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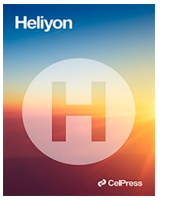

Case report

Late-stage borreliosis and substance abuse

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ABSTRACT

Background: Infectious diseases can contribute to substance abuse. Here, a fatal case of borreliosis and substance abuse is reported. This patient had a history of multiple tick bites and increasing multisystem symptoms, yet diagnosis and treatment were delayed. He experimented with multiple substances including phencyclidine (PCP), an N-methyl-D-aspartate (NMDA) receptor antagonist that opposes NMDA agonism caused by *Borrelia* infection. During PCP withdrawal, he committed one homicide, two assaults, and suicide.

Methods: Brain tissue was obtained from autopsy and stained for microglial activation and quinolinic acid (QA). Immunoflouresence (IFA) and fluorescence *in situ* hybridization (FISH) were used to identify the presence of pathogens in autopsy tissue.

Results: Autopsy tissue evaluation demonstrated *Borrelia* in the pancreas by IFA and heart by IFA and FISH. Activated microglia and QA were found in the brain, indicating neuroinflammation. It is postulated that PCP withdrawal may exacerbate symptoms produced by *Borrelia*-induced biochemical imbalances in the brain. This combination may have greatly increased his acute homicidal and suicidal risk. Patient databases also demonstrated the risk of homicide or suicide in patients diagnosed with borreliosis and confirmed multiple symptoms in these patients, including chronic pain, anxiety, and anhedonia.

Conclusions: Late-stage borreliosis is associated with multiple symptoms that may contribute to an increased risk of substance abuse and addictive disorders. More effective diagnosis and treatment of borreliosis, and attention to substance abuse potential may help reduce associated morbidity and mortality in patients with borreliosis, particularly in endemic areas.

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Key messages

- **What is already known on this topic** – *Mental health disorders are known to be associated with chronic infections. However, clear evidence of persistent infections and disturbances in brain biochemistry is rarely reported.*
- **What this study adds** – *We present a case of tick-borne disease with mental health disorder and substance abuse which led to a homicide-suicide event. Persistent spirochetes were identified in autopsy tissues, along with quinolinic acid accumulation in the brain. A patient database further demonstrates the propensity of borreliosis patients to become suicidal and/or homicidal.*
- **How this study might affect research, practice or policy** – *Consideration of borreliosis as a contributor to mental health disorders in endemic areas could lead to reduced morbidity and mortality if a diagnosis is confirmed and the infection is adequately treated.*

1Introduction

Infectious diseases, including Acquired Immune Deficiency Syndrome, tuberculosis, and COVID-19, contribute to substance abuse and addictive disorders [1–3]. Lyme disease/Lyme borreliosis (LD) and addictive disorders have been reviewed [4], and studies show an association between LD and substance abuse [5–8], with some people becoming dependent upon psychoactive substances [6].

Borreliosis is a tick-borne infection caused by *Borreliaceae* family spirochetes that includes Lyme disease (LD) and relapsing fever (RF) [9]. LD is the most common vector-borne illness in the United States (US) with an annual incidence of approximately 476,000 [10–13]. RF is widespread, found on five continents [14]. Late-stage persistent manifestations of borreliosis, such as musculoskeletal, cardiac and neurologic symptoms, may result from diagnostic and treatment delays [10,15–18], with patients remaining ill for prolonged periods [15,19,20].

Substance use disorders (SUD) are chronic, relapsing disorders characterized by compulsively seeking a substance, thing, or activity, that continue despite harmful consequences, resulting in long-lasting changes in the brain. SUD are complex brain disorders and a mental illness, with severity dependent on the number of symptoms [21]. Substances with potential for abuse include opioids, alcohol, sedatives, marijuana, and stimulants. Those at risk for addiction describe a very different reaction to potentially addictive substances compared to those not at risk, with patients sometimes stating that they feel more normal/alive when exposed to their substance of abuse. In the US, 46.3 million people (16.5 % of the population) met the DSM-5 substance use disorder criteria [22], and over 111,000 died from overdoses [23].

A recent large-scale study using Danish patient registries demonstrated that individuals with LD as a group had higher rates (28 %) of any mental disorder, including depression and suicidality (75 % higher rate of suicide), compared to those without LD [24]. An earlier study focused on patients with intrathecal antibody indicative of neuroborreliosis and found no significant differences in seeking psychiatric care or medictions between those patients and the general population [25]. While the study populations and outcome measures are drastically different, the reports highlight the value of large-scale studies in determining risk of mental illness following infection.

One hypothesis explaining the impact of chronic infectious disease upon mental functioning is chronic inflammation and increasing indoleamine-2,3-dioxygenase (IDO), adversely altering tryptophan catabolism and the kynurenine pathway (KP). This association between chronic infections and tryptophan catabolism plays a vital role in both health and disease [26]. The majority of available L-tryptophan (L-TrP) is metabolized through the KP, and ~5 % is converted to serotonin. IDO is the first and the rate-limiting step, which branches with the synthesis of kynurenic acid (KA), anthranilic acid, or 3-hydroxykynurenine (3-HK) and downstream metabolites including quinolinic acid (QA). While KA, an NMDA (N-methyl-D-aspartate) receptor antagonist, is thought to be neuroprotective, QA, an NMDA agonist, is neurotoxic. NMDA is a receptor for glutamate, the primary excitatory neurotransmitter in the brain. Reduced NMDA activity can cause cognitive defects, while overstimulation can lead to neuronal death and neurodegeneration [27]. Thus, the induction of this pathway has both protective and harmful consequences [28,29].

