause of death and disability by the year 2020. With an estimated 10 million people affected annually by TBI, the burden of mortality and morbidity that this condition imposes on society makes TBI a pressing public health and medical problem (Hyder et al. 2007). TBIs are categorized into mild, moderate and severe based on clinical factors such as the severity of the injury, and loss of consciousness. Eighty to ninety percent of TBIs are classified as mild and labeled concussions. Despite many concussions healing relatively quickly, a number of these patients are refractory to treatment and have persistent disabling symptoms referred to as PCS. Furthermore, according to

the Centers for Disease Control and Prevention (CDC), Lyme disease is the most commonly reported vector-borne illness and the fifth most common disease in the National Notifiable Diseases Surveillance System, making it a significant public health concern (Younger et al. 2016). The Neurological manifestations of Lyme disease, called Neuroborreliosis, are reported in up to 15% of patients with Lyme disease (Rice et al. 2018, Yang et al. 2019) with symptoms similar to those of PCS. Despite numerous studies and increased awareness of concussions, there continues to be a paucity of understanding regarding why some patients recover and others remain symptomatic. Our clinical team attends TBI, PCS and Lyme patients that are referred to us from around the globe. We have identified an alarming number of individuals suffering from PCS that are refractory to care and that have serologically tested positive for Lyme disease. As a consequence, we were interested in testing PCS patients for Lyme disease that had no history of or testing for Lyme disease.

Research Question

We desired to investigate the prevalence of Lyme disease and co-infections in our PCS patients that remained symptomatic over one year after a TBI. We searched a variety of databases for randomized controlled trials of PCS and Lyme Disease up until January 2018 without success. Our search included Cochrane Injuries Group's specialized register, Cochrane Depression, Anxiety and Neurosis Group's specialized register, Cochrane Central Register of Controlled Trials, MEDLINE, PsycINFO, EMBASE, CINAHL, AMED, ERIC, and PsycBITE. Because of the lack of research in this area, we decided to perform a retrospective chart review of our patients that were symptomatic a minimum of one year after a TBI that we also had tested for Lyme disease to ascertain if there was a relationship.

Hypothesis

Based on our experience and clinical observations, we hypothesized that a significant percentage of patients with PCS symptomatology that are symptomatic after 1 year from the date of injury might continue to be symptomatic due to ongoing undiagnosed and untreated Lyme disease or associated co-infection.

SUBJECTS AND METHODS

The study was a single-center retrospective review of patient charts performed at our clinical facility in San Francisco, California. All charts were anonymized ensuring patient confidentiality appropriate to the Declaration of Helsinki and approved by the Carrick Institute for Graduate Studies Institutional Review Board. We reviewed the complete history of current complaints, past history, social history, surgical and medication history, social history, review of symptoms and family history to identify all inclusionary and exclusionary factors. Each record that was accepted in our review met the study criteria for inclusion and was not disqualified by any of the exclusionary criteria.

Inclusion criteria

- All participants had at least one PCS symptom (e.g., headache, irritability, dizziness, vertigo, difficulty concentrating) for more than 12 months in combination with a negative brain computed tomography (CT) or magnetic resonance imaging (MRI) scan.
- All participants had undergone testing for Lyme disease at our facility that included IgG Western Blot and IgM Western Blot.

Exclusion criteria

- Patients that previously tested serologically positive for Lyme and /or co-infection.
- Patients that have had ≥ 2 weeks of antibiotics since the date of injury.
- Patients with other diagnosed primary neurological illness such as seizure disorder, or multiple sclerosis.
- Post-stroke syndrome.

Statistical Analysis

The statistical analysis was performed using STATA 14 (College Station, Texas). Linear and Logistic regression models and correlations were fitted to identify any laboratory predictors of TBI and effect size was identified by Eta Squared and Cohen d calculations.

