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Title: Neuropsychiatric Borreliosis/Tick-Borne Disease: An Overview

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Neuropsychiatric Borreliosis/Tick-Borne Disease: An Overview

Abstract

There is increasing evidence and recognition that Lyme borreliosis, and other associated tick-borne diseases (LB/TBD) cause mental symptoms. Data was drawn from databases, search engines and clinical experience to review current information on LB/TBD. LB/TBD infections cause immune and metabolic effects that result in a gradually developing spectrum of neuropsychiatric symptoms, usually presenting with significant comorbidity and 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, anhedonia, depersonalization, dissociative episodes, derealization and other impairments. Screening assessment followed by a comprehensive psychiatric clinical exam relevant to patient's complaints and findings with a thorough history, mental status exam, review of systems, neurological exam, physical exam, a knowledgeable interpretation of laboratory findings, pattern recognition and clinical judgment facilitate diagnosis. Psychotropics and antibiotics may help improve functioning and prevent further disease progression. Awareness of the association between LB/TBD and neuropsychiatric impairments and studies of their prevalence in neuropsychiatric conditions can improve understanding of the causes of mental illness and violence and result in more effective prevention, diagnosis and treatment.

Keywords: Lyme disease; *Borrelia burgdorferi*; tickborne diseases; persistent infection; treatment; assessment; depression; anxiety; sleep disorders; opioid addiction

Background

Lyme disease is caused by *Borrelia burgdorferi*, other *Borrelia* species and other tick-borne and opportunistic infections may be present as well [1]. There is increasing evidence and recognition that Lyme borreliosis and other associated tick-borne diseases (LB/TBD) cause mental symptoms. Currently there are over 400 peer-reviewed articles addressing different aspects of neuropsychiatric symptoms caused by LB/TBD [2].

Although mental illnesses have been categorized based upon symptoms and syndromes since 1952 by the American Psychiatric Association in Diagnostic and Statistical Manuals (DSM), this categorization does not address the actual cause of mental illnesses [3]. Mental illness is associated with an impairment of adaptive capabilities and the causes of these impairments need to be viewed from perspectives of the multisystem interaction of multiple contributors and deterrents and how this impacts pathological process that progresses over time. Less complex and better understood disease models consist of well-defined and more limited causes, pathophysiology and clinical presentations. The diseases that are more challenging to understand consist of multiple contributors, multiple pathophysiological pathways and multiple disease presentations.

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Several developments have helped our understanding of complex disease—evolutionary medicine, the better recognition of the role of chronic infections in chronic disease and attention to the human microbiome. Evolutionary or Darwinian medicine, recognizes a significant cause of disease is trauma from competing organisms, such as microbes [4]. The Center for Disease and Prevention of the United States (CDC) has stated that clinicians and policymakers must recognize that many chronic diseases may indeed have infectious origins [5]. The National Institute of Health Human Microbiome Project recognizes bacterial cells outnumber human cells by 10 to 1, humans depend on their microbiome and a person should really be considered a superorganism [6]. Although the Infectome is beneficial to health in many ways, there are thousands of articles demonstrating a causal association between infections and mental illness, especially viral, venereal and vector-borne diseases [2].

When mental hospitals were filled with syphilitic patients everyone recognized infections caused mental illness. After penicillin helped control this epidemic there was a reduced attention to the association between infectious disease and mental illness. Subsequently, attention to evolutionary concepts, the microbiome and psychoimmunology facilitated by microarray testing and further research reactivated attention to the role of infectious contributors to the pathogenesis of mental illness. There are currently over 100 different infectious agents known to cause mental illnesses, including spirochetes, other bacteria, viruses, parasites, protozoa, parasites, yeast, fungi and prion [7,8].

One of the contributors to mental illness includes infectious diseases and the immune reactions to them. A number of infections, including LB/TBD have evolved as particularly significant models explaining the association between infections and the development of mental illness. Although there have been some prior neuropsychiatric LB/TBD general review articles, no other neuropsychiatric LB/TBD journal articles have been published recently and a more current review was needed. [7,9,10,11].

Materials and Method

Data for this article was drawn from a database maintained by the author that includes all the journal articles addressing LB/TBD and their association with neuropsychiatric symptoms, other articles and presentations on the subject and experience from treating thousands of LB/TBD patients over decades. These articles were reviewed to look for current information on LB/TBD and neuropsychiatric symptoms. The medical literature was also reviewed with PubMed and Google Scholar searches for additional information in a number of categories which included pathophysiology, clinical presentations, assessment and treatment. Particular attention was given to valid research articles that calculated the prevalence of acquired neuropsychiatric findings in LB/TBD patients post infection. When statistics were drawn from the Aggressiveness, Violence, Homicidality, Homicide and Lyme Disease article; the non-homicidal group was used unless otherwise stated [12].