Clearly, the possible association between SUD and *Borrelia* infection deserves greater attention. Here we review a fatal case of borreliosis and substance abuse, comparing patient history to symptoms from LD patients. We also evaluate brain tissue for microglial activation and QA, and interrogate postmortem tissue for *Borrelia* using immunoflouresence (IFA) and fluorescence *in situ* hybridization (FISH) [30,31].

2Materials and methods

Autopsy tissue: Autopsy tissue was obtained from the Lyme Disease Biobank (LDB) through their partnership with the National Disease Research Interchange (NDRI). University of Pennsylvania (IRB#5 FWA00004028) approved the authorization/consent forms for research tissue donation to LDB under NDRI's Protocol (#704541; NDRI Tissue Procurement Program). Medical records from healthcare providers, hospitals, and the mother's description of illness were redacted. Brain tissue (141 g) was received, fixed in formalin, and portions were embedded into paraffin blocks. Cassettes of fixed tissue from other organs (detailed below) were also received. From each sample, a small piece was removed and stored in PBS/0.02 % sodium azide at 4 °C, and the remainder was embedded in paraffin. A total of 23 tissues were processed.

DNA isolation: Genomic DNA from the tissue samples was extracted using QIAamp DNA FFPE kit (Qiagen, 56404). Initially, slides were deparaffinized using a Leica Autostainer X, and tissue sections were scraped into a 1.5 ml microcentrifuge tube using sterile blades. For each preparation, tissue sections with a thickness of 30–50 μm and a surface area of up to 250 mm^2 or piece of tissue weighing <25 mg was added to a tube. Tissue sections were resuspended in a mixture containing 180 μl of buffer ATL and 20 μl of proteinase K as previously described [30].

PCR and primers: After decontaminating the workspace, initial PCR was performed using either Q5 Hot start High-Fidelity DNA polymerase (NEB, M0493L) or Taq DNA polymerase (Qiagen, 201203), and 5 μl of isolated DNA. Primers are listed below.

Target	Primer	5′-3′ nucleotide sequence	Reference
B. burgdorferi 23S rDNA	Bb23Sf	F: CGAGTCTTAAAAGGGCGATTTAGT	[32,33]
	Bb23Sr	R: GCTTCAGCCTGGCCATAAATAG	
B. miyamotoi glpQ	MGlpQF	F: GATAATATTCCTGTTATAATGC	[33,34]
	MGlpQR	R: CACTGAGATTTAGTGATTTAAGTTC	
Borrelia spp. *flagellin*	FLA120F	F: AGAATTAATMGHGCWTCTGATGATG	[33,35]
	FLA920R	R: TGCYACAAYHTCATCTGTCATT	
B. turicatae glpQ	BTGlpQF	F: GCCTGTCAGAATGAAAAA	[36]
	BTGlpQR	R: CACCTCTGTGAGCTATAATT	
B. hermsii glpQ	BHGlpQF	F: TCCTGTCAGGGCGAAAAAAT	[36]
	BHGlpQR	R: GCTGGCACCTCTGTGAGCTAT	
B. burgdorferi 16S–23S ITS	BobuITS120	F: AGGTCATTTTGGGGGTTTAGCTCAGTTGGCT	[30,37]
	BobuITS720	R: AGTGTCGGGCAAATCCAAACTGAAATCTG	
Bartonella 16S–23S ITS	BsppITS325s	F: CCTCAGATGATGATCCCAAGCCTTCTGGCG	[38]
	BsppITS1100as	R: GAACCGACGACCCCCTGCTTGCAAAGCA	

Microglial staining: Sections were stained with ionized calcium-binding adaptor molecule 1 (Iba1) and CD68 double immunohistochemistry with a pale Verhoeff counterstain to facilitate delineation of gray and white matter as described previously [39].

Immunofluorescence (IFA): Formalin-fixed, paraffin-embedded (FFPE) tissues from the following (precentral gyrus, cingulate gyrus, rostral hippocampus, superior and middle temporal gyri, inferior parietal lobule, caudal basal ganglia, thalamus with mamillary body, midbrain, pons, medulla, cerebellar cortex, cerebellar dentate nucleus, dura mater, pancreas, lung, testis, lymph node, spleen, heart, liver, kidney, adrenal gland, and skeletal muscle) were sectioned, in a dedicated room where no *Borrelia* experiments are conducted, at 5 μm in thickness and stained for *B. burgdorferi* as previously described [30] with slight modifications in antibody incubation times. After blocking, tissue sections were also incubated overnight at room temperature with primary rabbit anti-rBipA immune serum (a kind gift from Dr. Job E. Lopez) [40] at a dilution of 1:300. The next day, tissue sections were washed with Triton-X (TX-100) and PBS/fish skin gelatin (FSG) buffer washes. Slides were then incubated with secondary antibody goat anti-rabbit IgG conjugated to Alexa-Fluor 594 (Thermo Fisher Scientific, R37117) diluted 1:1000 in blocking buffer, and incubated for 2 hrs. Slides were washed after incubation with primary antibody and counterstained with DAPI (Millipore Sigma# CAS 28718-90-3) for 10 min to stain nuclei. Uninfected non-human primate (NHP) heart and pancreas tissues were used as controls (Supplemental Fig. 1).

Thalamus with mamillary body and pons were stained for QA based on microglial activation in these regions. A similar protocol as described above was followed. Tissues were subjected to pH-9 antigen retrieval after deparaffinization, followed by overnight incubation with primary anti-Quinolinic acid rabbit polyclonal antibody (Immusmol, IS1010) diluted in blocking buffer at 1:1000 dilution. After washes, tissues were then incubated for 2 hours with the secondary antibody goat anti-rabbit IgG conjugated to AlexaFluor 594 (Thermo Fisher Scientific, R37117) diluted 1:1000 in blocking buffer. Slides were washed and counterstained with DAPI, and Prolong™Gold Anti-fade mountant (ThermoFisher) was applied. Slides were coverslipped before visualization.