RESULTS

Our review identified 217 PCS patient records that met our criterion (93 females with a mean age of 34 years, 120 males with a mean age of 40 years and 4 individuals with unknown gender). The normality of the distributions of data was verified using Kolmogorov-Smirnov with Lilliefors Significance Correction and Shapiro-Wilk tests of normality. A linear regression model including all laboratory tests and including males and females revealed a high statistically significant predictor of PCS if the patient had a positive Western Blot Igenex IgM test ($P<0.0001$). We removed the subjects that had unknown values for TBI and Western Blot Igenex IgM from the analysis to consider only those subjects with data for both of these variables. This reduced the sample from 217 to 87 subjects (18 without a history of TBI and 69 with a history of TBI). Of the remaining subjects with a history of TBI, 37.68% had a positive Western Blot Igenex IgM while 62.32% did not. For those remaining patients without a history of TBI, 72.22% had a positive Western Blot Igenex IgM, and 27.78% had a negative Western Blot Igenex IgM. An examination of the relationship between a history of

TBI and Western Blot Igenex IgM revealed a Pearson $\chi^2(1)=6.8866$, P=0.009 and a Fisher's exact score p=0.015. ϕ was calculated as 0.2813 representing a moderate effect size. A ϕ with an absolute value from 0.0 to 0.19 is considered weak, from 0.20 to 0.49 is considered moderate, and from 0.50 and above is considered strong (Table 1).

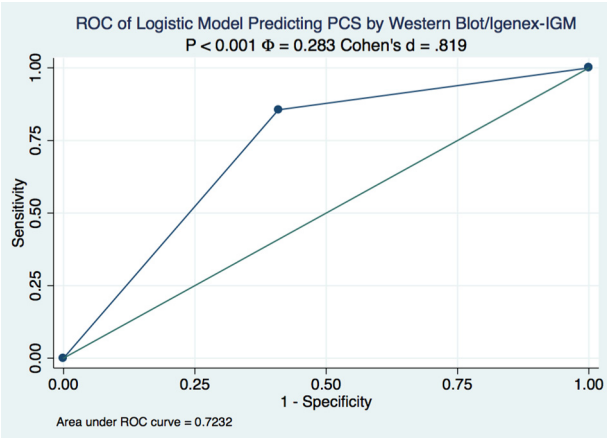

Figure 1. ROC of Logistic Model Predicting PCS by Western Blot/Igenex-IGM

We desired to assess the discrimination of a fitted logistic model, via the receiver operating characteristic (ROC) curve in patients with chronic PCS and Western Blot Igenex-IgM. We plotted the values of sensitivity against one minus specificity, as the value of the cut-point was increased from 0 through to 1. A model with high discrimination ability will have high sensitivity and specificity simultaneously, leading to a ROC curve which goes close to the top left corner of the plot. A model with no discrimination ability will have a ROC curve that is the 45-degree diagonal line. The area under the ROC curve (AUC) can range from 1 (perfect discrimination) to 0.5 (no discrimination). A fitted logistic model of PCS subjects predicted by Western Blot Igenex-IgM had good discrimination values (AUC=0.7232). The Cohen's d=0.819 representing a strong effect size (Figure 1).

We analyzed male and female subjects removing those that had unknown values for TBI and Western Blot Igenex IgM from the analysis (50 females and 36 males). Of the female subjects with a history of TBI, 36.59% had a positive Western Blot Igenex IgM while 63.41% did not. For those remaining female subjects without a history of TBI but with PCS like symptoms, 77.78% had a positive Western Blot Igenex IgM, and 22.22% had a negative Western Blot Igenex IgM. An examination of the relationship between a history of TBI and Western Blot Igenex IgM in female subjects revealed a Pearson $\chi^2(1)=5.0822$, P=0.024 and a Fisher's exact score p=0.032. ϕ was calculated as 0.3188 representing a moderate effect size (Table 2).