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Results

Pathophysiology

Many infections are associated with an early inflammatory reaction followed by adaptive immunity and a resolution of symptoms, but in some chronic infections that evade and suppress the immune system, such as *B. burgdorferi and other Borrelia*, inflammation can persist without adaptive immunity, autoimmune symptoms may occur, and reinfections are common. [2,13,14,15,16,17].

There are three basic types of *B. burgdorferi* infections causing neuropsychiatric symptoms—the meningovascular form associated with cerebrovascular infarcts; infection within the central nervous system (CNS) which is the atrophic form of Lyme meningoencephalitis and is associated with cortical atrophy, gliosis and dementia and the third is infection outside the CNS causing immune and other effects within the CNS that contribute to neuropsychiatric symptoms. A LB/TBD patient with neuropsychiatric symptoms may have one or more than one of these three types of infections [18,19,20].

Although some injury to the host is a result of the direct action of the parasite upon the host, more often the immune reaction to the infection that results in symptoms in the host. Articles have described how the immune and psychoimmune response to *B. burgdorferi* have resulted in psychiatric symptoms. Immune mediated effects are significant contributors to the pathophysiological processes and disease progression. These immune effects include persistent inflammation with cytokine effects and autoimmunity and both of these mechanisms may occur at the same time in persistent infections [2,21].

Lyme disease has been associated with the proinflammatory cytokines interleukin-6, interleukin-8, Iinterleukin-12, interleukin-18 and interferon-gamma, the chemokines CXCL12, CXCL13 and CCL19 and increased levels of proinflammatory lipoproteins [20,22,23,24]. *B. burgdorferi* surface glycolipids and flagella antibodies appear to elicit anti-neuronal antibodies and anti-neuronal antibodies and *B. burgdorferi* lipoproteins can disseminate from the periphery to inflame the brain" and these persistent inflammatory effects are associated with neurodegenerative changes [20]. Persistent inflammation is also associated with metabolic changes provoked by these immune reactions and include oxidative stress, excitotoxicity, changes in homocysteine metabolism, mitochondrial dysfunction, altered tryptophan catabolism, decreased serotonin and increased quinolinic acid [20]. The presence of chronic inflammation is associated with increased proinflammatory cytokines which increase levels of indoleamine 2,3-dioxygenase, which converts tryptophan into quinolinic acid which is a neurotoxic metabolite and is a known agonist of N-methyl-D-aspartate synaptic function and increases depressive, cognitive and other symptoms [25]. Quinolinic acid is significantly elevated in cerebral spinal fluid in *B. burgdorferi* infections, more significantly in patients with CNS inflammation than in encephalopathy and correlates with the severity of CNS symptoms, including depression [23,26].

Besides *B. burgdorferi,* other known and unknown interactive tick-borne diseases such as *Babesia*, *Bartonella*, *Ehrlichia*, and *Mycoplasma* have immune and metabolic effects that further add to the complexity of the pathophysiology of tick-borne infections

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[27,28,29,30,31]. Opportunistic coinfections which may or may not be tickborne pathogens may also add to the complex interactive infectious process [32].

Some chronic symptoms are associated with injury and resulting dysfunction from past infection(s), other chronic symptoms are associated with chronic persistent or latent and relapsing infections [20]. In spite of considerable evidence supporting persistent infection with LB/TBD, some speculate that disease progression is caused by some continuing self-perpetuating post-infectious pathological process, although no viable mechanism has ever previously been demonstrated. However, what starts a disease process may be different from what causes further disease progression. Non-restorative sleep and chronic unremitting stress appear to play a significant role in disease progression in LB/TBD. In one study all Lyme disease patients studied had acquired sleep disorders [33]. Both non-restorative sleep and the chronic unremitting stress seen in these chronically ill patients contribute to disease perpetuation and progression and are associated with fatigue, cognitive impairments, decreased regenerative functioning, compromised immunity, decreased resistance to infectious disease and neurodegenerative processes [34,35,36,37,38].

Clinical presentations

It is recognized up to 40% of patients with Lyme disease develop neurologic involvement of either the peripheral or central nervous system. Similar to syphilis, Lyme disease may have a latency period of years before symptoms of late infection emerge. A broad range of psychiatric findings associated with Lyme disease include paranoia, dementia, schizophrenia, bipolar disorder, panic attacks, major depression, anorexia nervosa, and obsessive-compulsive disorder [10].

In reviewing multiple articles, it was apparent that each patient can have a unique and variable clinical presentation, however common symptom patterns are seen. Pre-infection most patients were young, quite active and healthy. A LB/TBD infection may have no or minimal effect in some, be severe in some, result in a latent infection in others, have a relapsing and remitting course in others, be slowly progressive in some and be rapidly progressive in others. It may cause a spectrum of multisystem symptoms which may include neuropsychiatric and somatic symptoms that may be initially subtle while becoming more severe with further disease progression. The neuropsychiatric manifestations may be cognitive, emotional, vegetative and behavioral and can be associated with almost any diagnosis in the DSM, but some psychiatric syndromes are more commonly seen than others. Significant psychiatric comorbidity is commonly seen. Infections at different times in the lifespan (congenital, infancy, childhood, adolescence, adulthood, geriatric) has different pathological effects [8,9,10,11,39].

