

Lyme disease and pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS): an overview

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Abstract: Lyme disease (LD) is a complex, multisystemic illness. As the most common vector-borne disease in the United States, LD is caused by bacterial spirochete *Borrelia burgdorferi* sensu stricto, with potential coinfections from agents of anaplasmosis, babesiosis, and ehrlichiosis. Persistent symptoms and clinical signs reflect multiorgan involvement with episodes of active disease and periods of remission, not sparing the coveted central nervous system. The capability of microorganisms to cause and exacerbate various neuropsychiatric pathology is also seen in pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS), a recently described disorder attributed to bacterium *Streptococcus pyogenes* of group A beta-hemolytic streptococcus in which neurologic tics and obsessive-compulsive disorders are sequelae of the infection. In the current overview, LD and PANDAS are juxtaposed through a review of their respective infectious etiologies, clinical presentations, mechanisms of disease development, courses of illness, and treatment options. Future directions related to immunoneuropsychiatry are also discussed.

Keywords: neuroborreliosis, infection, obsessive-compulsive disorder, tic disorder, *Borrelia burgdorferi*, strep throat

Introduction

Lyme disease (LD) and pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) are mutually exclusive disease states which share similarities but also important differences. Symptomatic overlap of LD and PANDAS raises the question of whether misdiagnoses may occur. Correct initial assessment is important since treatment for each may differ and delay may result in worsening symptoms, as evidenced in LD.^{1,2} In this current overview, LD and PANDAS are juxtaposed through a review of their respective infectious etiologies, clinical presentations, mechanisms of disease development, courses of illness, and treatment options. Future directions related to immunoneuropsychiatry are also discussed.

LD is attributed to infection from *Borrelia burgdorferi* and potential coinfections transmitted to humans via the *Ixodes scapularis* tick bite.³ A recent report from the Centers for Disease Control and Prevention (CDC)³ shows an annual increase of reported cases despite increased public awareness and preventative measures. From 1992 to 2006, most reported cases occurred during the summer months; average annual rates peaked for 5- to 9-year-olds and for 55- to 59-year-olds, with rates increasing disproportionately among males. Proportion of cases developing disseminated disease states has not decreased.³ Additionally, natural history and epidemiology of coinfections are not fully known, and some clinicians may have limited experience in recognizing and managing them.⁴

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PANDAS is attributed to the relatively abrupt onset and recurrence of pediatric obsessive-compulsive disorders (OCD) and neurologic tic disorders (as defined by the outdated *Diagnostic and Statistical Manual of Mental Disorders: DSM-IV* [DSM-IV®]⁵ criteria) following bacterial infection *Streptococcus pyogenes* of group A beta-hemolytic streptococcus (GAβHS). Sore throat and flu-like symptoms often precedes the neuropsychiatric sequelae. Five diagnostic criteria, outlined in Table 1, are needed to diagnose PANDAS.^{6,7} Incidence per 100 child-years of acute sore throat, GAβHS swab-positive pharyngitis, and serologically confirmed GAβHS pharyngitis were 33, 13, and 8, respectively, in 5- to 12-years-olds according to one study.^{8,9} Overall prevalence or percentage of infected children who then develop PANDAS is not yet known. It was first described in a landmark study by Swedo and Grant⁷ in 1998 but since its inception, PANDAS has become a controversial subject in the medical literature and across the Internet.¹⁰⁻¹²

The bacteria

Understanding LD and PANDAS begins with knowledge of their respective infectious agents. Although *B. burgdorferi* and GAβHS are vastly different microorganisms, their ability to evade the immune system and invade a wide variety of tissues, including the coveted central nervous system (CNS), is a paradigm of survival. The mechanism with which it then results in diverse somatic symptoms and neuropsychiatric sequelae underscores the need for experienced clinicians, laboratory testing, and early treatment.

LD is caused by an infection from the bacterial spirochete *B. burgdorferi* and potential coinfections from agents of anaplasmosis, babesiosis, and ehrlichiosis carried by the primary tick vector *Ixodes scapularis*, which bites its human host to transmit microorganisms.^{4,13,14} The white-footed mouse is a commonly cited *B. burgdorferi* host, but at least ten other wild and domestic mammalian species harbor *B. burgdorferi*,

including dogs, horses, cows, rabbits, and raccoons.¹⁵ Various species of *Borrelia* with numerous antigenic heterogeneity have been implicated in LD.^{13,14} *B. burgdorferi* was initially isolated and described in the 1970s during an epidemic of pediatric arthritic cases in the northeastern United States (US);^{16,17} however, similar descriptions have been observed in Europe since the 1800s.^{18,19} Today *B. burgdorferi* is reported worldwide, possibly distributed via migratory birds.^{20,21}

B. burgdorferi is a pleomorphic bacterial spirochete enclosed in a cell cylinder covered with multiple periplasmic flagella, surrounded by an outer membrane sheath;²² it exists in elongated, atypical, or cystic forms.²³ After the tick bite injects *B. burgdorferi* and potential coinfections into the host, ideally the innate immune cells engulf the spirochete, digesting it enzymatically, which generally succeeds in killing the invading organisms. However, an unknown number of *B. burgdorferi* may survive for days and even weeks after initial infection and continue the invasion, evading humoral immunity possibly by manipulating antigenic surface proteins or a weakened host immune response.²⁴⁻²⁶ *B. burgdorferi* has not yet been found to cause tissue damage by releasing toxins or proteases itself, but may in fact over-activate the host immune system, which may then lead to inflammation and tissue damage. Significance of *B. burgdorferi* adhesive properties with regard to host cells has also been reported.²⁷ Cellular immunity and secretion of its factors have been well characterized in the murine model, but the exact mechanism in humans is not well known.²⁶

GAβHS in PANDAS is a spherical, Gram-positive, non-motile organism and the most common bacterial cause of acute pharyngitis (“strep throat”) in children.^{9,28} Numerous serotypes of GAβHS have varying degrees of disease activity with classification based on antigenic surface proteins M and T. They are the infectious agents of scarlet fever, acute rheumatic fever (ARF), glomerulonephritis, toxic shock syndrome, and necrotizing fasciitis, amongst others. Its armament of antigenic surface proteins and pyrogenic exotoxins, as well as its ability to lyse its way systemically and evade the immune system effectively, have been well characterized. M protein, for example, is the major virulence factor preventing phagocytosis, multiplying rapidly in human tissue and initiating the disease process. More than 80 types of *S. pyogenes* M proteins alone have been isolated.²⁹ The serotype(s) in PANDAS is not yet known. GAβHS is generally spread by direct personal contact, most likely through droplets of saliva or nasal secretions. Crowding increases transmission, and outbreaks are common through chronic asymptomatic carriers and in institutional settings, such as the military, daycare centers, and within households. Human contamination of food has also been

Table 1 Diagnostic criteria for PANDAS (pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections)^{5,6}

Criteria

1. OCD and/or neurological tic disorder (met by DSM-IV⁹⁵ criteria)
2. Onset before puberty
3. Clinical course is episodic with acute, severe onset; symptom exacerbations are dramatic
4. During symptom exacerbations, neurological abnormalities are present
5. GAβHS infection and symptom exacerbations occurring temporally

Abbreviations: DSM-IV®, *Diagnostic and Statistical Manual of Mental Disorders: DSM-IV*; GAβHS, group A beta-hemolytic streptococcus; OCD, obsessive-compulsive disorder.

reported.^{30–32} Resurgence of invasive streptococcal diseases and the continued presence of ARF in the US predicates continued surveillance.^{33,34}

Somatic signs and symptoms

The somatic clinical course of LD and PANDAS share notable characteristics. Both may cycle between episodes of active disease and periods of quiescence. Distinctions between the two may also be made (Table 2).