Fluorescence in situ hybridization (FISH): Heart and pancreas tissue were fixed, embedded in methacrylate and sectioned as described previously [41]. FISH hybridization mix contained a *Borrelia* genus-specific oligonucleotide probe (reBorr0) labeled with Cy3, a panbacterial probe (EUB338) labeled with Cy5, and a nonsense Probe (NOS338) labeled with FITC, to exclude unspecific binding [42–44], and the nucleic acid stain DAPI. Sections were hybridized as described [45]. To control for probe specificity, positive control *Borrelia burgdorferi* (0 MM) and negative controls *Treponema pallidum* (2MM) and *Treponema denticola* were included in each FISH experiment (see Supplemental Fig. 2). For microscopy, an epifluorescence microscope (Axio Imager Z2; Carl Zeiss, Jena, Germany) equipped with narrow-band filter sets (AHF; Analysentechnik,Tübingen, Germany) was used.

Patient Databases: Databases of LD cases were developed by the first author [46,47]. The first database included 100 well characterized LD patients from the US who met CDC surveillance criteria. Symptoms (n = 280) were clinician-documented before and after infection in patients with late-stage disease [47]. A second database of 253 LD patients meeting CDC surveillance criteria or LD clinical/laboratory criteria was characterized by symptoms and stratified by being suicidal and homicidal [46,48] (Hackensack Meridian Health Institutional Review Board, Neptune, NJ, IRB # 201704192J).

3Results

3.1Clinical course

This patient was a healthy child with an intelligence quotient of 148, living in an area highly endemic for LD. His first suspected tick exposure was around age 2–3, with a rash and bite marks, and he was treated with 7 days amoxicillin. On at least 15 occasions, ticks were found on him (5 embedded). He engaged in frequent outdoor activities and traveled to Eastern Europe and Germany. At age 14, an embedded tick was noted, and he developed a summer flu-like illness, which the pediatrician considered a virus not needing antibiotics. The flu-like illness improved, but afterwards there were increasing multisystem symptoms which included forgetfulness, distractibility, and difficulty organizing school work and turning in assignments. He also developed psychiatric symptoms including anxiety, social anxiety, depression, and headaches. He was diagnosed with attention deficit hyperactivity disorder (ADHD), but methylphenidate and amphetamine treatments were ineffective. The patient began having almost daily headaches at school that could

not be explained and he dropped out of high school at age 17, followed by episodic use of marijuana. He later obtained his GED. He experimented with several diifferent drugs and stated phencyclidine (PCP) "seemed to alleviate anxiety, social anxiety, depersonalization, inability to feel pleasure, brain fog, and difficulty focusing." At age 20, he was diagnosed with LD and ehrlichiosis (test results not available) and prescribed 21 days doxycycline.

At age 23 his PCP usage resulted in an episode of howling on the front porch. This episode resulted in a hospital emergency department visit for observation followed by a period of relative stability. There were periodic returns to PCP usage. At 24, a single photon emission computed tomography (SPECT) scan showed decreased activity both at rest and while concentrating, with decreased activity more severe at rest (Fig. 1). Decreased activity (indicated in green) was seen in the frontal cortex, prefrontal cortex, medial prefrontal cortex, inferior prefrontal cortex, medial inferior prefrontal cortex, and temporal lobes, while increased activity (indicated in red) was observed in the anterior cingulate gyrus, lateral prefrontal cortices, and temporal lobes with concentration.

One month before his 30th birthday, he had an embedded tick and irregular rash, was treated with 21 days doxycycline. Multisystem symptoms, including fatigue and joint pain, increased after stopping doxycycline. He was prescribed a second doxycyline course and referred to a rheumatologist; tests for anti-nuclear antibodies were negative and rheumatoid factor levels were within the normal range. LD Western blot testing performed at the time of tick bite was negative by CDC criteria, with 1 positive IgM band (p23) and 3 positive IgG bands (p41,p58,p66). One month later, follow-up testing showed reactivity to 4 IgG bands (p41,p45,p58,p66) and one IgM band (p39). Five months later, testing showed reactivity to 4 IgG bands (p39,p45,p58,p66) and one IgM band (p41). PCR testing was negative for *Babesia microti*, *A. phagocytophilum*, and *Ehrlichia chaffeensis* at all 3 timepoints. Testing performed 2 months later was IgM positive/IgG negative for RF borreliosis by immunoblot.

He was treated with antibiotics that did not resolve symptoms, including another 30 days doxycycline and azithromicin for ~4 months (250 mg twice daily) that was discontinued due to tinnitis. He returned to episodic PCP usage with multiple ineffective psychiatric treatment attempts including 6 ED visits. His psychiatric symptoms worsened with repeated PCP exposure. Documented symptoms (Table 1) were worse on the side of the recent tick bite. He was obese, with elevated blood glucose levels and hypertension, and an echocardiogram suspected dilated cardiomyopathy. Around his 32nd birthday he was admitted for right arm tingling and a possible stroke. An acute cerebrovascular accident was ruled out by CT scan and MRI. At this time his blood glucose level was 108 mg/dL (normal range 65–99) and hbA1c was 5.8 (normal is < 5.6). While his total cholesterol was <200 mg/dL, his LDL was elevated at 111 mg/dL. He tested positive for cannabis and PCP. He became increasingly paranoid over the next several months.

Four months later, he took 5 ounces of PCP within 8–10 hours, was found clutching his head and was evaluated at the ED. The physician indicated PCP did not need detox, and no beds were available, a common obstacle during the early COVID-19 pandemic. A few days later, he was experiencing auditory hallucinations and police were called after he secluded himself at home with an unloaded rifle. He was screened at another ED but was not admitted. His blood glucose level was 114 mg/dL and hbA1c was at the top of the normal range. He again tested positive for cannabis and PCP. He agreed to enter a rehabilitation center, but no beds were available. Two days after being discharged and six days after his last PCP exposure, he walked to his best friend's house, began talking in a delusional manner, and became acutely aggressive. He committed a homicide, assaulted 2 others, and then committed suicide at age 32.