Studies have looked at both the presence of LB/TBD in identified psychiatric patents and the emergence of neuropsychiatric symptoms in identified LB/TBD patients after becoming infected. In identified psychiatric patients, a higher prevalence of antibodies to *B. burgdorferi* was seen in hospitalized psychiatric patients when compared to matched pairs of healthy subjects (33% vs. 19%) and 80% of children with psychiatric illness referred to a child psychiatrist tested positive for LB/TBD and 74% of children with an onset of bipolar

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disorder referred to a child psychiatrist tested positive for LB/TBD [40,41]. In identified LB/TBD patients a number of studies have looked at the percentages of different psychiatric findings that emerged post infection. These studies were on patients who were mostly young and healthy pre-infection and studies also identified the same patients prior to infection as a control group [12,42]. The details of these studies shall be discussed further when discussing different disease presentations.

The total neuropsychiatric symptoms associated with LB/TBD results in a significant amount of impairment, disability and death [12,42,43,44].

Developmental disorders

Congenital LB/TBD infections can contribute to developmental disorders and neuropsychiatric impairments [45,46,47,48]. Since 1985 there are over 60 references documenting congenital transmission and associated pathological outcomes with LB/TBD [2,49]. The most comprehensive study was a review of 263 cases and included cases of miscarriage, stillbirth, perinatal death, congenital anomalies, systemic illness, early onset fulminant sepsis and later-onset chronic progressive symptoms associated with gestational LB [50].

The study most relevant to neuropsychiatric symptoms was an analysis of 102 gestational LB/TBD cases which demonstrated 9% had been diagnosed with autism and 56% with attention deficit disorder in addition to a broad spectrum of multisystem symptoms. Other psychiatric symptoms included irritability or mood swings (54%), anger or rage (23%), anxiety (21%), depression (13%), emotional lability (13%), obsessive compulsive disorder (11%), suicidal thoughts (7%), developmental delays (18%), tic disorders (14%), seizure disorders (11%), involuntary athetoid movements (9%), photophobia (43%), auditory hyperacuity (36%), other sensory hyperacuity (tactile, taste or smell) (23%), poor memory (39%), cognitive impairments (27%), speech delays (21%), reading/writing impairments (19%), articulation impairments (17%), auditory/visual processing impairments (13%), word selectivity impairments (12%), and dyslexia (18%). In the control group of 66 mothers with Lyme disease who were treated with antibiotics prior to conception and during the entire pregnancy; all gave birth to normal healthy infants. However, in the control group there were eight pregnancies that resulted in *B. burgdorferi* and/or *Bartonella henselae* positive placentas, umbilical cords, and or foreskin remnants. The PCR positive cases were treated successfully with oral antibiotics [51,52].

Autism spectrum disorders

Autism spectrum disorder (ASD) is associated with LB/TBD [7,52,53,54,55,56,57,58,59,60]. ASD results from multiple etiologies with both genetic and environmental contributions, including at least 23 different infections, seven of which are chronic infections (*Babesia*, *Bartonella*, *B. burgdorferi*, *Ehrlichia*, *Human herpesvirus-6*, *Chlamydia pneumoniae* and *Mycoplasma*), and the immune reactions associated with them [7]. The timing of the infection and immune response is critical in determining the pathophysiology. In congenital infections maternal immune reactions to infections appear to adversely affect fetal brain development and possible pathophysiological mechanisms include both autoimmune and inflammatory processes [7,52]. The association between

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ASD and LB/TBD is often overlooked since 94% of LB/TBD initially tested negative on two tier CDC *B. burgdorferi* surveillance criteria testing, however 92% of LB/TBD patients with ASD had reactivity of the 31 and 34 bands (outer surface protein-A and outer surface protein-B) on Western blot testing which is not reported on many of the commercially available tests for *B. burgdorferi* [61].

Treatment of LB/TBD during pregnancy can prevent the development of ASD associated with LB/TBD [51,52]. Another study demonstrated antibiotic treatment can reduce symptoms of ASD associated with LB/TBD [62].

States in the United States with the highest prevalence of ASD have the highest prevalence of *B. burgdorferi* and states with the lowest prevalence of ASD have the lowest prevalence of *B. burgdorferi* [62]. Possibly 20-25% of ASD are associated with LB/TBD [7,52].

Schizophrenia and Schizoaffective disorder

Schizophrenia has been associated with a number of infections rather than LB/TBD and evidence drawing an association between LB/TBD is limited [63,64]. There is however a significant geographical correlation between *Ixodes* ticks, LB/TBD and schizophrenia in the United States [65]. When schizophrenia is seen with LB/TBD, it is most commonly schizoaffective disorder [66,67,68,69,70,71,72]. In late stage LD/TBD patients paranoia has a prevalence of 36% and 88% in homicidal patients and hallucinations has a prevalence of 42% and 47% in homicidal patients [12].