Table 1. TBI and Western Blot Igenex-IgM History in Subjects with chronic PCS Symptoms

		Western Blot/Igenex-IgM for All Subjects					
	TBI	Negative	Positive	Total	χ^2	ϕ	P
Frequency	No	5	13	18			
χ^2 contribution		2.40	3.00	5.50			
Row percentage		27.78	72.22	100.00			
Frequency	Yes	43	26	69			
χ^2 contribution		0.60	0.80	1.40	6.866	0.2813	0.009
Row percentage		62.32	37.68	100.00			
Frequency	Total	48	39	87			
χ^2 contribution		3.10	3.80	6.90			
Row percentage		55.17	44.83	100.00			

Table 2. TBI and Western Blot Igenex-IgM History in Females with chronic PCS Symptoms

		Western Blot/Igenex-IgM for Female Subjects					
	TBI	Negative	Positive	Total	χ^2	ϕ	P
Frequency	No	2	7	9			
χ^2 contribution		1.80	2.30	4.20			
Row percentage		22.22	77.78	100.00			
Frequency	Yes	26	15	41			
χ^2 contribution		0.40	0.50	0.90	5.0822	0.3188	0.024
Row percentage		63.41	36.59	100.00			
Frequency	Total	28	22	50			
χ^2 contribution		2.20	2.80	5.10			
Row percentage		56.00	44.00	100.00			

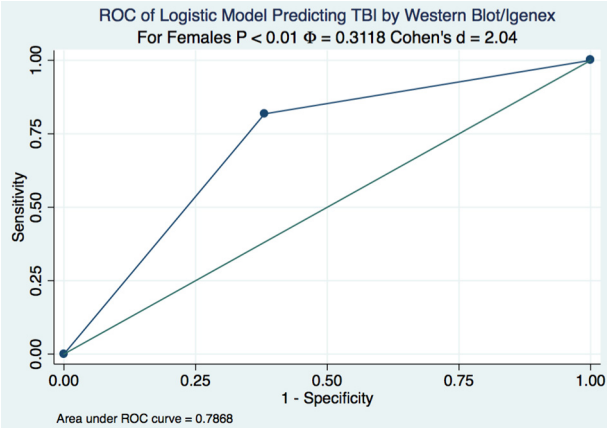

Figure 2. ROC of Logistic Model Predicting TBI by Western Blot/Igenex for Females

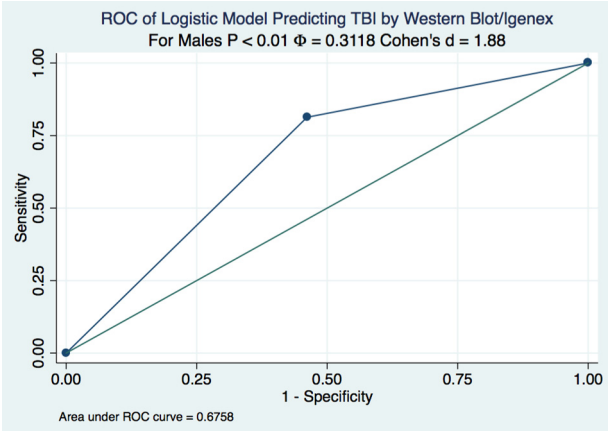

Figure 3. ROC of Logistic Model Predicting TBI by Western Blot/Igenex for Males

We desired to assess the discrimination of a fitted logistic model, via the receiver operating characteristic (ROC) curve in female patients with chronic PCS and Western Blot Igenex-IgM. We plotted the values of sensitivity against one minus specificity, as the value of the cut-off point was increased from 0 through to 1. A fitted logistic model of PCS subjects predicted by Western Blot Igenex-IgM had good discrimination values (AUC=0.7470). The Cohen's d =0.819 represents a strong effect size (Figure 2).

Of the male subjects with a history of TBI, 39.29% had a positive Western Blot Igenex IgM while 60.71% did not. For those remaining male subjects without a history of TBI but with chronic PCS like symptoms, 75.00% had a positive Western Blot Igenex IgM, and 25.00% had a negative Western Blot Igenex IgM. An examination of the relationship between a history of TBI and a positive Western Blot Igenex IgM in male subjects revealed a Pearson $\chi^2(1)=3.1844$, P=0.074 and a Fisher's exact score of 0.114. ϕ was calculated as 0.2974 representing a moderate effect size (Table 3).