B. burgdorferi may spread systemically localizing in somatic regions such as skin and joints,^{23,35,36} but can also maintain the ability to remain in a dormant, remissive state sequestered in collagen tissues, evading the immune system.³⁷ Successful immune response clears the infection, but continued activation due to persistent infection may lead to chronic inflammation, lesion development, and subsequent multisystemic disease formation.^{38,39} Arthritis, for example, is generally attributed to chronic neutrophilic activation, whereas carditis is associated with macrophytic and T lymphocytic activities in murine studies.^{40,41}

Somatic signs and symptoms in LD children resemble those seen in adults.⁴² Findings most commonly reported to the CDC were erythema chronicum migrans (ECM), arthritic, neurologic, and cardiac abnormalities. Early

stages may present with ECM, which is often described as a “bull’s-eye” rash, but the CDC reports 31% had none.³ Variability in gross appearance of ECM has also been noted, including homogeneous erythema, multiple annular lesions, and vesicular or centrally-ulcerated dermal pathology.^{43,44} Aucott et al⁴⁶ reported misdiagnoses occurred with greater frequency in patients with objective extracutaneous manifestations without ECM than in patients with ECM (83% vs 23%; $P = 0.004$). LD rashes were most often misdiagnosed as cellulitis, spider bites, or shingles. Of misdiagnosed cases, 41% received antibiotics not recommended for LD treatment and 30% were given steroids⁴⁶ which have been shown to decrease patient response to antibiotics.⁴⁷ Additionally, number of ECM or the disappearance of rash may not be indicative of disseminated state of disease.^{48,49}

Other LD somatic signs and symptoms may include fatigue, arthralgia(s), cardiopathy, hepatitis, or splenomegaly.^{50,51} Patients may also present with flu-like symptoms such as sore throat, nonproductive cough, fever and chills, or lymphadenopathy. Somatic disease may also be migratory and episodic over several weeks.⁵⁰ Of note, children over 10 years of age with arthritis and cardiopulmonary symptoms were more likely to be diagnosed with carditis.⁵² LD children with arthralgias have been misdiagnosed with septic arthritis or juvenile rheumatoid arthritis, resulting in delayed treatment.⁵³ Of patients who do not receive proper early treatment, more than half may go on to develop recurrent arthralgias,¹⁶ and children may not receive proper treatment for over a year.⁵⁴

In contrast to LD, somatic signs and symptoms of PANDAS may begin as streptococcal pharyngitis or “strep throat” which may later manifest as OCD or neurologic tics.⁶ Pharyngitis may also present with a fever greater than 38°C and with cervical lymphadenopathy. Examination of oral mucosa may show erythema or exudates present on tonsillopharyngeal regions along with palatal petechiae.³² Reports of children with stomach pains, emesis, and other upper respiratory illnesses such as new-onset asthma, sinus infections, and severe recurrent ear infections have also been noted.^{32,55} Although GABHS is reportedly a cause of acute pharyngitis in up to 30% of children,⁹ viral or other bacterial etiologies may need further consideration.

Neuropsychiatric signs and symptoms

Symptomatic presentation of LD and PANDAS may cross paths in the nervous system. From the original port of entry,

Table 2 General clinical presentations

Sign/symptom	LD	PANDAS
Flu-like symptoms	+++ ^a	+++
Lethargy	+++	++
Rash	++	NS
Sore throat	++	+++
Other upper respiratory infection	++	++
Arthralgia	+++	NS
Carditis	++	NS
Enuresis	NS	++
Headache	+++	++
Neuropathies	+++	+++
Choreiform movements	NS	+
Neurological tics	+	+++
Mood disturbances	+++	+
Psychosis	+	+
Obsessions/compulsions	+	+++
Hyperactivity	+	++
Problems concentrating	+++	+++
Separation anxiety	+	++
Handwriting changes	+	++
Decline in school performance	+++	+++
Suicidal ideations	+	NS
Homicidal ideations	NS	+

Note: ^aNumber of “+” symbols denotes relative reporting in referenced publications.

Abbreviations: LD, Lyme disease; NS, not significant; PANDAS, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections.

whether it be punctured epidermis or upper respiratory tract, invading microorganisms may make their way systemically, potentially resulting in neuropsychiatric pathology impacting the child's quality of life, school performance, and relationships with family and friends. Untreated LD may develop neurologic sequelae in up to 15% of cases.⁵⁶

In LD, the mechanism *B. burgdorferi* utilizes to evade immune defenses and enter the nervous system has been the focus of intense research. Differences in disease severity⁵⁷ have been attributed to genomic variations of bacterial strains⁵⁸ or host responses as observed in murine models.⁴¹ Animal studies have shown spirochete load is not associated with severity of illness^{59,60} suggesting *B. burgdorferi* may not be directly involved in neuronal damage. Spirochetes have also been observed localized in collagenous areas and along perivascular spaces in the human brain.¹ Entry of *B. burgdorferi* into the CNS may be attributed to its adherence along the endothelial lining of blood vessels resulting in an immune response releasing cytokines, initiating fibrinolysis, and recruiting leukocytes, causing damage to the blood–brain barrier. Other recent studies have suggested, at least in part, ligand-gated or paracellular routes of transmigration without endothelial basement membrane pathology.^{61–65} Groundbreaking in vivo murine studies by Norman et al⁶⁶ and Moriarty et al⁶⁷ used genetically engineered fluorescent *B. burgdorferi* strains expressing green fluorescent proteins to visualize their movements. They filmed in real time *B. burgdorferi* glowingly tether, drag, and adhere to the vessel wall of endothelium along much of their length. In addition, stationary adhesions were usually followed by extravasations at intercellular junctions.^{66,67} In humans, cortical regions sans blood–brain barrier include the posterior pituitary gland (site of hormones oxytocin and vasopressin release), pineal gland (site of hormone melatonin release and control of circadian rhythm), median eminence of the hypothalamus (site of pituitary hormones release), and the area postrema (site eliciting nausea and vomiting in response to serum toxins).⁶⁸ But, because murine brain lacks collagen, relevance to human pathology may be limited.¹

Within the cerebral cortex, pleomorphic *B. burgdorferi* may also exist in alternate forms, possibly explaining a prolonged latent stage and persistent infection in neuroborreliosis. Using atomic force and dark-field microscopy in postmortem studies of patients with chronic Lyme neuroborreliosis, Miklossy et al²³ collaborated with the US Army to photograph atypical and cystic states which were then successfully cultured in growth media. Weis et al⁶⁹ attributed cellular damage to robust induction of cytokines by *B. burgdorferi* antigens, up to 500-fold greater than *Escherichia coli*.

Evidence suggests macrophages of innate immunity ingest *B. burgdorferi*, activate cellular immunity, and through cytosolic signaling undergo programmed cell death.⁷⁰ Ramesh et al^{71,72} studied ex vivo and in vivo nonhuman primates stereotactically infected with *B. burgdorferi* directly into the brain. Their findings suggest *B. burgdorferi* induces inflammatory mediators leading to glial and neuronal apoptosis consistent with the bystander effect. Neuronal and Schwann cell apoptosis in dorsal root ganglia may be a mechanism whereby *B. burgdorferi* affects the peripheral nervous system as well. Subsequent research by Myers et al⁷³ confirmed proinflammatory cytokines released from resident microglia were implicated as mediators to neuronal apoptosis via the p53 pathway. However, antineuronal antibodies suggestive of molecular mimicry have also been debated.^{74–76} Interestingly, Newell et al⁷⁷ concluded rogue nonantigen-primed B-cell proliferation failing to apoptose after TLR-dependent B-cell polyclonal activation may be a mechanism to chronic inflammation. Genetic MHC variants in patients may determine T-cell receptor-dependent B-cell death.⁷⁷ Development of antineuronal antibodies from renegade B cells associated with *B. burgdorferi* patient-human leukocyte antigen (HLA) haplotyping is not yet known.

Neurologic pathology in children resulting from *B. burgdorferi* infection is wide-ranging. The majority of young patients do not develop problems if treated promptly and appropriately; however, *B. burgdorferi* has been observed to exhibit CNS dissemination within 2 weeks of active disease.⁷⁸ A study of LD children by Belman et al⁷⁹ reported the most frequent symptom was headache and the most common sign was facial palsy. Less common were sleep disturbances and papilledema associated with increased intracranial pressure; peripheral nervous system involvement was infrequent. Other findings were mild encephalopathy, lymphocytic meningitis, and cranial neuropathy, as well as anecdotal reports of pseudotumor cerebri-like disease.⁸⁰

LD psychiatric manifestations such as behavioral changes and memory deficits may have its greatest impact on school performance and quality of life. Intellectual functioning may be normal but auditory or visual sequential processing pathology have been reported.^{81–83} In a well-designed controlled study investigating cognitive impairment in children having already received antibiotic therapy (previous medication type, dose, and treatment duration not reported), a significant number continued to experience problems. Neurocognitive testing revealed frequent and severe headaches (100%), brain fog (88%), short-term memory loss (94%), word-finding problems

(82%), distractibility (82%), schoolwork deterioration (94%), irritability/depression (94%), insomnia (82%), and sensitivity to sound (58%) and/or light (74%).⁵⁴ Another study reported LD children with oppositional behavior, anxiety disorders, and attention-deficit/hyperactivity disorder (ADHD).⁸² Of special interest, a report by Riedel et al⁸⁴ described an LD child presenting with Tourette's syndrome, a neurologic tic disorder also seen in PANDAS, which resolved with antibiotic treatment. Although psychiatric manifestations of pediatric LD appear to have little or no mortality risk, Tager et al⁵⁴ reported 40% had suicidal thoughts and parents indicated 11% "had made a suicide gesture." However, larger, more in-depth studies are needed to better assess suicide risk in this patient population.