Bipolar disorder

Bipolar disorder has been associated with a number of infections including LB/TBD [66,73,74]. When bipolar disorder is seen, it is invariably rapid cycling [12]. The prevalence of bipolar illness in LB/TBD is 74% (in children) [75], 47% **(**mood swings) [76]**,** 28% (homicidal) and 10% [12].

Depression

Depression from LB/TBD can frequently be prevented with early diagnosis and effective treatment [77]. However, when LB/TBD has not been adequately diagnosed and treated, it is a common finding. Studies of different groups with have shown a prevalence of depression of 0% pre-infection [12] and a post-infection incidence of 98% (with homicidal tendencies) [12], 94% [78], 80% (with intrusive symptoms) [79], 76% [12] 64% [76], 51% [80], 50% [81], 37% [82], 37% [83].

Anxiety disorders

Different types of anxiety are caused by LB/TBD. An early manifestation of hyperarousal may present as hypervigilance (54%) [12] and (84%) (homicidal) and/or low frustration tolerance (80%) [42] and 98% (homicidal) [12]. Further symptoms may then include mixed anxiety or different anxiety disorders, such as panic disorder, social anxiety disorder, generalized anxiety disorder, obsessive compulsive disorder and posttraumatic stress disorder. Panic disorder has been associated with LB/TBD [84,85,86,87,88]. Panic disorder has demonstrated a prevalence of 82% (homicidal), 54% (children) [83] and 50% [12].

Although no article has ever specifically addressed social anxiety disorder associated with LB/TBD, it is a common finding in patients. The prevalence of social anxiety disorder in LB/TBD was been demonstrated to be 70% [12] and 66% (homicidal) [12]. Generalized

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anxiety has been associated with LB/TBD and was 50% [42] and 86% (homicidal) [12]. Obsessive compulsive disorder has been reported with LB/TBD, can have an autoimmune pathophysiology and can have a very sudden onset [89,90,91]. The Prevalence of obsessive compulsive disorder in LB/TBD was 84% [92], 51% (homicidal) and 32% [12]. Posttraumatic stress disorder has been associated with LB/TBD [93,94]. The prevalence of posttraumatic stress disorder was 24% [12] and 36% (homicidal) [12].

Intrusive Symptoms are associated with LB/TBD and may be present with obsessive compulsive disorder, posttraumatic disorder or be present without either of these conditions and demonstrated a prevalence of 34% and included aggressiveness in 89%, altered sexual imagery in 18% and 40% had other intrusive symptoms including bizarre and horrific images [79]. In another study intrusive aggressive images were seen in 62% of homicidal LB/TBD patients but in only 16% of non-homicidal LB/TBD patients. Intrusive sexual images were seen in 26% of homicidal LB/TBD patients while they were seen in only 6% of non-homicidal LB/TBD patients [12]. LB/TBD patients with intrusive symptoms also had cognitive impairments (100%), neurological 98%, obsessiveness (89%), depersonalization (87%), depression (80%), low frustration tolerance (80%), explosive anger (73%), suicidal (69%), social isolation (67%), anhedonia (62%), disinhibition (62%), paranoia (49%), hallucinations (42%) and homicidality (31%) [79].

Eating disorders

A number of eating disorders are associated with LB/TBD. Some LB/TBD patients lose weight early in the disease process and later gain weight. Cases of anorexia nervosa, bulimia and excessive weight gain have been reported [10,95,96,97]. In some cases, tick saliva has resulted in food allergies and intolerances [98].

Sleep disorders

Sleep disorders acquired as a result of LB/TBD are quite significant and include insomnia (early, mid, late), non-restorative sleep, restless leg, paroxysmal nocturnal leg movements, sleep apnea (obstructive and central), nightmares, circadian rhythm shift and narcolepsy (with sleep attacks, cataplexy, sleep paralysis and hypnagogic hallucinations). [33,99,100,101,102,103,104,105,106,107]. Poor sleep quality is associated with impaired immunocompetence and contributes to disease progression [108,109]. Studies have demonstrated a prevalence of sleep disorders in LB/TBD patients at 100% [33], 96% [12], 92% [110], 82% [78] and 66% [76]. Among homicidal LD/TBD patients 82% had vivid nightmares [12].

Addiction

The prevalence of chronic pain in suicidal LB/TBD patients is 65%, in suicidal and homicidal LB/TBD patients the prevalence is 57% and in LB/TBD patients who are not suicidal or homicidal the prevalence is 35% [42]. Some LB/TBD patients with chronic pain are treated with opioids [111,112]. In addition, the majority of opioid users have a recognized mental illness [113]. However, unrecognized and inadequately treated mental and physical illnesses are also well recognized risk of substance abuse. The prevalence of substance abuse in LB/TBD patients is 33% (homicidal) [12], 28% (suicidal and homicidal) [42] and 10% (not homicidal or suicidal) [12]. Some LB/TBD patients who have been

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inadequately diagnosed and treated develop impaired dopamine functioning, have significant disease progression and self-medicate their psychiatric symptoms and pain, then become dependent, lose a sense of purpose and engage in drug-seeking behavior with benzodiazepines, hypnotics, alcohol, pain medication and marijuana. Some of these patients then die from overdoses, including, but not limited to opioid overdoses [114,115,116,117,118,119,120]. Also, some LB/TBD are alcohol sensitive (44%) [12] and drug sensitive and can demonstrate toxic symptoms with exposure to minimal substance exposure [120].