We desired to assess the discrimination of a fitted logistic model, via the receiver operating characteristic (ROC) curve in male patients with chronic PCS and Western Blot Igenex-IgM. We plotted the values of sensitivity against one minus specificity, as the value of the cut-off point was increased from 0 through to 1. A fitted logistic model of PCS subjects predicted by Western Blot Igenex-IgM had fair discrimination values (AUC=0.6758) that were less than those calculated for females, however, the Cohen's d=1.18 represented a strong effect size but less than that calculated for females (Figure 3).

37.68% of the sample of subjects that had suffered a TBI and had longstanding PCS symptoms had a positive Western Blot Igenex IgM. Males were more likely to have a positive Western Blot Igenex IgM (39.29%) than females (36.59%).

We removed the subjects that had unknown values for TBI and Western Blot Igenex IgG from the analysis to consider only those subjects with data for both of these variables. This reduced the sample from 217 to 87 subjects (18 without a history of TBI and 70 with a history of TBI). Of the remaining subjects with a history of TBI, 25.71% had a positive Western Blot Igenex IgG IgM while 74.29% did not. For those remaining patients without a history of TBI, 33.33% had a positive Western Blot Igenex IgG, and 66.67% had a negative Western Blot Igenex IgG. An examination of the relationship between a history of TBI and Western Blot Igenex IgG revealed a Pearson $\chi^2(1)=0.4190$, P=0.517 that was not statistically significant with a Fisher's exact score p=0.559. ϕ was calculated as 0.0690 representing a weak effect size (Table 4).

Table 3. TBI and Western Blot Igenex-IgM History in Males with chronic PCS Symptoms

		Western Blot/Igenex-IgM for Male Subjects					
	TBI	Negative	Positive	Total	χ^2	ϕ	P
Frequency	No	2	6	8			
χ^2 contribution		1.20	1.30	2.50			
Row percentage		25.00	75.00	100.00			
Frequency	Yes	17	11	28			
χ^2 contribution		0.30	0.40	0.70	3.1844	0.3188	0.074
Row percentage		60.71	39.29	100.00			
Frequency	Total	19	17	36			
χ^2 contribution		1.50	1.70	3.20			
Row percentage		52.78	47.22	100.00			

Table 4. TBI and Western Blot Igenex-IgG History in Subjects with chronic PCS Symptoms

		Western Blot/Igenex-IgG for all Subjects					
	TBI	Negative	Positive	Total	χ^2	ϕ	P
Frequency	No	12	6	18			
χ^2 contribution		0.10	0.20	0.30			
Row percentage		66.67	33.33	100.00			
Frequency	Yes	52	18	70			
χ^2 contribution		0.00	0.10	0.10	0.4190	0.0690	0.517
Row percentage		74.29	25.71	100.00			
Frequency	Total	64	24	88			
χ^2 contribution		0.10	0.30	0.40			
Row percentage		72.73	44.00	100.00			

Table 5. TBI and Western Blot Igenex-IgG History in Females with chronic PCS Symptoms

		Western Blot/Igenex-IgG for Female Subjects					
	TBI	Negative	Positive	Total	χ^2	ϕ	P
Frequency	No	9	0	9			
χ^2 contribution		0.60	2.00	2.50			
Row percentage		100.00	0.00	100.00			
Frequency	Yes	30	11	41			
χ^2 contribution		0.10	0.40	0.60	3.0957	0.2488	0.079
Row percentage		73.17	26.83	100.00			
Frequency	Total	39	11	50			
χ^2 contribution		0.70	2.40	3.10			
Row percentage		78.00	22.00	100.00			

Table 6. TBI and Western Blot Igenex-IgG History in Males with chronic PCS Symptoms