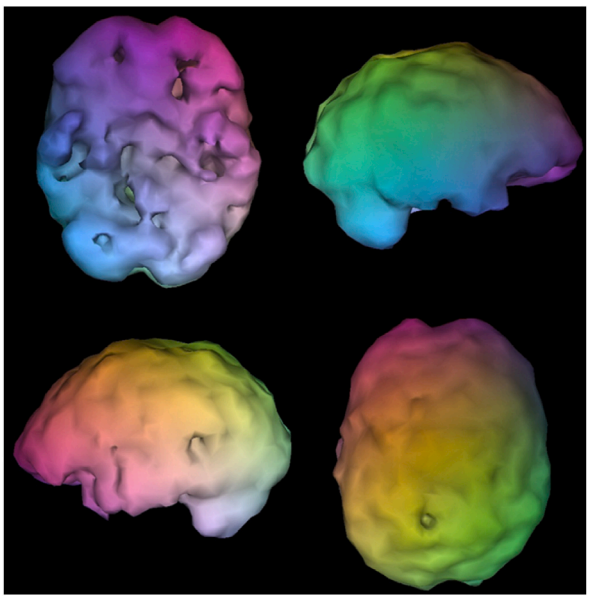

Fig. 1. SPECT scan of the patient's brain. Decreased activity is shown in green, while increased activity is shown in red. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Table 1
Documented symptoms of the patient in early 30's.

Category	Symptoms
Memory and Cognition	Decreased attention span, distractibility, reduced short term memory, decreased name recall, word finding problems, impaired receptive processing, decreased expressive processing, decreased organizational skills, difficulty multitasking
Mood and Psychiatric	Impulsive behavior, loss of temper, agitation, loss of interest, decreased motivation, generalized anxiety, social anxiety, depression, feeling worthless, feeling helpless, feeling hopeless, restlessness
Pain	Headaches, back and neck pain, shooting pains, stabbing pains, sharp pain, muscle weakness, muscle aches, joint pains
Cardiovascular and Metabolic	Racing heart, increased appetite, weight gain
Sleep issues	Insomnia, nightmares
Fatigue	General fatigue, post-exertional fatigue
Other	Optic ataxia, hearing loss, tinnitus

3.2Pathology findings

Postmortem toxicology studies by the medical examiner detected caffeine; ethanol, 37 mg/dl (BAC = 0.037 g/100 ml); phencyclidine, 100 ng/ml; delta-9 carboxy THC, 8.2 ng/ml; delta-9 THC, 3.0 ng/ml. Gross and microscopic examination of the following brain regions did not demonstrate any pathology: precentral gyrus, cingulate gyrus, rostral hippocampus, superior and middle temporal gyri, inferior parietal lobule, caudal basal ganglia, thalamus with mammillary body, midbrain, pons, medulla, cerebral cortex, cerebellar dentate nucleus, and dura mater. However, further examination revealed a perivascular accumulation of phagocytes in white matter of the inferior parietal lobule, including macrophages and activated microglia (Fig. 2). Activated microglia are characterized by short processes and abundant immunoreactivity for CD68 (black staining), whereas in the longer, thinner processes of surveilling/resting microglia, CD68 immunoreactivity is limited to puncta. Iba1 immunoreactivity (brown staining) was present throughout all types of phagocytic cells [39].

3.3Pathogen detection

Given the case history of multiple tick bites and potential exposure to Lyme and RF spirochetes, tissues were examined using PCR primers for both species and multiple *Borrelia*-specific antibodies, including those targeting outer surface protein A (*B. burgdorferi*) and BipA (RF species). Spirochetes were observed in heart and pancreas (Fig. 3 A-G). Immunofluorescent staining with polyclonal anti-*Borrelia* antibodies, anti-FlaB (also cross-species) and anti-BipA (RF species-specific) indicates that the *Borrelia* are likely from a RF species. Anti-OspA monoclonal antibody did not stain the spirochetes in tissue (data not shown). One limitation of the study is that we were unable to acquire PCR product sequences, which could have speciated the Borrelia. This was thought to be a result of the tissue fixation.

Heart and pancreas were subsequently evaluated by FISH, a tool to localize bacteria in the tissue and to detect presumably metabolically active microorganisms at the time of fixation based on the ribosomal content of the bacterial cell. FISH analysis revealed a few spirochetal morphotypes positive with the EUB333 and reBorr0 probes in heart tissue between the muscle layers pointing to *Borrelia* that was presumptively living in the heart tissue at the time of fixation (Fig. 4 A-F). In pancreas tissue sections, only DAPI-positive rod shaped bacteria were found (data not shown).