GABHS infection in PANDAS is a well-characterized bacterium implicated in other neuropsychiatric disease states.⁸⁵⁻⁸⁷ In the case of PANDAS, passive antibody transfer in murine models,⁸⁸ maternal history of autoimmune disease,⁸⁹ and reports of positive antineuronal antibodies in patient sera⁹⁰ suggest molecular mimicry, at least in part, as a cause of disorder development.

Movement of immune products into the CNS has been illustrated in animal models. In mouse studies of nascent autoimmune CNS lesions, Bartholomäus et al⁹¹ filmed in real time effector T cells trekking their way upstream against tides of vascular flow and their subsequent diapedesis across the blood-brain barrier whereupon encountering microglia presenting antigen. Stimulated effector T cells then produced proinflammatory mediators, resulting in tissue invasion and inflammatory infiltration. Lipopolysaccharide epitopes or ligand epinephrine may alter permeability, allowing cellular immunity to penetrate into the brain.⁹² Once inside the cerebral cortex, antibodies may also cross-react with neuronal cells. Kirvan et al⁹⁰ reported antibodies from PANDAS serum reacted in vitro with caudate and putamen neuronal lysoganglioside G_{M1}, inducing calcium/calmodulin-dependent protein (CaM) kinase II activity. Removal of immunoglobulins from patient serum extinguished CaM kinase II cell signaling, and cerebrospinal fluid (CSF) reactivity was then successfully blocked by GABHS cell wall epitope *N*-acetyl-beta-*D*-glucosamine.

Resulting neuropsychiatric pathology seen in PANDAS meeting the 1998 criteria⁷ is episodic and acute OCD and/or neurologic tics (defined by the outdated *DSM-IV*⁸⁵ criteria) in temporal relation with GABHS infection. Generally well-adjusted children may develop changes within days and resolution up to 8 weeks later.⁹³ However, the summarized definition of OCD as defined by the *DSM-IV-TR*,⁹⁴

the latest version of the manual replacing the *DSM-IV*,⁸⁵ are recurrent and persistent thoughts, impulses, or images which are intrusive and inappropriate, causing distress and anxiety beyond excessive worries about real-life problems. Children may attempt to ignore, suppress, or neutralize them with other thoughts or actions. Resulting compulsions are repetitive behaviors or mental acts performed ritualistically in response to obsessions, the purpose of which is to prevent or reduce distress or actions. Importantly, there is no logical cause and effect relationship between obsessions and compulsions. Children would not necessarily have insight into their pathology which can be time consuming and may interfere with normal daily activities.⁹⁴ An example of this is a child who brushes his teeth exactly ten strokes several times daily, believing it keeps the wind from blowing his parents away. The most current *DSM-IV-TR* defines Obsessive-Compulsive Disorder as not having disturbances attributed to a general medical condition (300.3). Therefore most appropriate diagnosis may be Anxiety Disorder Due to [Streptococcal Infection], with Obsessive-Compulsive Symptoms (293.84) which also requires clinical coding on Axis III of the multiaxial diagnostic assessment.

In the case of neurologic tic disorders, they are defined as vocal or motor repetitions which are rapid, sudden, repetitive, nonrhythmic but stereotyped (eg, eye blinking, coughing, sniffing, throat clearing). They may occur multiple times daily for many weeks or cycles. Tourette's disorder (307.23), Chronic Motor or Vocal Tic Disorder (307.22), and Transient Tic Disorder (307.21) exclude general medical conditions. Therefore, most appropriate diagnosis may be Tic Disorder Not Otherwise Specified (307.20)⁹⁴ with congruent Axis III coding. The American Psychiatric Association established a task force to update and release the new *DSM-5* in 2013.⁹⁵ Definition of general medical condition may need further clarification.

PANDAS characteristics not generally seen in OCD alone have been reported. A study by Bernstein et al⁹⁶ found urinary urgency, hyperactivity, impulsivity, deterioration in handwriting, separation anxiety, and decline in school performance as significant traits in the initial neuropsychiatric episode. Other traits in the sentinel event included inattention, mood swings, and oppositional defiant behavior. Most common obsessions were aggression and contamination, and most common compulsions were washing, cleaning, and checking rituals. Most common symptoms associated with exacerbations were labile emotions, decline in school performance, personality change, bedtime fears/rituals, and restlessness. In addition, motor hyperactivity and adventitious

movements were not infrequently reported and should be distinguished from Sydenham's chorea, a criterion for ARF which necessitates antibiotic treatment because of its association with endocarditis. Use of prophylactic antimicrobials in PANDAS remains controversial.^{7,97}

An interesting case of an 8-year-old boy with PANDAS who developed OCD and an eating disorder was recently described. When asked about his ritualistic behavior, the child replied, "it helps me to relax. It distracts me from the images in my head." Statements of his internal running monologues were "you must do the hand thing before you eat or the food will poison you," and "your mommy is a criminal and contaminating your favorite things." The child only walked on his father's right-hand side so as "not to give off fat cells to people walking by." He later developed ritualistic behaviors such as finger snapping to "undo contamination." The boy also developed signs of paranoia, believing hospital staff were "evil" and trying to poison him. He recognized these fears were not real but coming from his imagination.⁹⁸ Another report described a child with PANDAS who experienced catatonic episodes but whose cognition, comprehension, and receptive language were otherwise intact. Subsequent magnetic resonance imaging showed swelling in both the caudate and the putamen with disruption of the blood-brain barrier resulting in vasogenic edema.⁹⁹ Reports of children having homicidal thoughts directed against their parents and others⁵⁵ may require further investigation.

Laboratory testing and radiographic studies

Objective laboratory testing may be of benefit in distinguishing between LD and PANDAS and in differential diagnosing. Although LD is a clinical assessment, enzyme-linked immunosorbent assay (ELISA) and Western blots can confirm diagnoses but may not be necessary for patients with ECM.¹⁰⁰ For those without dermal pathology, diagnoses by experienced LD clinicians, in conjunction with high-quality laboratory testing, are important to prevent treatment delays. CSF studies have also been examined^{101–103} but with anecdotal reports of LD misdiagnosed as malignancies,⁸⁰ a high index of suspicion from experienced LD clinicians remains the gold standard.

In the case of PANDAS, confirmation of GABHS infection is generally performed with the rapid antigen detection test (RADT) in the physician's office. However, throat culture is considered the gold standard and may require up to 2 days for confirmation. Modified Centor scoring^{9,104} and

McIsaac scoring¹⁰⁵ approaches to management have been utilized. Both have similar sensitivities of over 85% and even higher specificities.⁹ Interestingly, the sensitivity of RADT may not be a fixed value but may vary with disease severity. Even among pediatric patients with a high Centor score, sensitivity of RADT remains too low to support the use of RADT without culture confirmation of negative results.¹⁰⁶ Ancillary studies such as serologies of antistreptolysin O and deoxyribonuclease-B antibodies,^{7,96,99,107–110} CSF from lumbar puncture,^{98,109,110} and radiographic findings^{6,7,99,111–114} have also been helpful in differential diagnosing but may not be required in fulfilling criteria for PANDAS.^{6,7}

Treatment

Primary treatment for children with LD utilizes antimicrobials in various doses, durations, and routes of administration.^{115–118} LD may be refractory to initial care because of coinfections, incorrect diagnoses, improper medications, or patient genetic variations.^{56,82,119,120} Treatment delays may compromise patient care. According to one study, average number of physicians consulted before correct diagnosis was 3.80, and mean time from parent-reported symptom onset to diagnosis was 47.3 weeks.⁵⁴