		Western Blot/Igenex-IgG for Male Subjects					
	TBI	Negative	Positive	Total	χ^2	ϕ	P
Frequency	No	3	5	8			
χ^2 contribution		1.10	2.20	3.30			
Row percentage		37.50	62.50	100.00			
Frequency	Yes	22	7	29			
χ^2 contribution		0.30	0.60	0.90	4.2109	0.2488	0.040
Row percentage		75.86	24.14	100.00			
Frequency	Total	25	12	37			
χ^2 contribution		1.40	2.80	4.20			
Row percentage		67.57	32.43	100.00			

We analyzed male and female subjects removing those that had unknown values for TBI and Western Blot Igenex IgG from the analysis (50 females and 36 males). Of the female subjects with a history of TBI, 26.83% had a positive Western Blot Igenex IgG while 73.17% did not. For those remaining female subjects without a history of TBI but with PCS like symptoms, none had a positive Western Blot Igenex IgG, and 100% had a negative Western Blot Igenex IgG. An examination of the relationship between a history of TBI and Western Blot Igenex IgG in female subjects revealed a Pearson $\chi^2(1)=3.0957$, P=0.079 that was not statistically significant with a Fisher's exact score p=0.177. ϕ was calculated as 0.2488 representing a moderate effect size (Table 5).

Of the male subjects with a history of TBI, 24.14% had a positive Western Blot Igenex IgG while 75.86% did not. For those remaining male subjects without a history of TBI but with PCS like symptoms, 62.50% had a positive Western Blot Igenex IgG, and 37.50% had a negative Western Blot Igenex IgG. An examination of the relationship between a history of TBI and Western Blot Igenex IgG in female subjects revealed a Pearson $\chi^2(1)=4.2109$, P=0.040 that was statistically significant with a Fisher's exact score p=0.083. ϕ was calculated as 0.3374 representing a moderate effect size (Table 6).

TBI and Western Blot Igenex-IgG history in Males with chronic PCS symptoms are statistically significant with a moderate effect size, whereas there is no significant relationship that was found in female subjects. TBI and Western Blot Igenex-IgM have both statistical and substantively significant relationships.