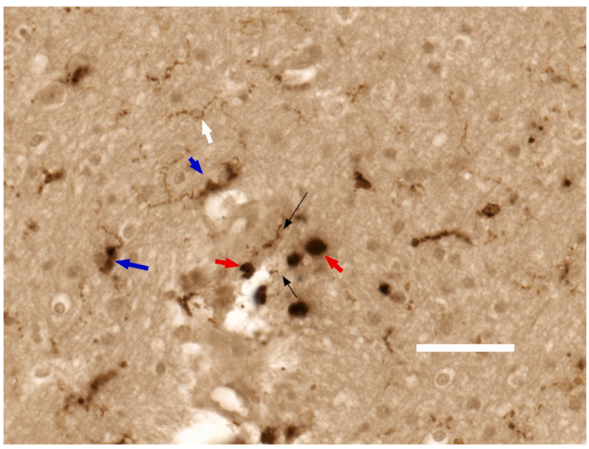

Fig. 2. Perivascular accumulation of phagocytes in white matter of inferior parietal lobule. Double immunohistochemistry for Iba1 (brown staining) and CD68 (black staining) is shown. Blue arrows indicate activated microglia and white arrow shows resting microglia. The red arrows point to macrophages and black arrows highlight the wall of a vessel. Scale bar = 50 μm. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

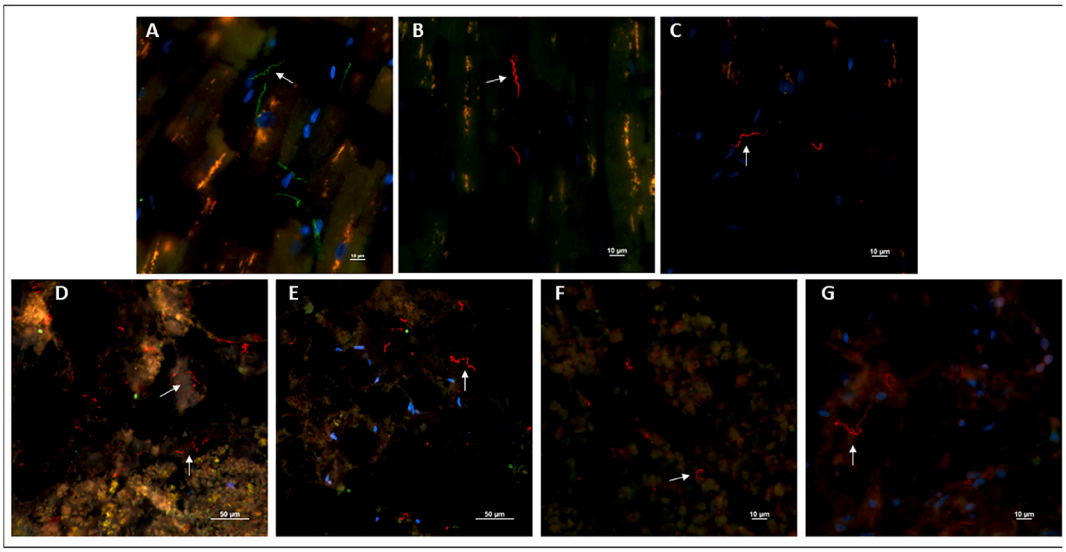

Fig. 3. Immunofluorescent antibody-based detection of spirochetes in the heart and pancreas. Heart tissues (A,B,C) and pancreas tissue (D,E, F,G) from FFPE sections were stained with: (A) chicken anti-FlaB primary followed by Alexa-488 secondary; (B,C,D,E) Rabbit antisera against BipA of *B. turicatae* followed by Alexa-594; and (F,G) rabbit antisera against *B. burgdorferi* followed by Alexa-594. White arrows point to some of the multiple spirochetes. Orange/yellow staining reflects tissue autofluorescence. Scale bar = 50 μm. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

While spirochetes were not found in the brain tissues examined, this patient had a history of mental health disturbances and a pathology report indicative of neuroinflammation. As such, we stained sections of the brain tissue containing activated microglia for QA production, a neurotoxic biomolecule that can accumulate in sites of inflammation. QA was observed in the pons and thalamus (Fig. 5 A-D) but not the midbrain (other brain sections were not evaluated). QA was not observed in brain tissue from an age-matched LD patient (see Supplemental Fig. 3)

3.4Patient database evaluation

The established patient database 1 showed that 12 % of patients experienced substance abuse post-infection compared to 1 % prior to infection [47]. Patients experiencing post-infection substance abuse also showed a statistically significant increase of 54 symptoms (Fig. 6). Symptoms before infection are indicated in blue, post-infection symptoms in orange, and post-infection symptoms from patients experiencing substance abuse in gray.

We identified 29 patients (11 %) in database 2 who were were homicidal and suicidal, with 28 % experiencing substance abuse [46]. Most were not adequately diganosed or treated during the initial infection, with many showing progression to late-stage disease with multiple chronic symptoms. Symptoms were often treated without addressing the underlying cause, with patients self-medicating, becoming involved in process addictions (eg gambling, shopping, sex), or exhibiting substance abuse, dependency, or addiction.

4. Discussion

This patient was inadequately diagnosed and treated, felt desperate, and turned to substance abuse for relief from multiple late-stage symptoms. While we cannot directly link the *Borrelia* findings to the mental health disturbances of the case, our study demonstrates an important association between chronic illness and SUD. Substance abuse can enhance cognitive, emotional, and behavioral symptoms, sometimes resulting in violence and aggressive behavior [4]. He experimented with many drugs, but chose PCP because it made him feel “normal”. The presence of perivascular accumulation of phagocytes and activated microglia suggests there was cerebral inflammation and may be why he chose PCP. PCP use has been associated with suicide, homicide, and psychosis [49].