Primary treatment for PANDAS has been less clear. Since its establishment as a subcategory of GABHS-induced neuropsychiatric disorder remains controversial, protocols are provisional at best. Irregardless of PANDAS diagnosis, children with evidence of GABHS infection based on clinical scoring systems or objective testing may necessitate antibiotic use to prevent disseminated disease states such as ARF.^{9,121} In the case of PANDAS, antibiotic treatment alone may be efficacious.¹²² Prophylactic use remains controversial.^{95,123} Aside from medications, reports of intravenous immunoglobulin (IVIG) or plasma exchange have also been noted.^{97,124,125} In one study, double-blind, randomized controlled trials of IVIG, plasma exchange (not blinded), or placebo showed statistically significant improvements in obsessive-compulsive behaviors, neurologic tics (plasma exchange only), global impairment, anxiety, global severity, and emotional lability. However, longitudinal studies with longer follow-up are needed to determine remission rates or rebound effects.¹²⁴ Surgery for adenoid and tonsil removal alone or in combination with medications may also be effective.^{55,98,113,126,127}

Secondary support for both LD and PANDAS may include use of psychotropics, therapy, education, and accommodations. Medications for OCD, neurological tics,

depression, anxiety, and ADHD have shown to benefit children and may not be required long-term.^{110,128,129} Cognitive behavioral therapy,^{130,131} supportive therapy, and academic accommodations are also useful. In the US, Individuals with Disabilities Education Act, Individualized Education Program, and Section 504 of the Rehabilitation Act of 1973 have been mobilized for LD schoolchildren to achieve their academic goals. Other educational assistance includes shorter school days, untimed tests, alternative testing methods, separate/quieter testing locations, modified home instruction programs, and elimination of unnecessary requirements.¹³²

Future directions

We have presented the first overview of both LD and PANDAS detailing microbial etiology, disease development, clinical overlap, and treatment options. Although LD as a clinical diagnosis is relatively established, PANDAS as a distinct subgroup remains controversial. GA β HS infection occurring temporally with OCD or neurologic tics may be coincidental, given the high incidence of GA β HS in this age group, and symptom etiology or exacerbation may be due to stress of the illness versus the infection itself.⁶ However, PANDAS research suggestive of molecular mimicry, clinical improvement with IVIG or plasmapheresis, and lack of cardiac involvement supports the existence of PANDAS as a distinct subgroup of GA β HS-induced neuropsychiatric disorders.^{112,113,133,134} Inconsistencies in defining PANDAS may preclude development of treatment protocols and comparison between studies. Quantifying temporal timelines between infection and symptomatic presentation may also serve to standardize research protocols. Incorporating the most current *DSM* may update the PANDAS definition but could also redefine PANDAS itself.

Other possible investigative directions may include adult PANDAS,^{108,114,135} familial occurrences,^{107,136} or various infectious etiologies such as *Mycoplasma*, which has also been associated with OCD, Tourette's syndrome, parkinsonism, and dystonia.^{137–139} Differential and working diagnoses need continued consideration^{11,111} since not all symptom exacerbations are preceded by GA β HS infections; viral infections or other illnesses could also trigger worsening of symptoms according to one study.⁷

In the interesting case of a 4-year-old boy with LD who developed a motor tic (eye blinking) coinciding with increased IgG titres for *B. burgdorferi* on ELISA, the child subsequently improved with antibiotic therapy. Infection with *B. burgdorferi* should be considered in cases of Tourette's syndrome

in endemic areas, according to one author.⁸⁴ However, a detailed description of the boy's initial clinical presentation was lacking and GA β HS testing was not mentioned. This may be attributed to publication coinciding with the first PANDAS study,⁷ both having occurred in February 1998.

Overlap between LD and ARF may warrant further discussion. The latter may also present with an annular "bull's-eye" lesion termed erythema marginatum rheumaticum (EMR)¹⁴⁰ grossly similar to that seen in LD.^{52,100,141} Definitive diagnosis may be confirmed by punch biopsy and histologic studies.^{43,140,142} Carditis, also observed in pediatric LD,^{52,143–145} and EMR are two major criteria in ARF diagnosis.^{146,147} Migratory arthritis usually involving large joints is often described in LD^{100,148,149} and is also, coincidentally, a third major criterion in ARF.^{146,147}

Immunoneuropsychiatry has brought forth a plethora of questions regarding the immunomolecule effect on the human mind. Current research suggests anti-neuronal rather than antimicrobial vaccine development for HLA haplotypes may be of future interest. However, the ubiquitous MHC-I molecule was recently found to possibly regulate synaptic density during development in murine studies and to affect balance between excitatory and inhibitory plasticity in nascent neurons, a property critical for information processing in young brains.¹⁵⁰ The potential to improve mentation with administration of anti-inflammatory medications would also be of future interest. Minocycline, a bacteriostatic tetracycline derivative with lipophilic properties and relatively high CNS penetration, has been extensively investigated as an inhibitor of apoptosis.^{115,151–159} Its use in treating negative signs and symptoms of schizophrenia has also shown benefit.^{160–162} Interestingly, a correlation between sporadic clusters of schizophrenia and seasonal distribution of *Ixodes* ticks attributed causality with intrauterine exposure to *B. burgdorferi*.^{163,164} The American College of Rheumatology supports use of minocycline as a disease-modifying antirheumatic drug,¹⁶⁵ irrespective of infectious etiology. Long-term minocycline use for its CNS-penetrating, anti-inflammatory effects in children over the age of 8 with "antibiotic-refractory (or slowly resolving) Lyme arthritis"¹⁶⁶ would be of significant interest in future studies, allowing opposing viewpoints^{166,167} to claim victory and, most importantly, for children to receive proper treatment.

Recognition and validation of LD has come a long way since the essay ridiculing "Lime" patients was first published in *Annals of Internal Medicine*.^{82,168} Astute parents partnered with experienced clinicians make a formidable team

in addressing the pediatric patient and treatment course. As families attempt to receive care for their children, it is hoped they would not face ridicule from the medical community as well.