DISCUSSION

Traumatic brain injuries are a significant cause of death and disability among people of all ages affecting approximately 10 million people worldwide (Yang et al. 2019). According to the US Center for Disease Control and Prevention (CDC), in 2010 about 2.5 million emergency department (ED) visits, hospitalizations, or deaths were associated with TBI (https://www.cdc.gov/). Over the past decade, concussions have been widely discussed concerning contact sports, motor vehicle accidents, and as the signature injury of soldiers. They also occur in falls among the elderly and victims of domestic abuse. Most patients with mild traumatic brain injury (mTBI) recover rather quickly, but other report persistent symptoms of PCS, the underlying pathophysiology of which is mostly unknown (Blennow et al. 2016). The CDC estimates the annual rate of concussion to be approximately 1.4–3.8 million. However, these numbers are likely to be an under-estimate, because a large number of concussions go unnoticed and unreported. PCS is a complex disorder characterized by multiple pathophysiological processes or "polypathology" whose main features are white matter degradation, neuronal loss, protein misfolding, and persistent neuroinflammation. Alterations in the neurotransmitter and neuroendocrine systems are also widespread (Newcombe et al. 2011, Stocchetti et al. 2016). The symptoms of PCS include headache, dizziness, neck pain, exercise intolerance, irritability, anxiety, insomnia or other sleep problems, cognitive problems and memory loss, poor concentration, difficulty with problem-solving, noise and light sensitivity and affective symptoms. In clinical practice, the symptoms are often subjective, vague, and non-specific, making the diagnosis of PCS difficult (Radhakrishnan et al. 2016). Despite emerging new understandings of the pathophysiology of these injuries, there is relatively little sound epidemiological data to predict risk factors for PCS accurately. Numerous studies have documented risk factors such as age (children and elderly being more susceptible than adults), female sex, injury-related litigation, pre-existing stress and premorbid psychiatric or cognitive conditions (such as learning disabilities) (Radhakrishnan et al. 2016, Bernard et al. 2016). Additionally, several genetic polymorphisms involving brain-derived neurotrophic factor (BDNF) and the interleukins (IL) have been shown to have a potential effect on the severity of an axonal injury, inflammation, blood-brain barrier disruption, neuronal survival, regeneration, and plasticity. One of the most documented allelic variations present in individuals who experience poor recovery post-TBI is the E4 allele. The apolipoprotein E4 allele is the most neurotoxic isoform due to an induction of neuropathology via proteolytic cleavage and reduced growth and branching of neurites (Davidson et al. 2015). It has long been known that the production of cytokines is increased in the brain following contusions, with an expression of IL-6, IL-1b, and TNF-a by mononuclear cells and IL-1b by astrocytes (Rathbone et al. 2015). However, there has been little reported on the role of systemic infections such as Lyme disease that present with a similar profile of symptoms. A relatively inexpensive and widely used blood test to assess the prevalence of Lyme disease in PCS would dictate the need for appropriate antimicrobial treatment to cure the infection. It is likely that this intervention, could also alleviate symptoms such as cognitive disturbances, dizziness, and fatigue. Given the cost of interventions for PCS, the diagnosis and treatment of co-morbid infections could prove to have a significant impact on the standard of care of PCS. We have identified that specific Lyme blood markers are statistically significant predictors of PCS in our patient population. We do not know if this correlation is specific to our clinical population of PCS patients or if there is a general or global association. Numerous plausible mechanisms may account for our findings correlating PCS and LNB that warrant further investigation. Furthermore, we believe that many of these individuals suffering from PCS are compromised due to secondary LNB. Despite numerous theories and much speculation, our extensive review of the literature reveals that several questions remain to be answered.

Is there a large subset of the population infected with the B. Burgdorferi spirochetes that are mostly asymptomatic or is their infection being misdiagnosed given we know LD to be the "great imitator? It has been well understood that despite inducing both innate and adaptive immune responses, B. burgdoferi senso latu species is one of the few extracellular pathogens that can cause persistent asymptomatic infection in various species, especially rodents (Tracy et al. 2017, Bernard et al. 2018). This mechanism of pathogens surviving with minimal effects on its host is referred to a reservoir host, and its persistence can be in part due to a multitude of factors that requires further study as to its relevance in humans. Tracy and Bumgarth, (Tracy et al. 2017) present a detailed overview of eight factors contributing to persistence of Borrelia burgdorferi in rodent hosts, some mechanisms of which have already been studied in humans: Spirochete shape (Charon et al. 2002, Moriarty et al. 2008) antigenic variation and changes in gene expression (Rogovskyy et al. 2015, Grimm et al. 2004, Norris et al. 2014) plasminogen binding and destruction of the extracellular matrix (Coleman et al. 1999) interference with the adaptive immune response, (Elsner et al. 2015a, Hastey et al. 2012, Elsner et al. 2015b) host-pathogen co-evolution, tick salivary

protein-mediated immunosuppression (Kotal et al. 2015) adhesions allowing entrance into the vasculature and tissue (Coburn et al. 2013, Brissette et al. 2014), and interference with complement via CRASPs, and BBK32 (Garcia et al. 2016, de Taeye et al. 2013, Kraiczy et al. 2016, Pietikainen et al. 2010). Bernard, Pal, et al. Recently reported a discovery of BBA57, a spirochete surface protein of unknown function that "orchestrates unique host immune evasion strategies crucial for early spirochete infection in mammals, suppresses host complement-mediated killing and neutrophil-derived microbicidal responses, including induction of antimicrobial peptides, and promotes pathogen dissemination by regulating type 1 interferon." (Bernard et al. 2018). Furthermore, earlier studies reported positive serology in a population at risk, but clinical disease occurred infrequently (Fahrer et al. 1991, Zhioua et al. 1998).