Borrelia burgdorferi is a tryptophan auxotroph. Several studies have explored the role of the kynurenine pathway in borreliosis. Kynurenine and neopterin, a proinflammatory marker, were elevated in the cerebrospinal fluid (CSF) of patients with Lyme neuroborreliosis [50]. The production of QA can indicate infection-induced neurotoxicity. QA was found in the pons and thalmus by antibody staining. QA, an NMDA receptor agonist, is associated with increased suicidal and homicidal risk [46,51]. Inflammation from infection shifts tryptophan catabolism towards reduced serotonin and increased QA [52]. Reduced serotonin, indicated by a reduction of the serotonin metabolite, 5-hydroxyindoleacetic acid (5-HIAA) in CSF, is associated with increased suicidal risk [53–55]. QA is also elevated in the central nervous system in patients with *B burgdorferi* infection, and may contribute to neurologic and cognitive deficits seen in LD patients [56]. Increased QA pathophysiology is likely a result of inadequately treated *Borrelia* infection, with persistent

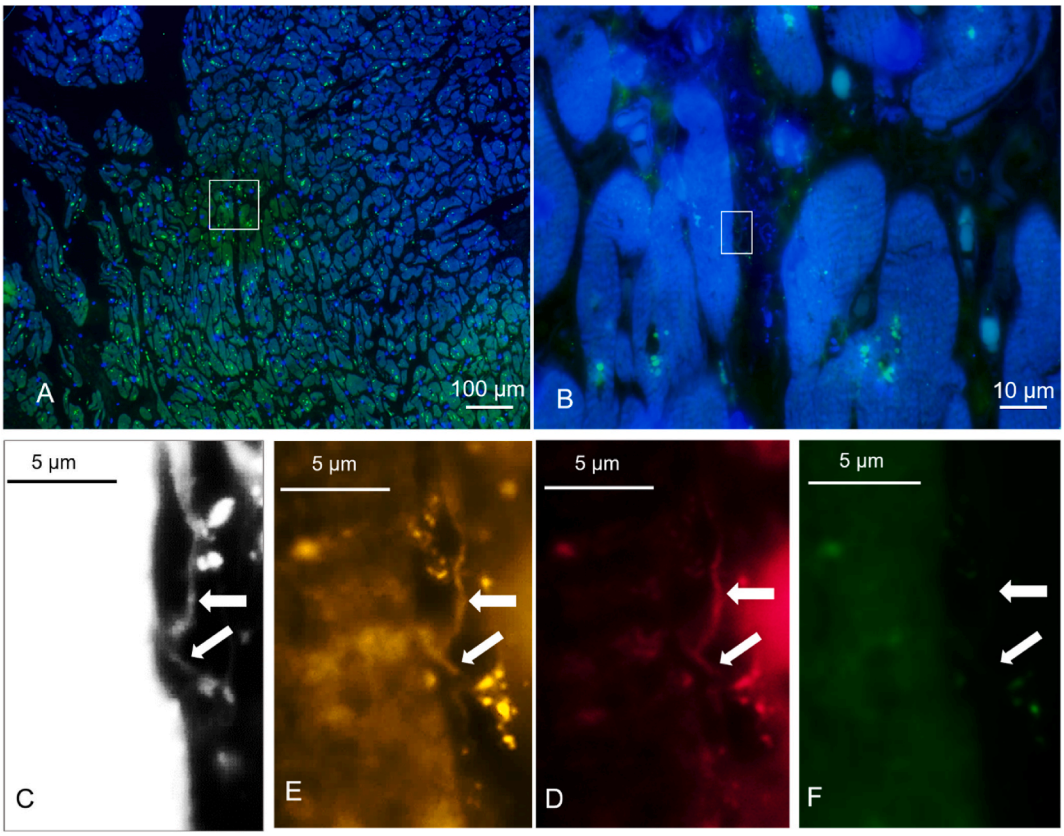

Fig. 4. Detection of Borrelia by FISH in heart tissue. Heart tissue FFPE sections were hybridized with Borrelia genus-specific probe reBorr0 (orange, E), a pan-bacterial probe (red,D), and a nonsense probe (green,F). Panel C is the differential interference contrast image with no stain. The white square in A is shown in panel B. C–F are areas inside the white square of B. White arrows show spirochetes. Scale bars are indicated on the individual panels. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

inflammatory cytokines, dysregulated tryptophan catabolism producing increased QA, NMDA receptor agonism, and glutamate dysregulation, leading to psychiatric symptoms (Fig. 5). Another mechanism that may contribute to the chronic neurological manifestations could be autoimmunity via molecular mimicry of *Borrelia* antigens with neuronal cells. Autoantibodies against γ enolase, a neuron-specific isoenzyme, could interfere with glycolysis in neuronal cells [57], contributing to the establishment of chronic symptoms and the subsequent dependence of patients to psychoactive substances.

PCP mostly acts as an NMDA antagonist, which may give short-term relief. However, tolerance to PCP followed by withdrawal would intensify NMDA receptor agonism symptoms, including suicide and homicide [46,48]. PCP withdrawal is associated with fear, agitation, anxiety, irritability, restlessness, flashbacks (intrusive symptoms), sweating, headache, hallucinations, seizures and hyperactive eye movements. Hyperactive eye movements were observed in this patient on his last day of life. Therefore it appears PCP withdrawal was greatly exacerbated in the presence of borreliosis due to the presence of QA and NMDA receptor agonism.

He also had metabolic and cardiovascular findings. He was overweight, had increased glucose, was hypertensive, and there was question of a stroke. Patients with Serious Mental Illness (SMI), including schizophrenia and bipolar disorder often have metabolic and cardiovascular polymorbidities [58–61] and often die from cardiovascular and metabolic disorders [62–65]. The presence of *Borrelia* in heart by IFA and FISH and pancreas by IFA may help explain the association between SMI and metabolic and cardiovascular disease [66].

He had symptoms similar to patients with LD and substance abuse in the databases developed by the first author. Symptoms of suicidal and homicidal patients included cognitive impairments (100 %), musculoskeletal symptoms (100 %), fatigue (97 %), depression (97 %), generalized anxiety (90 %), neurological symptoms (86 %), anhedonia (72 %), pain (57 %), and social anxiety (55 %). Chronic pain, anxiety disorders, and anhedonia (discussed below) were associated with increased risk of substance abuse [46,47]. In a recent prospective observational cohort study of patients with post-treatment Lyme disease, the predictors of persistent symptoms were poorer physical and social functioning, higher depression, and anxiety scores, in addition to the well-established symptoms of fatigue, cognitive impairment, and pain [67,68].