Cognitive impairments

Studies with different study designs reported a number of acquired cognitive impairments in LB/TBD patients [121,122,123,124,125,126]. The prevalence of these impairments in LB/TBD patients are encephalopathy (89%), Memory Loss (81%) [82]; attention/concentration impairments (77%), memory complaints (65%), mental fatigue (70%), (children) [83]; attention and concentration impairments (77%), memory complaints (65%), mental fatigue (70%), cognitive impairment (92%) [110]; memory loss (63%), poor concentration (60%), difficulty finding words (46%), confusion (44%), inattention (44%), [76]; impairments of reasoning (93%), memory (92%) and attention (91%), with speaking (75%), listening (73%), reading and/or writing (79%) [127]; short-term memory problems (94%), schoolwork deterioration (94%), brain fog (88%), distractibility (82%), word-finding problems (82%), and moderate to severe sensory hyperacusis to sound (58%) and /or light (74%); word-finding problems (79%)(children) [78]; memory impairments (76%), processing impairments (78%), dyslexia symptoms (68%) [12] and among homicidal subjects: impaired capacity for sustained and/or selective attention (98%), auditory hyperacusis (88%), sensory hyperacusis to light, touch, and/or smell (86%), memory impairments, most commonly working memory and short-term memory (98%), processing impairments (94%), dyslexia symptoms (78%), and executive functioning impairments (98%) [12].

Dementia

There are over 60 articles that address the causal association between LB/TBD and dementia [2]. Two of the three basic types of *B. burgdorferi* infections can contribute to a more rapidly developing dementia—the meningovascular form with cerebrovascular infarcts and the atrophic form with meningoencephalitis, cortical atrophy and gliosis. The atrophic form is associated with a more rapidly progressive dementia [128,129,130]. Infection outside the CNS causing immune effects within the CNS can be associated with a very slowly progressive dementia [2,20].

Seizure disorders

A number of articles have documented an association between LB/TBD and seizures [131,132,133,134,135]. Seizures have also been documented associated with *Bartonella* [136]. Seizure disorders are more common when there is a lengthy delay in diagnosis and effective treatment. Most commonly the seizures are complex partial seizures with significant postictal confusion and are sometimes referred to psychiatrists because they are misdiagnosed and being “psychogenic” or so called “pseudoseizures.” The prevalence of

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seizures in homicidal LB/TBD patients is 20% and were mostly complex partial seizures [12].

Suicide and Violence

Suicidality seen in LB/TBD contributes to causing a significant number of previously unexplained suicides and is associated with immune-mediated and metabolic changes resulting in psychiatric and other symptoms which are probably worsened by negative attitudes about LB/TBD from others. Some LD/TBD suicides are associated with being overwhelmed by multiple debilitating symptoms, and others are impulsive, bizarre, and unpredictable. Negative attitudes about LB/TBD from family, friends, doctors, and the health care system also appeared to contribute to suicide risk. By indirect calculations, it is estimated there are possibly over 1,200 LAD suicides in the US per year [42].

Although most LD/TBD patients have no aggressiveness tendencies or mild impairments of frustration tolerance and irritability and pose no danger, a lesser number of patients experience explosive anger, a lesser number experience homicidal thoughts and impulses and much lesser number commit homicides When homicides have occurred, they have been associated with predatory aggression, poor impulse control and psychosis. Since such large numbers are affected by LB/TBD, a very small percent of patients with these impairments can be highly significant. Most aggression with LB/TBD was impulsive, sometimes provoked by intrusive symptoms, sensory stimulation or frustration and the aggressive behavior was invariably bizarre and senseless. LB/TBD and the associated immune, biochemical, neurotransmitter, and neural circuit reactions to them can cause impairments that increase the risk of violence. In late stage LB/TBD the prevalence of suicidality is 43% [42] and 98% in homicidal LB/TBD patients [12].