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References

- Committee on Lyme Disease and Other Tick-Borne Diseases: The State of the Science, Institute of Medicine. *Critical Needs and Gaps in Understanding Prevention, Amelioration, and Resolution of Lyme and Other Tick-Borne Diseases: The Short-Term and Long-Term Answers; Workshop Report*. Washington DC: National Academies Press; 2011.
- Cameron DJ. Consequences of treatment delay in Lyme disease. *J Eval Clin Pract*. 2007;13(3):470–472.
- Bacon RM, Kugeler KJ, Mead PS; for Centers for Disease Control and Prevention. Surveillance for Lyme disease: United States, 1992–2006. *MMWR Surveill Summ*. 2008;57(10):1–9.
- Swanson SJ, Neitzel D, Reed KD, Belongia EA. Coinfections acquired from *Ixodes* ticks. *Clin Microbiol Rev*. 2006;19(4):708–727.
- American Psychiatric Association, Task Force on DSM-IV. *Diagnostic and Statistical Manual of Mental Disorders: DSM-IV*. 4th ed. Washington DC: American Psychiatric Association; 1994.
- Swedo SE, Grant PJ. Annotation: PANDAS; a model for human autoimmune disease. *J Child Psychol Psychiatry*. 2005;46(3):227–234.
- Swedo SE, Leonard HL, Garvey M, et al. Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections: clinical description of the first 50 cases. *Am J Psychiatry*. 1998;155(2):264–271.
- Danchin MH, Rogers S, Kelpie L, et al. Burden of acute sore throat and group A streptococcal pharyngitis in school-aged children and their families in Australia. *Pediatrics*. 2007;120(5):950–957.
- Choby BA. Diagnosis and treatment of streptococcal pharyngitis. *Am Fam Physician*. 2009;79(5):383–390.
- Swedo SE, Schrag A, Gilbert R, et al. Streptococcal infection, Tourette syndrome, and OCD: is there a connection? PANDAS: horse or zebra? *Neurology*. 2010;74(17):1397–1398; author reply 1398–1399.
- Gilbert DL, Kurlan R. PANDAS: horse or zebra? *Neurology*. 2009;73(16):1252–1253.
- Packer LE. New research calls connection between strep infections and tics and obsessive-compulsive symptoms into question. The TS+ blog: the companion blog to Tourette syndrome “plus”; January 26, 2011. Available from: <http://www.tsplusblog.com/2011/01/new-research-calls-connection-between-strep-infections-and-tics-and-obsessive-compulsive-symptoms-into-question/>. Accessed September 16, 2011.
- Barbour AG, Hayes SF. Biology of *Borrelia* species. *Microbiol Rev*. 1986;50(4):381–400.
- Tilly K, Rosa PA, Stewart PE. Biology of infection with *Borrelia burgdorferi*. *Infect Dis Clin North Am*. 2008;22(2):217–234, v.
- Anderson JF. Epizootiology of *Borrelia* in *Ixodes* tick vectors and reservoir hosts. *Rev Infect Dis*. 1989;11 Suppl 6:S1451–S1459.
- Steere AC, Malawista SE, Snyderman DR, et al. Lyme arthritis: an epidemic of oligoarticular arthritis in children and adults in three Connecticut communities. *Arthritis Rheum*. 1977;20(1):7–17.
- Benach JL, Bosler EM, Hanrahan JP, et al. Spirochetes isolated from the blood of two patients with Lyme disease. *N Engl J Med*. 1983;308(13):740–742.
- Matuschka FR, Ohlenbusch A, Eiffert H, Richter D, Spielman A. Antiquity of the Lyme-disease spirochaete in Europe. *Lancet*. 1995;346(8986):1367.
- Matuschka FR, Ohlenbusch A, Eiffert H, Richter D, Spielman A. Characteristics of Lyme disease spirochetes in archived European ticks. *J Infect Dis*. 1996;174(2):424–426.
- Schmid GP. The global distribution of Lyme disease. *Rev Infect Dis*. 1985;7(1):41–50.
- Comstedt P, Bergstrom S, Olsen B, et al. Migratory passerine birds as reservoirs of Lyme borreliosis in Europe. *Emerg Infect Dis*. 2006;12(7):1087–1095.
- Sal MS, Li C, Motalab MA, Shibata S, Aizawa S, Charon NW. *Borrelia burgdorferi* uniquely regulates its motility genes and has an intricate flagellar hook-basal body structure. *J Bacteriol*. 2008;190(6):1912–1921.
- Miklossy J, Kasas S, Zurn AD, McCall S, Yu S, McGeer PL. Persisting atypical and cystic forms of *Borrelia burgdorferi* and local inflammation in Lyme neuroborreliosis. *J Neuroinflammation*. 2008;5:40.
- Hovius JW. Spitting image: tick saliva assists the causative agent of Lyme disease in evading host skin's innate immune response. *J Invest Dermatol*. 2009;129(10):2337–2339.
- Diterich I, Rauter C, Kirschning CJ, Hartung T. *Borrelia burgdorferi*-induced tolerance as a model of persistence via immunosuppression. *Infect Immun*. 2003;71(7):3979–3987.
- Steere AC, Drouin EE, Glickstein LJ. Relationship between immunity to *Borrelia burgdorferi* outer-surface protein A (OspA) and Lyme arthritis. *Clin Infect Dis*. 2011;52 Suppl 3:S259–S265.
- Coburn J, Fischer JR, Leong JM. Solving a sticky problem: new genetic approaches to host cell adhesion by the Lyme disease spirochete. *Mol Microbiol*. 2005;57(5):1182–1195.
- Bisno AL, Gerber MA, Gwaltney JM Jr, Kaplan EL, Schwartz RH; for Infectious Diseases Society of America. Practice guidelines for the diagnosis and management of group A streptococcal pharyngitis. *Clin Infect Dis*. 2002;35(2):113–125.
- Cunningham MW. Pathogenesis of group A streptococcal infections. *Clin Microbiol Rev*. 2000;13(3):470–511.
- Eisenhut M. Food as source of outbreaks of group A streptococcal disease. *Arch Dis Child*. 2011;96(3):323.
- Aguero J, Ortega-Mendi M, Eliecer Cano M, et al. Outbreak of invasive group A streptococcal disease among children attending a day-care center. *Pediatr Infect Dis J*. 2008;27(7):602–604.
- Hayes CS, Williamson H Jr. Management of group A beta-hemolytic streptococcal pharyngitis. *Am Fam Physician*. 2001;63(8):1557–1564.
- Bisno AL. The resurgence of acute rheumatic fever in the United States. *Annu Rev Med*. 1990;41:319–329.
- Erdem G, Mizumoto C, Esaki D, Abe L, Reddy V, Effler PV. Streptococcal emm types in Hawaii: a region with high incidence of acute rheumatic fever. *Pediatr Infect Dis J*. 2009;28(1):13–16.
- de Koning J, Tazelaar DJ, Hoogkamp-Korstanje JA, Elema JD. Acrodermatitis chronica atrophicans: a light and electron microscopic study. *J Cutan Pathol*. 1995;22(1):23–32.
- Girschick HJ, Huppertz HI, Rüssmann H, Krenn V, Karch H. Intracellular persistence of *Borrelia burgdorferi* in human synovial cells. *Rheumatol Int*. 1996;16(3):125–132.
- Barthold SW, Hodzic E, Tunev S, Feng S. Antibody-mediated disease remission in the mouse model of Lyme borreliosis. *Infect Immun*. 2006;74(8):4817–4825.