Chronic pain (headaches, neurological, musculoskeletal) occurred in 24 % of US confirmed and treated LD patients with severity comparable to post-surgical pain [19,69,70]. Database 1 findings showed 41 % experienced chronic pain post-infection compared to 0 % pre-infection [47]. Further, chronic pain was more prevalent in suicidal (65 %) or suicidal and homocidal (57 %) LD patients

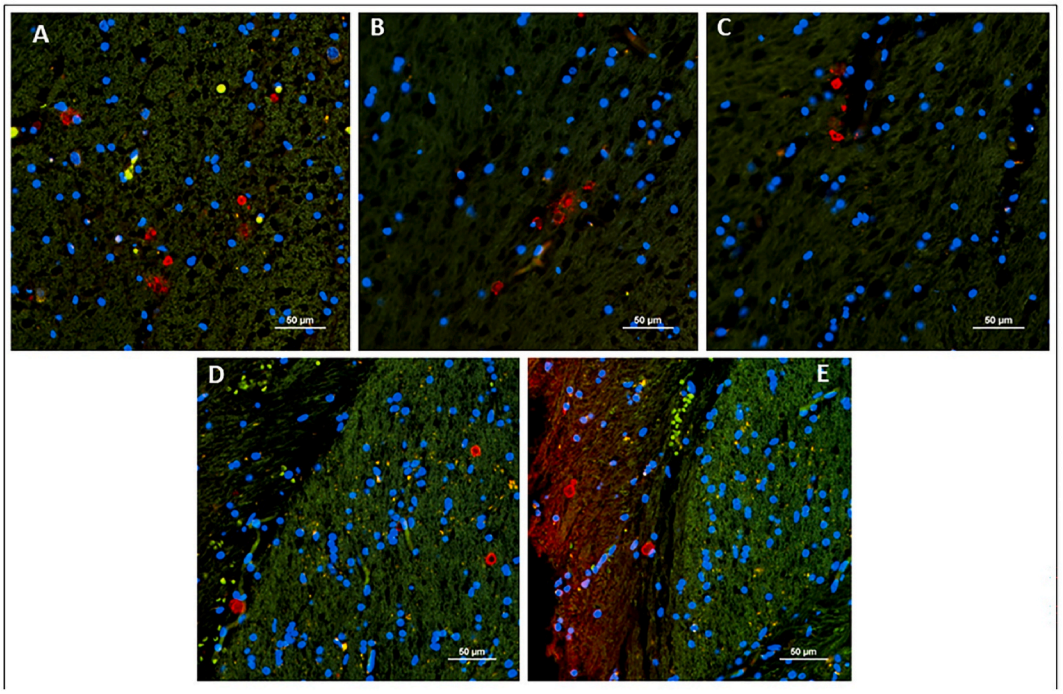

Fig. 5. Polyclonal antibody testing demonstrating the presence of quinolinic acid in the pons and thalamus. FFPE tissue sections of pons (A, B,C) and thalamus (D,E) were stained using quinolinic acid polyclonal antibody (red) from immuSmol (l#IS1010) and counterstained with DAPI (blue) for nuclei. Scale bar = 50 μm. Green is tissue autofluorescence. Control stains are shown in Supplemental Fig. 3. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

compared to late-stage neuropsychiatric LD patients not suicidal or homicidal (35 %) [46]. Finally, patient registry data (N = 3900) showed that 26 % of LD patients are administered prescription pain medications compared to 16 % of age matched controls [71,72]. Prompt recognition and treatment of LD is imperative in reducing the incidence of painful sequelae [69].

LD contributes to generalized anxiety disorder (53 %), panic disorder (49 %), social anxiety disorder (36 %), obsessive compulsive disorder (24 %), posttraumatic stress disorder (16 %), and intrusive symptoms (34 %) [46,48,73,74]. Anxiety disorders have a well-recognized impact upon substance abuse and addictive disorders [75,76]. Many LD patients describe stimulation overload or impairment in filtering out stimuli contributing to sensory overload. This, combined with processing impairments, contribute to hyperarousal and persistent anxiety [47]. Hyperintensities in the thalamus seen with LD may explain the diminished capability of the thalamus to filter out this sensory overload [77,78].

Anhedonia is the inability to feel pleasure from activities that are pleasurable, resulting in reduced motivation and increased suicidal risk. Individuals with anhedonia may compensate through excessive hedonistic (pleasure seeking) behavior including substance abuse [79]. Database 1 findings showed 64 % experienced anhedonia post-infection compared to 3 % pre-infection [47]. Protracted LD sequelae may be associated with impairment of dopaminergic function of the brain reward circuitry [5]. Memory of aversive events and memory of reward and pleasure share a common dopamine pathway to the medial prefrontal cortex [80], which may have been affected in this patient biochemically, despite the lack of histopathological findings.

5Conclusions

Patients with borreliosis who are depressed, anxious, and unmotivated may turn towards drugs with abuse potential; and substance abuse further increases the severity of borreliosis symptoms. We are experiencing an epidemic of both tick-borne infections and substance abuse, and it is plausible that a significant number of drug-related deaths may be attributed to inadequately diagnosed and inadequately treated borreliosis. Screening patients with SUD for history and clinical presentation compatible with tick-borne illnesses may help reduce substance abuse deaths. We have the potential to prevent future tragedies by recognizing that borreliosis can be a contributor to substance abuse and SUD. Comorbid borreliosis and mental health disorders, fostering substance abuse, have not been adequately studied and deserve greater attention and investigation.