Although many LB/TBD recognized and unrecognized fatalities are associated with suicides, drug overdoses and homicides, there are other LB/TBD fatalities. Fatalities associated with other neuropsychiatric conditions include congenital Lyme infections, Lyme meningitis, symptomatic late Lyme neuroborreliosis, late Lyme neuritis or neuropathy, meningovascular and neuroborreliosis with cerebral infarcts, intracranial aneurysm, late Lyme encephalitis, late Lyme meningo-encephalitis or meningomyelo encephalitis, atrophic form of Lyme meningo- encephalitis with dementia & subacute presenile dementia. Fatalities associated with somatic impairments include Lyme nephritis, Lyme hepatitis, Lyme aortic aneurysm, coronary artery aneurysm, late Lyme endocarditis, Lyme carditis, late Lyme disease of liver and other viscera, late Lyme disease of kidney & ureter and late Lyme disease of bronchus & lung. [43]

Other psychiatric findings

Other psychiatric findings caused by LB/TBD include anhedonia (56%), anhedonia in homicidal patients (86%), exaggerated startle reflex (66%), exaggerated startle reflex in homicidal patients (84%), disinhibition (32%) disinhibition in homicidal patients (84%), nightmares (58%), depersonalization (52%), depersonalization in homicidal patients (71%), dissociative episodes (12%) dissociative episodes in homicidal patients (38%), derealization (24%), derealization in homicidal patients (37%) and decreased libido (44%), abrupt mood swings in homicidal patients (94%), a decline in social functioning in

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homicidal patients (91%), a decline in school work or work productivity in homicidal patients (90%), marital and/or family problems in homicidal patients (80%) and legal problems in homicidal patients (42%) [12].

Assessment

Screening assessments are advisable when evaluating psychiatric symptoms when the possibility of LB/TBD may be present [8]. Screening questions include:

- Do you live, vacation or engage in activities in areas that may expose you to ticks?
- Have family members, neighbors, or the family dog been infected?
- Is there a history of a tick bite, possibly with a flu-like illness and/or a bull's eye or other rash?
- Is there a point at which your health declined, followed by a fluctuating progression and development of multi-systemic symptoms, including cognitive, psychiatric, neurological, and somatic symptoms adversely impacting school, social life, family life?
- Have you ever been treated for Lyme disease, suspected you had Lyme disease but was told it was ruled out?
- Have antibiotics ever caused a sudden worsening followed by an improvement of symptoms?

If the screening assessment increases diagnostic suspicion a further assessment is indicated. LB/TBD is diagnosed just like any other neuropsychiatric condition by a comprehensive psychiatric clinical exam relevant to patient's complaints and findings with a through history, mental status exam, review of systems, neurological exam, physical exam, a knowledgeable interpretation of laboratory findings, pattern recognition and clinical judgment. In considering the diagnosis it is important to look for relapsing progressive multi-systemic symptoms, including cognitive, psychiatric, neurological, and somatic symptoms and to remember the greater the multisystemic comorbidity, the greater the likelihood of a condition impacting the entire body such as a complex infectious disease. The presence of a comorbid condition does not rule out the presence of LB/TBD [42, 137,138,139].

A comprehensive assessment includes an assessment of the following:

- **Cognitive:** Attention (sustained attention, allocation of attention, distracted by frustration), sensory hyperacusis (auditory, visual, tactile, olfactory); inability to filter sensory input resulting in stimulation overload; memory (working memory, working spatial memory, short-term memory, long-term memory, word retrieval, number retrieval, name recall, facial recognition, procedural memory, geographical memory); processing (slow processing, letter reversals, spelling errors, word substitution errors, number reversals, reading comprehension impairments, auditory comprehension impairments, sound localization impairments, spatial perceptual distortions, optic ataxia, impaired transposition of laterality, left-right confusion, impaired calculation abilities, impaired fluency of speech, stuttering, slurred speech, impaired fluency of writing, impaired handwriting); executive functioning

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(unfocused concentration, brain fog, prioritizing multiple tasks, multitasking, racing thoughts, intrusive thoughts, obsessive thoughts, mental apathy, abstract reasoning impairments, time management impairments)

- **Imagery**: depersonalization, derealization, capacity for visual imagery, hypnagogic hallucinations, vivid nightmares, illusions (auditory, visual), hallucinations (auditory, especially musical, visual, olfactory, sensory).
- **Emotional**: decreased frustration tolerance, abrupt mood swings, hypervigilance, paranoia, anhedonia
- **Behavioral**: disinhibition, exaggerated startle reflex, explosive anger, suicidal, homicidal, accident prone, decreased social functioning, decreases school or job productivity, family and marital conflicts, substance abuse, legal difficulties, dissociative episodes, compensatory compulsions, dropping objects, crying spells, self-mutilation
- **Psychiatric syndromes**: depression, rapid cycling bipolar illness, panic disorder, obsessive compulsive disorder, social anxiety disorder, generalized anxiety disorder, posttraumatic stress disorder
- **Sleep disorders**: non-restorative sleep, early insomnia, middle of night insomnia, early morning insomnia, hypersomnia, loss or reversal of circadian rhythm, restless leg, paroxysmal nocturnal limb movements, sleep apnea (central and/or obstructive), sleep paralysis, hypnagogic hallucinations, sleep attacks, cataplexy, narcolepsy
- **Eating disorders**: anorexia, weight loss, emotional overeating, carbohydrate craving, weight gain (with or without increased food intake)
- **Sexual**: decreased libido, increased libido, decrease capacity for arousal, decreased capacity for orgasm, altered sexual imagery
- **Temperature control**: body temperature fluctuations, flushing, intolerance to heat, intolerance to cold, decreased body temperature, low grade fevers, night sweats, chills
- **Headaches**: cervical radiculopathy, migraine, thunderclap, tension, cluster, sinus, scalp tenderness, temporal mandibular joint, coital cephalalgia
- **Cranial nerves:** I: loss of smell, altered taste; II/eye: blurred vision, photophobia, intolerance of fluorescent or flickering light, floaters, flashes, conjunctivitis, eye pain, dry eyes, blind spots, night blindness, peripheral shadows, panopsia, papilledema, iritis, uveitis, optic neuritis; II, IV, VI: double vision, eye drifts when tired, ptosis; V: sensory loss and/or pain in any of the three branches on either side; VII: Bell's Palsy; VIII: tinnitus, hearing loss, dizziness, vertigo, motion sickness, Tulio's sign, mal de debarquement; IX, X: episodic loss of speech, choking on food, difficulty swallowing; XI: sternocleidomastoid, trapezius pain and/or weakness; XII: tongue deviates to side
- **Seizures:** complex partial, grand mal