38. Berende A, Oosting M, Kullberg BJ, Netea MG, Joosten LA. Activation of innate host defense mechanisms by *Borrelia*. *Eur Cytokine Netw*. 2010;21(1):7–18.
39. Schröder NW, Eckert J, Stübs G, Schumann RR. Immune responses induced by spirochetal outer membrane lipoproteins and glycolipids. *Immunobiology*. 2008;213(3–4):329–340.
40. Ruderman EM, Kerr JS, Telford SR 3rd, Spielman A, Glimcher LH, Gravalles EM. Early murine Lyme carditis has a macrophage predominance and is independent of major histocompatibility complex class II-CD4+ T cell interactions. *J Infect Dis*. 1995;171(2):362–370.
41. Barthold SW, Beck DS, Hansen GM, Terwilliger GA, Moody KD. Lyme borreliosis in selected strains and ages of laboratory mice. *J Infect Dis*. 1990;162(1):133–138.
42. DePietropaolo DL, Powers JH, Gill JM, Foy AJ. Diagnosis of Lyme disease. *Am Fam Physician*. 2005;72(2):297–304.
43. Smith RP, Schoen RT, Rahm DW, et al. Clinical characteristics and treatment outcome of early Lyme disease in patients with microbiologically confirmed erythema migrans. *Ann Intern Med*. 2002;136(6):421–428.
44. Hengge UR, Tannapfel A, Tyring SK, Erbel R, Arendt G, Ruzicka T. Lyme borreliosis. *Lancet Infect Dis*. 2003;3(8):489–500.
45. Berger BW. Dermatologic manifestations of Lyme disease. *Rev Infect Dis*. 1989;11 Suppl 6:S1475–S1481.
46. Aucott J, Morrison C, Munoz B, Rowe PC, Schwarzwaldner A, West SK. Diagnostic challenges of early Lyme disease: lessons from a community case series. *BMC Infect Dis*. 2009;9:79.
47. Dattwyler RJ, Halperin JJ, Volkman DJ, Luft BJ. Treatment of late Lyme borreliosis – randomised comparison of ceftriaxone and penicillin. *Lancet*. 28 1988;1(8596):1191–1194.
48. Bhat C, Schwartz RA. Lyme disease Part I. Advances and perspectives. *J Am Acad Dermatol*. 2011;64(4):619–636.
49. Nowakowski J, McKenna D, Nadelman RB, et al. Failure of treatment with cephalexin for Lyme disease. *Arch Fam Med*. 2000;9(6):563–567.
50. Steere AC, Bartenhagen NH, Craft JE, et al. The early clinical manifestations of Lyme disease. *Ann Intern Med*. 1983;99(1):76–82.
51. Centers for Disease Control and Prevention (CDC). Lyme disease (*Borrelia burgdorferi*): 2011 case definition. Atlanta, GA: CDC; 2011 [updated August 5, 2011]. Available from: http://www.cdc.gov/osels/ph_surveillance/nndss/casedef/lyme_disease_Current.htm. Accessed September 16, 2011.
52. Costello JM, Alexander ME, Greco KM, Perez-Atayde AR, Laussen PC. Lyme carditis in children: presentation, predictive factors, and clinical course. *Pediatrics*. 2009;123(5):e835–e841.
53. Davidson RS. Orthopaedic complications of Lyme disease in children. *Biomed Pharmacother*. 1989;43(6):405–408.
54. Tager FA, Fallon BA, Keilp J, Rissenberg M, Jones CR, Liebowitz MR. A controlled study of cognitive deficits in children with chronic Lyme disease. *J Neuropsychiatry Clin Neurosci*. 2001;13(4):500–507.
55. Chmelik E, Awadallah N, Hadi FS, Quinn K, Franco K. Varied presentation of PANDAS: a case series. *Clin Pediatr (Phila)*. 2004;43(4):379–382.
56. Fallon BA, Levin ES, Schweitzer PJ, Hardesty D. Inflammation and central nervous system Lyme disease. *Neurobiol Dis*. 2010;37(3):534–541.
57. Steere AC, Coburn J, Glickstein L. The emergence of Lyme disease. *J Clin Invest*. 2004;113(8):1093–1101.
58. Wang G, Ojaimi C, Wu H, et al. Disease severity in a murine model of Lyme borreliosis is associated with the genotype of the infecting *Borrelia burgdorferi* sensu stricto strain. *J Infect Dis*. 2002;186(6):782–791.
59. Weis JJ, McCracken BA, Ma Y, et al. Identification of quantitative trait loci governing arthritis severity and humoral responses in the murine model of Lyme disease. *J Immunol*. 1999;162(2):948–956.
60. Pachner AR, Cadavid D, Shu G, et al. Central and peripheral nervous system infection, immunity, and inflammation in the NHP model of Lyme borreliosis. *Ann Neurol*. 2001;50(3):330–338.
61. García-Moncó JC, Fernández Villar B, Benach JL. Lyme borreliosis: neurologic manifestations. *Neurologia*. 1990;5(9):315–322. Spanish.
62. Coleman JL, Sellati TJ, Testa JE, Kew RR, Furie MB, Benach JL. *Borrelia burgdorferi* binds plasminogen, resulting in enhanced penetration of endothelial monolayers. *Infect Immun*. 1995;63(7):2478–2484.
63. Sellati TJ, Burns MJ, Ficazzola MA, Furie MB. *Borrelia burgdorferi* upregulates expression of adhesion molecules on endothelial cells and promotes transendothelial migration of neutrophils in vitro. *Infect Immun*. 1995;63(11):4439–4447.
64. Grab DJ, Perides G, Dumler JS, et al. *Borrelia burgdorferi*, host-derived proteases, and the blood-brain barrier. *Infect Immun*. 2005;73(2):1014–1022.
65. Phillips SE, Harris NS, Horowitz R, Johnson L, Stricker RB. Lyme disease: scratching the surface. *Lancet*. 2005;366(9499):1771.
66. Norman MU, Moriarty TJ, Dresser AR, Millen B, Kubes P, Chaconas G. Molecular mechanisms involved in vascular interactions of the Lyme disease pathogen in a living host. *PLoS Pathog*. 2008;4(10):e1000169.
67. Moriarty TJ, Norman MU, Colarusso P, Bankhead T, Kubes P, Chaconas G. Real-time high resolution 3D imaging of the Lyme disease spirochete adhering to and escaping from the vasculature of a living host. *PLoS Pathog*. 2008;4(6):e1000090.
68. Kandel ER, Schwartz JH, Jessell TM. *Principles of Neural Science*. 4th ed. New York, NY: McGraw-Hill, Health Professions Division; 2000.
69. Weis JJ, Ma Y, Erdile LF. Biological activities of native and recombinant *Borrelia burgdorferi* outer surface protein A: dependence on lipid modification. *Infect Immun*. 1994;62(10):4632–4636.
70. Cruz AR, Moore MW, La Vake CJ, Eggers CH, Salazar JC, Radolf JD. Phagocytosis of *Borrelia burgdorferi*, the Lyme disease spirochete, potentiates innate immune activation and induces apoptosis in human monocytes. *Infect Immun*. 2008;76(1):56–70.
71. Ramesh G, Borda JT, Dufour J, et al. Interaction of the Lyme disease spirochete *Borrelia burgdorferi* with brain parenchyma elicits inflammatory mediators from glial cells as well as glial and neuronal apoptosis. *Am J Pathol*. 2008;173(5):1415–1427.
72. Ramesh G, Borda JT, Gill A, et al. Possible role of glial cells in the onset and progression of Lyme neuroborreliosis. *J Neuroinflammation*. 2009;6:23.
73. Myers TA, Kaushal D, Philipp MT. Microglia are mediators of *Borrelia burgdorferi*-induced apoptosis in SH-SY5Y neuronal cells. *PLoS Pathog*. 2009;5(11):e1000659.
74. Chandra A, Wormser GP, Klempner MS, et al. Anti-neural antibody reactivity in patients with a history of Lyme borreliosis and persistent symptoms. *Brain Behav Immun*. 2010;24(6):1018–1024.
75. Volkman D. Letter to the editor re “Anti-neural antibody reactivity in patients with a history of Lyme borreliosis and persistent symptoms” by Chandra et al. *Brain Behav Immun*. 2010;24(6):1027; author reply 1028.
76. Stricker RB, Johnson L. Letter to the editor re “Anti-neural antibody reactivity in patients with a history of Lyme borreliosis and persistent symptoms” by Chandra et al. *Brain Behav Immun*. 2010;24(6):1025; author reply 1026.
77. Newell MK, Tobin RP, Cabrera JH, et al. TLR-mediated B cell activation results in ectopic CLIP expression that promotes B cell-dependent inflammation. *J Leukoc Biol*. 2010;88(4):779–789.
78. Luft BJ, Steinman CR, Neimark HC, et al. Invasion of the central nervous system by *Borrelia burgdorferi* in acute disseminated infection. *JAMA*. 1992;267(10):1364–1367.
79. Belman AL, Iyer M, Coyle PK, Dattwyler R. Neurologic manifestations in children with North American Lyme disease. *Neurology*. 1993;43(12):2609–2614.
80. Kieslich M, Fiedler A, Driever PH, Weis R, Schwabe D, Jacobi G. Lyme borreliosis mimicking central nervous system malignancy: the diagnostic pitfall of cerebrospinal fluid cytology. *Brain Dev*. 2000;22(6):403–406.