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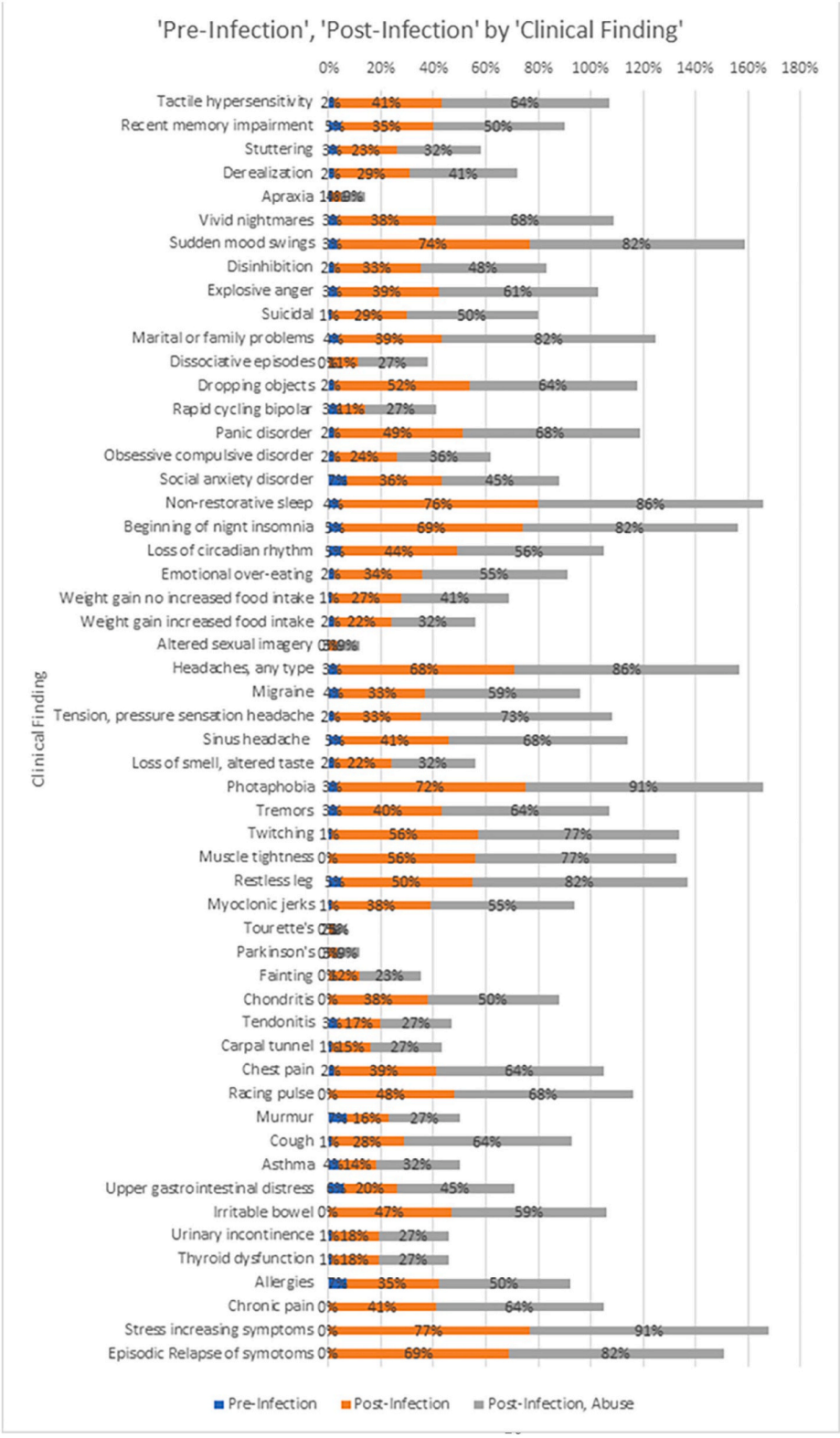

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Fig. 6. Lyme patient symptoms categorized by pre-infection, post infection, and substance abuse.Blue bars indicate % of patients with symptom pre-infection, orange bars indicate % of patients with symptom post-infection, and gray bars indicate % patients with symptom post-infection who developed substance abuse. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

anonymous donor.

Institutional review board statement

University of Pennsylvania IRB#5 (FWA00004028) approved the authorization/consent forms for research tissue donation to LDB under NDRI's Protocol (#704541; NDRI Tissue Procurement Program). Hackensack Meridian Health Institutional Review Board, Neptune, NJ, (IRB # 201704192J approved consent forms the patient databases.

Informed consent statement

All involved persons (participants or legally authorized representative) gave their informed consent prior to study inclusion. Consent for publication of the case report was provided by the next of kin.

Data availability statement

All relevant data that were generated are described within the manuscript and supplementary materials. Collective information regarding the patient database (data gathering and results) can be found at https://doi.org/10.2147/NDT.S136137.

CRediT authorship contribution statement

Robert C. Bransfield: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Shiva Kumar Goud Gadila:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation. **Laura J. Kursawe:** Writing – review & editing, Writing – original draft, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Andrew J. Dwork:** Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Gorazd Rosoklija:** Writing – review & editing, Visualization, Investigation, Formal analysis, Data curation. **Elizabeth J. Horn:** Writing – review & editing, Writing – original draft, Resources, Project administration, Funding acquisition, Conceptualization. **Michael J. Cook:** Validation, Formal analysis. **Monica E. Embers:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Funding acquisition, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:Monica E. Embers, Liz Horn reports financial support was provided by Bay Area Lyme Foundation. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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We acknowledge the irreparable trauma to all involved in this event. We also appreciate the assistance of the family to provide an opportunity to help prevent future similar losses. In a state of health, this patient was described as a kind and gentle person with a desire to increase world peace. The authors believe he would have approved of our efforts to improve peace by exploring the scientific basis of this tragedy to increase our understanding of borreliosis and substance abuse to help others suffering from these conditions.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e31159.

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