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- **Neuropathy:** numbness, tingling, sensory loss, burning, crawling sensation (formication), static electricity sensation, stabbing sensation, weakness
- **Other neurological:** fatigue, tremor, twitching, muscle tightness, myoclonic jerks, tics, Tourette's, ataxia, spasticity, meningismus, disc disease, positive Romberg, postural tachycardia syndrome (POTS), ortho static hypotension, gait disturbances, spinal cord signs, gait disturbances, white matter lesions, sensation of vibration
- **Musculoskeletal:** Joint pain, migratory joint pain, swelling, tightness, crepitations, neck and back discomfort; periostitis and bone tenderness of tibia, ribs, iliac crest, sternum, clavicle; epicondylitis; plantar fasciitis, foot tenderness; fibromyalgia; myalgia, costochondritis (ear, nose, costochondral junctions, xyphoid); tendonitis; carpal tunnel syndrome
- **Cardiac:** chest pain, heart block, irregular heart rate, mitral valve prolapse, racing pulse, POTS, pericarditis, cardiomyopathy, murmur, hypertension, hypertensive crisis
- **Pulmonary/upper respiratory:** shortness of breath, air hunger, cough, sore throats, swollen glands, asthma
- **Gastrointestinal:** Reflux, irritable gut, nervous stomach, irritable bowel, abdominal bloating, reduced gastrointestinal motility, gastroparesis, cholecystitis, gall stones
- **Genitourinary:** Irregular periods, genital pain, breast tenderness, sexual dysfunction, irritable bladder, interstitial cystitis, urinary incontinence
- **GU:** Spastic bladder, testicular pain/pelvic pain, menstrual irregularity, sexual dysfunction, decreased libido.
- **Immune:** fevers, sweats, chills
- **Other:** alcohol intolerance, hair loss, thyroid disease, adrenal insufficiency, hypoglycemia, ankle edema, tooth pain, periodontal disease, nose bleeds, ecchymoses, splenomegaly, multiple chemical sensitivities, allergies, lymphocytoma, stria, acrodermatitis chronicum atrophicans

The more common symptoms seen in LB/TBD include poor attention span, being easily distracted by frustration, sensory hypersensitivity causing patients to feel overwhelmed, poor short-term memory, dyslexia symptoms, slow processing, executive dysfunction, brain fog, poor time management, depersonalization, intrusive images and thoughts, musical hallucinations, low frustration tolerance, abrupt mood swings, impulsivity, paranoia, explosive anger, suicidality, anhedonia, decreased productivity, depression, long duration panic attacks, social anxiety, generalized anxiety, obsessiveness, non-restorative sleep, appetite disturbances, decreased libido, headaches, cranial nerve symptoms, neuropathy, autonomic nervous system symptoms, musculoskeletal symptoms, gastrointestinal symptoms, genitourinary symptoms, cardiovascular symptoms, fatigue, chronic pain and alcohol intolerance [12,39,42,137]

After an adequate clinical assessment is performed, laboratory testing with proper interpretation may add to the assessment. It is important to remember that no test can rule

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out the possibility of LB/TBD [140,141]. The differential diagnosis is complex but the more common differential diagnosis includes other chronic systemic conditions and infections, since many of the symptoms and syndromes seen with LB/TBD may overlap with conditions other than LB/TBD [142].