81. Bloom BJ, Wyckoff PM, Meissner HC, Steere AC. Neurocognitive abnormalities in children after classic manifestations of Lyme disease. *Pediatr Infect Dis J*. 1998;17(3):189–196.
82. Fallon BA, Kochevar JM, Gaito A, Nields JA. The underdiagnosis of neuropsychiatric Lyme disease in children and adults. *Psychiatr Clin North Am*. 1998;21(3):693–703, viii.
83. McAuliffe P, Brassard MR, Fallon B. Memory and executive functions in adolescents with posttreatment Lyme disease. *Appl Neuropsychol*. 2008;15(3):208–219.
84. Riedel M, Straube A, Schwarz MJ, Wilske B, Muller N. Lyme disease presenting as Tourette's syndrome. *Lancet*. 1998;351(9100):418–419.
85. Branson WP. A Clinical study on the avenues of rheumatic infection: based upon examination of 75 cases of Sydenham's chorea. *Br Med J*. 1912;2(2708):1429–1432.
86. Poynton FJ. Remarks on the infective nature of rheumatic fever, Illustrated by the study of a fatal case: read before the Medical Society of London, May 9th, 1904. *Br Med J*. 1904;1(2263):1117–1120.
87. Walker KG, Wilmshurst JM. An update on the treatment of Sydenham's chorea: the evidence for established and evolving interventions. *Ther Adv Neurol Disord*. 2010;3(5):301–309.
88. Yaddanapudi K, Hornig M, Serge R, et al. Passive transfer of streptococcus-induced antibodies reproduces behavioral disturbances in a mouse model of pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection. *Mol Psychiatry*. 2010;15(7):712–726.
89. Murphy TK, Storch EA, Turner A, Reid JM, Tan J, Lewin AB. Maternal history of autoimmune disease in children presenting with tics and/or obsessive-compulsive disorder. *J Neuroimmunol*. 2010;229(1–2):243–247.
90. Kirvan CA, Swedo SE, Snider LA, Cunningham MW. Antibody-mediated neuronal cell signaling in behavior and movement disorders. *J Neuroimmunol*. 2006;179(1–2):173–179.
91. Bartholomäus I, Kawakami N, Odoardi F, et al. Effector T cell interactions with meningeal vascular structures in nascent autoimmune CNS lesions. *Nature*. 2009;462(7269):94–98.
92. Huerta PT, Kowal C, DeGiorgio LA, Volpe BT, Diamond B. Immunity and behavior: antibodies alter emotion. *Proc Natl Acad Sci U S A*. 2006;103(3):678–683.
93. Murphy TK, Kurlan R, Leckman J. The immunobiology of Tourette's disorder, pediatric autoimmune neuropsychiatric disorders associated with *Streptococcus*, and related disorders: a way forward. *J Child Adolesc Psychopharmacol*. 2010;20(4):317–331.
94. American Psychiatric Association. *Diagnostic Criteria from DSM-IV-TR*. Washington DC: American Psychiatric Association; 2000.
95. American Psychiatric Association DSM-5 Development [home page on the Internet]. Arlington (VA): American Psychiatric Association; 2011. Available from: <http://www.dsm5.org/Pages/Default.aspx>. Accessed September 16, 2011.
96. Bernstein GA, Victor AM, Pipal AJ, Williams KA. Comparison of clinical characteristics of pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections and childhood obsessive-compulsive disorder. *J Child Adolesc Psychopharmacol*. 2010;20(4):333–340.
97. Snider LA, Lougee L, Slattery M, Grant P, Swedo SE. Antibiotic prophylaxis with azithromycin or penicillin for childhood-onset neuropsychiatric disorders. *Biol Psychiatry*. 2005;57(7):788–792.
98. Calkin CV, Carandang CG. Certain eating disorders may be a neuropsychiatric manifestation of PANDAS: case report. *J Can Acad Child Adolesc Psychiatry*. 2007;16(3):132–135.
99. Elia J, Dell ML, Friedman DF, et al. PANDAS with catatonia: a case report. Therapeutic response to lorazepam and plasmapheresis. *J Am Acad Child Adolesc Psychiatry*. 2005;44(11):1145–1150.
100. Division of Vector-Borne Infectious Diseases, Centers for Disease Control and Prevention (CDC). Lyme disease diagnosis. Atlanta (GA): CDC; 2010. Available from: http://www.cdc.gov/ncidod/dvbid/lyme/ld_humanidisease_diagnosis.htm. Accessed September 16, 2011.
101. Schutzer SE, Angel TE, Liu T, et al. Distinct cerebrospinal fluid proteomes differentiate post-treatment Lyme disease from chronic fatigue syndrome. *PLoS One*. 2011;6(2):e17287.
102. Tumani H, Cadavid D. Are high CSF levels of CXCL13 helpful for diagnosis of Lyme neuroborreliosis? *Neurology*. 2011;76(12):1034–1035.
103. Tveitnes D, Oymar K, Natas O. Laboratory data in children with Lyme neuroborreliosis, relation to clinical presentation and duration of symptoms. *Scand J Infect Dis*. 2009;41(5):355–362.
104. McIsaac WJ, Goel V, To T, Low DE. The validity of a sore throat score in family practice. *CMAJ*. 2000;163(7):811–815.
105. Tanz RR, Gerber MA, Kabat W, Rippe J, Seshadri R, Shulman ST. Performance of a rapid antigen-detection test and throat culture in community pediatric offices: implications for management of pharyngitis. *Pediatrics*. 2009;123(2):437–444.
106. Hall MC, Kieke B, Gonzales R, Belongia EA. Spectrum bias of a rapid antigen detection test for group A beta-hemolytic streptococcal pharyngitis in a pediatric population. *Pediatrics*. 2004;114(1):182–186.
107. Dranitzki Z, Steiner I. PANDAS in siblings: a common risk? *Eur J Neurol*. 2007;14(6):e4.
108. Church AJ, Dale RC. Antistreptolysin-O titers: implications for adult PANDAS; pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections. *Am J Psychiatry*. 2002;159(2):320.
109. Orvidas LJ, Slattery MJ. Pediatric autoimmune neuropsychiatric disorders and streptococcal infections: role of otolaryngologist. *Laryngoscope*. 2001;111(9):1515–1519.
110. Mink J, Kurlan R. Acute postinfectious movement and psychiatric disorders in children and adolescents. *J Child Neurol*. 2011;26(2):214–217.
111. Kuluva J, Hirsch S, Coffey B. PANDAS and paroxysms: a case of conversion disorder? *J Child Adolesc Psychopharmacol*. 2008;18(1):109–115.
112. Fusco FR, Pompa A, Bernardi G, et al. A case of PANDAS treated with tetrabenazine and tonsillectomy. *J Child Neurol*. 2010;25(5):614–615.
113. Segarra AR, Murphy TK. Cardiac involvement in children with PANDAS. *J Am Acad Child Adolesc Psychiatry*. 2008;47(5):603–604.
114. Bodner SM, Morshed SA, Peterson BS. The question of PANDAS in adults. *Biol Psychiatry*. 2001;49(9):807–810.
115. Bernardino AL, Kaushal D, Philipp MT. The antibiotics doxycycline and minocycline inhibit the inflammatory responses to the Lyme disease spirochete *Borrelia burgdorferi*. *J Infect Dis*. 2009;199(9):1379–1388.
116. Cameron D, Gaito A, Harris N, et al. Evidence-based guidelines for the management of Lyme disease. *Expert Rev Anti Infect Ther*. 2004;2(1 Suppl):S1–S13.
117. Wormser GP, Dattwyler RJ, Shapiro ED, et al. The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis*. 2006;43(9):1089–1134.
118. Johnson L. Lyme disease: two standards of care. Bethesda (MA): International Lyme and Associated Diseases Society; 2005 [updated Feb 2005]; Available from: http://www.ilads.org/lyme_research/lyme_articles4.html. Accessed September 16, 2011.
119. Steere AC, Klitz W, Drouin EE, et al. Antibiotic-refractory Lyme arthritis is associated with HLA-DR molecules that bind a *Borrelia burgdorferi* peptide. *J Exp Med*. 2006;203(4):961–971.
120. Seward RJ, Drouin EE, Steere AC, Costello CE. Peptides presented by HLA-DR molecules in synovia of patients with rheumatoid arthritis or antibiotic-refractory Lyme arthritis. *Mol Cell Proteomics*. 2011;10(3):M110.002477.
121. Wessels MR. Clinical practice: streptococcal pharyngitis. *N Engl J Med*. 2011;364(7):648–655.