Some theorize that the majority of Lyme disease patients are cured relatively quickly; however, approximately 10% have prolonged somatic and neurocognitive symptoms, such as fatigue, difficulty in sleeping, arthralgia, myalgia, memory impairment, and headache (Cairns 2005) termed Post Lyme disease syndrome (PLDS) or post-treatment Lyme disease syndrome (PTLDS). A recent study conducted at Tulane University revealed that spirochetes, that can evade the immune response, were able to infect vital organs such as the brain and heart, despite a traditional 28-day course of Doxycycline (Embers et al. 2017). It was also found that all subjects treated with antibiotics were found to have some level of infection 7 -12 months post-treatment, and despite testing negative by antibody tests for Lyme disease, two of 10 subjects were still infected with Lyme bacteria in heart and bladder (Embers et al. 2017). Fallon et al. observed significantly reduced blood flow in certain white matter areas of the brain, particularly in the posterior temporal and parietal lobes bilaterally, in patients with post-LB syndrome compared with healthy subjects, flow reductions in white matter areas were significantly associated with deficits in memory and visuospatial organization. These studies do not explore whether the patients that have such sequela have had a history of TBI or PCS (Fallon et al. 2003, Fallon et al. 2009).

The anatomic and physiologic changes witnessed following a TBI, such as hypoxia, alteration in glucose metabolism, a significant increase in proinflammatory cytokines IL-6, IL-1b, and TNF-a by mononuclear cells and IL-1b by astrocytes to the blood-brain barrier, maybe allow pre-existing autoreactive T-cells to transmigrate into the central nervous system (Pachter et al. 2003). We anticipate that future epidemiological investigation can determine the likelihood of patients developing PLDS/PTLDS or PCS secondary to previous exposure of LD or TBI. Understanding such might provide significant impact in understanding the pathophysiology of PCS and neurodegenerative conditions such as Chronic Traumatic Encephalopathy (CTE). Hazeldine et al. provide a comprehensive overview of the underlying mechanisms of systemic immune suppression involving neutrophils, monocytes, natural killer cells, and T cells, following TBI (Hazeldine et al. 2015). These mechanisms substantially increase the risk of infections. We opine that if a high number of subclinical infections, asymptomatic, and/or misdiagnosed cases exist, then compromise of the blood-brain barrier and immunological suppression as a result of TBI might explain our observations.

CONCLUSIONS

Our retrospective review of records of patients seen in our facility suffering from mental health issues and PCS over one year's duration is significantly associated with undiagnosed Lyme disease. We found that there was statistical and substantive significance between individuals with chronic PCS who had suffered a TBI and having a positive Western Blot Igenex-IgM test. We also found that males who had suffered a TBI and had chronic PCS also had statistical and substantively significant relationships with a positive Western Blot Igenex-IgG. 37.68% of the sample of subjects that had suffered a TBI and had longstanding PCS symptoms had a positive Western Blot Igenex IgM. Males were more likely to have a positive Western Blot Igenex IgM (39.29%) than females (36.59%). This relationship demands an adequately designed multi-site randomized controlled study that might provide insights into the relationship of undiagnosed Lyme disease complicating recovery in PCS patients. We suggest that it may be worthwhile to test for Lyme Disease in PCS patients, with and without mental health issues even if they have no history of a known Tick bite.

Limitations

This is a single site review of records that does not allow generalization to the global population of PCS patients. Furthermore, due to the lack of standardization of Lyme disease laboratory testing, it is possible that differing labs will yield varying results. As a records review, the report does not have the benefit of a robustly designed randomized controlled trial.

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Conflict of interest: *None to declare.*

Contribution of individual authors:

Sergio Azzolino conceived the idea for the study and contributed to the literature review, statistical analysis and revised the manuscript.

Rashid Zaman & Ahmed Hankir contributed to the literature review and revised the manuscript.

Frederick Carrick collected and analysed the data and contributed to the literature review and revised the manuscript.

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