If an inadequate clinical exam is performed it can result in viewing the symptoms as being vague and subjective. Caution must be used in considering the symptoms as having a psychogenic basis, such as hypochondriasis, somatization disorder, or a psychosomatic condition. Both hypochondriasis and psychosomatic illnesses begin in childhood and are lifelong conditions with a psychodynamic explanation and vary in intensity depending upon life stressors. If a complex, progressive multisystemic illness begins in a person who was reasonably healthy throughout most of their life, the likelihood that this is psychosomatic or has some other psychogenic basis is very remote. Another diagnostic error by clinicians who lack psychiatric diagnostic capability is to consider these symptoms as being so called "medically unexplained symptoms" or "bodily distress syndrome." The concept of medically unexplained symptoms was removed from DMS-5 since these symptoms were often instead medically unexamined symptoms. [3]

Treatment

All treatments are a risk vs. benefit decision and inadequately treated LB/TBD can result in a broad spectrum of risks as previously described. A complex, chronic, LB/TBD patient may have a multitude of different symptoms. What causes a condition may be different from what perpetuates a condition. It is best to make a list with the patient ranking which symptoms are the most severe and most impede recovery and consider how the symptoms interact with each other. This will determine the sequence of initiating different treatment strategies. One major question is considering whether antibiotic or symptomatic treatment has higher priority. When a patient has been treated with just antibiotics and has not adequately responded, consider treating the symptoms with psychotropics or other symptomatic treatments. When a patient has been treated with just psychotropics and has not adequately responded, consider treating the symptoms with antibiotics [143,144]. When a patient is treatment resistant consider both symptomatic and antibiotic treatment.

Although each patient may have a unique presentation, the most common symptoms impeding recovery are non-restorative sleep and/or chronic unremitting stress. Both are associated with a high allostatic load and compromised immune functioning. Non-restorative sleep is often associated with the terrible triad which consists of non-restorative sleep, fatigue and cognitive impairments [143].

Chronic unremitting stress is often associated with hyperarousal and emotional symptoms such as depression, anxiety, depersonalization, mood swings and psychosis. Other symptoms that may be a focus of treatment may include chronic pain (headaches, neuropathy, radiculopathy, musculoskeletal, etc.), complex partial seizures, dysautonomia, gastrointestinal symptoms, genitourinary symptoms, substance abuse and addiction [143].

Regardless of the debate surrounding the chronicity of infection and the chronicity of symptoms with LD/TBD, treating psychiatric symptoms with psychotropics can prevent

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and sometimes reverse progression of illness. Since non-restorative sleep and chronic unremitting stress contribute to disease progression, impaired functioning and compromised immune functioning; improvement in these areas can prevent disease progression, improve functioning and improve immune functioning and resistance to infection. Successful psychiatric management can sometimes result in reduction of infection and successful reduction of infection can sometimes result in reducing psychiatric symptoms and reducing the need for psychotropics [143].

No drugs are specifically approved by the Federal Drug Administration (FDA) for the treatment of psychiatric symptoms associated with LB/TBD. Since LB/TBD can be associated with the full spectrum of psychiatric symptoms, all psychotropic are sometimes used and these medications may or may not be FDA approved to treat the relevant symptom [143].

Separate and apart from the potential benefit of psychotropic benefits when used as psychotropics, some also have some antimicrobial and immune effects [145].

When the symptoms are caused by persistent relapsing infection, antibiotic treatment late in the course of the illness may prevent some further neuropsychiatric disease progression but may be unable to reverse all the previously established neuropsychiatric impairments. Since our current technological limitations prevent us from being sure all tick-borne infections have been eradicated, after stabilization constant vigilance is needed to recognize a possible relapse that may require further treatment [143].

Conclusion

Infections, tick-borne infections and persistent complex interactive infections with associated immune evasion and suppression in the body can cause acute and chronic immune effects and biochemical changes in the brain causing neuropsychiatric symptoms. The sleep disorders and chronic unremitting stress associated with these impairments contribute to further disease progression of neuropsychiatric disorders. The pathological effects of these processes result in 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, sleep disorders, decreased libido, addiction, opioid addiction, cognitive impairments, dementia, seizure disorders, suicide, violence, anhedonia, depersonalization, dissociative episodes, derealization and other impairments. Prior studies looked mostly at the prevalence of neuropsychiatric impairments following Lyme borreliosis/tick-borne disease infections, but future studies are needed to look more at the prevalence of these infections in patients with identified neuropsychiatric impairments. Diagnosis of LB/TBD cases can be facilitated by a screening assessment followed by a comprehensive psychiatric clinical exam relevant to patient's complaints and findings with a through history, mental status exam, review of systems, neurological exam, physical exam, a knowledgeable interpretation of laboratory findings, pattern recognition and clinical judgment are helpful.

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Treatment approaches that reduce symptoms that contribute to disease progression (sleep disorders, fatigue, cognitive impairments, depression anxiety disorders, chronic pain) in combination with antimicrobial and other treatments can be beneficial.

Sir William Osler, the father of American Medicine said— "He who knows syphilis knows medicine." It can now be said—He who knows Lyme disease knows medicine, neurology, psychiatry, immunology, psychoimmunology, neurochemistry, ecology, law, politics, and ethics.

Awareness of the association between Lyme borreliosis/tick-borne diseases and neuropsychiatric impairments and studies of their prevalence in neuropsychiatric conditions can improve understanding of the causes of mental illness and violence and result in more effective prevention, diagnosis and treatment.

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