122. Murphy ML, Pichichero ME. Prospective identification and treatment of children with pediatric autoimmune neuropsychiatric disorder associated with group A streptococcal infection (PANDAS). *Arch Pediatr Adolesc Med.* 2002;156(4):356–361.
123. Garvey MA, Perlmutter SJ, Allen AJ, et al. A pilot study of penicillin prophylaxis for neuropsychiatric exacerbations triggered by streptococcal infections. *Biol Psychiatry.* 1999;45(12):1564–1571.
124. Perlmutter SJ, Leitman SF, Garvey MA, et al. Therapeutic plasma exchange and intravenous immunoglobulin for obsessive-compulsive disorder and tic disorders in childhood. *Lancet.* 1999; 354(9185):1153–1158.
125. Nicolson R, Swedo SE, Lenane M, et al. An open trial of plasma exchange in childhood-onset obsessive-compulsive disorder without poststreptococcal exacerbations. *J Am Acad Child Adolesc Psychiatry.* 2000;39(10):1313–1315.
126. Heubi C, Shott SR. PANDAS: pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections; an uncommon, but important indication for tonsillectomy. *Int J Pediatr Otorhinolaryngol.* 2003;67(8):837–840.
127. Batuecas Caletrio A, Sanchez Gonzalez F, Santa Cruz Ruiz S, Santos Gorjon P, Blanco Perez P. PANDAS syndrome: a new tonsillectomy indication? *Acta Otorrinolaringol Esp.* 2008;59(7):362–363. Spanish.
128. Coffey B, Wieland N. Tics, anxiety, and possible PANDAS in an adolescent. *J Child Adolesc Psychopharmacol.* 2007;17(4):533–538.
129. Chadehumbe MA, Greydanus DE, Feucht C, Patel DR. Psychopharmacology of tic disorders in children and adolescents. *Pediatr Clin North Am.* 2011;58(1):259–272, xiii.
130. Flessner CA. Cognitive-behavioral therapy for childhood repetitive behavior disorders: tic disorders and trichotillomania. *Child Adolesc Psychiatr Clin N Am.* 2011;20(2):319–328.
131. Storch EA, Murphy TK, Geffken GR, et al. Cognitive-behavioral therapy for PANDAS-related obsessive-compulsive disorder: findings from a preliminary waitlist controlled open trial. *J Am Acad Child Adolesc Psychiatry.* 2006;45(10):1171–1178.
132. Hamlen RA, Kliman DS. Pediatric Lyme disease: a school issue; tips for school nurses. *NASN Sch Nurse.* 2009;24(3):114–115, 118.
133. Pavone P, Bianchini R, Parano E, et al. Anti-brain antibodies in PANDAS versus uncomplicated streptococcal infection. *Pediatr Neurol.* 2004;30(2):107–110.
134. Snider LA, Sachdev V, MaCkaronis JE, St Peter M, Swedo SE. Echocardiographic findings in the PANDAS subgroup. *Pediatrics.* 2004;114(6):e748–e751.
135. Edwards MJ, Dale RC, Church AJ, et al. Adult-onset tic disorder, motor stereotypies, and behavioural disturbance associated with antibasal ganglia antibodies. *Mov Disord.* 2004;19(10):1190–1196.
136. Lewin AB, Storch EA, Murphy TK. Pediatric autoimmune neuropsychiatric disorders associated with streptococcus in identical siblings. *J Child Adolesc Psychopharmacol.* 2011;21(2):177–182.
137. Ercan TE, Ercan G, Sevrge B, Arpaozu M, Karasu G. *Mycoplasma pneumoniae* infection and obsessive-compulsive disease: a case report. *J Child Neurol.* 2008;23(3):338–340.
138. Termine C, Uggetti C, Veggiotti P, et al. Long-term follow-up of an adolescent who had bilateral striatal necrosis secondary to *Mycoplasma pneumoniae* infection. *Brain Dev.* 2005;27(1):62–65.
139. Muller N, Riedel M, Forderreuther S, Blendinger C, Abele-Horn M. Tourette's syndrome and *Mycoplasma pneumoniae* infection. *Am J Psychiatry.* 2000;157(3):481–482.
140. Wolff K, Johnson RA. *Fitzpatrick's Color Atlas and Synopsis of Clinical Dermatology.* 6th ed. New York (NY): McGraw-Hill Professional; 2009.
141. Goldberg EM, Rotondo KM. Complete atrioventricular block due to Lyme reinfection in a six year-old boy. *Med Health R I.* 2010;93(5): 158–160.
142. Perry CB. Erythema marginatum (rheumaticum). *Arch Dis Child.* 1937;12(70):233–238.
143. Frank DB, Patel AR, Sanchez GR, Shah MJ, Bonney WJ. Junctional tachycardia in a child with Lyme carditis. *Pediatr Cardiol.* 2011;32(5): 689–691.
144. Lo R, Menzies DJ, Archer H, Cohen TJ. Complete heart block due to lyme carditis. *J Invasive Cardiol.* 2003;15(6):367–369.
145. McAlister HF, Klementowicz PT, Andrews C, Fisher JD, Feld M, Furman S. Lyme carditis: an important cause of reversible heart block. *Ann Intern Med.* 1989;110(5):339–345.
146. Alto WA, Gibson R. Acute rheumatic fever: an update. *Am Fam Physician.* 1992;45(2):613–620.
147. Special Writing Group of the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the Council on Cardiovascular Disease in the Young of the American Heart Association. Guidelines for the diagnosis of rheumatic fever: Jones Criteria, 1992 update. *JAMA.* 1992;268(15):2069–2073.
148. Steere AC, Malawista SE, Hardin JA, Ruddy S, Askenase W, Andiman WA. Erythema chronicum migrans and Lyme arthritis: the enlarging clinical spectrum. *Ann Intern Med.* 1977;86(6):685–698.
149. Szer IS, Taylor E, Steere AC. The long-term course of Lyme arthritis in children. *N Engl J Med.* 1991;325(3):159–163.
150. Glynn MW, Elmer BM, Garay PA, et al. MHCI negatively regulates synapse density during the establishment of cortical connections. *Nat Neurosci.* 2011;14(4):442–451.
151. Xia D, Shen K, Zhong W, Pan H. Administration of minocycline ameliorates damage in a renal ischemia/reperfusion injury model. *Clin Invest Med.* 2011;34(2):E55.
152. Sinha-Hikim I, Shen R, Nzenwa I, Gelfand R, Mahata SK, Sinha-Hikim AP. Minocycline suppresses oxidative stress and attenuates fetal cardiac myocyte apoptosis triggered by in utero cocaine exposure. *Apoptosis.* 2011;16(6):563–573.
153. Dumont EA, Lutgens SP, Reutlingsperger CP, Bos GM, Hofstra L. Minocycline inhibits apoptotic cell death in a murine model of partial flap loss. *J Reconstr Microsurg.* 2010;26(8):523–528.
154. Kernt M, Neubauer AS, Eibl KH, et al. Minocycline is cytoprotective in human trabecular meshwork cells and optic nerve head astrocytes by increasing expression of XIAP, survivin, and Bcl-2. *Clin Ophthalmol.* 2010;4:591–604.
155. Kernt M, Hirneiss C, Neubauer AS, Kampik A. Minocycline is cytoprotective in human corneal endothelial cells and induces anti-apoptotic B-cell CLL/lymphoma 2 (Bcl-2) and X-linked inhibitor of apoptosis (XIAP). *Br J Ophthalmol.* 2010;94(7):940–946.
156. Griffin MO, Ceballos G, Villarreal FJ. Tetracycline compounds with non-antimicrobial organ protective properties: possible mechanisms of action. *Pharmacol Res.* 2011;63(2):102–107.
157. Yang L, Kim JH, Kovacs KD, Arroyo JG, Chen DF. Minocycline inhibition of photoreceptor degeneration. *Arch Ophthalmol.* 2009;127(11):1475–1480.
158. Kim HS, Suh YH. Minocycline and neurodegenerative diseases. *Behav Brain Res.* 2009;196(2):168–179.
159. Kikuchi K, Kawahara K, Biswas KK, et al. Minocycline attenuates both OGD-induced HMGB1 release and HMGB1-induced cell death in ischemic neuronal injury in PC12 cells. *Biochem Biophys Res Commun.* 2009;385(2):132–136.
160. Levkovitz Y, Mendlovich S, Riwkes S, et al. A double-blind, randomized study of minocycline for the treatment of negative and cognitive symptoms in early-phase schizophrenia. *J Clin Psychiatry.* 2010; 71(2):138–149.
161. Miyaoka T. Clinical potential of minocycline for schizophrenia. *CNS Neurol Disord Drug Targets.* 2008;7(4):376–381.
162. Horiyaka T, Yasukawa R, Yasuda H, Hayashida M, Inagaki T, Horiguchi J. Minocycline as adjunctive therapy for schizophrenia: an open-label study. *Clin Neuropharmacol.* 2008;31(5):287–292.
163. Fritzsche M. Seasonal correlation of sporadic schizophrenia to *Ixodes* ticks and Lyme borreliosis. *Int J Health Geogr.* 2002;1(1):2.
164. Fritzsche M, Schmidli J. Seasonal fluctuation in schizophrenia. *Am J Psychiatry.* 2002;159(3):499–500.

165. Cannon M. Minocycline (Minocin). Atlanta, GA: American College of Rheumatology; 2010 [updated Sep 2009]. Available from: <http://www.rheumatology.org/practice/clinical/patients/medications/minocycline.asp>. Accessed September 21, 2011.
166. Steere AC, Angelis SM. Therapy for Lyme arthritis: strategies for the treatment of antibiotic-refractory arthritis. *Arthritis Rheum*. 2006;54(10):3079–3086.
167. Stricker RB, Johnson L. Searching for autoimmunity in “antibiotic-refractory” Lyme arthritis. *Mol Immunol*. 2008;45(11):3023–3024.
168. Lettau LA. From the centers for fatigue control (CFC) weekly report: Lyme disease; United States. *Ann Intern Med*. 1991;114:602.

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