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REVIEW

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 Grant[7] 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, nonmotile 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-IV*®[5] 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 al[46] 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 steroids[46] 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 GAβHS is reportedly a cause of acute pharyngitis in up to 30% of children,[9] viral or other bacterial etiologies may need further consideration.

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: [a]Number of "+" symbols denotes relative reporting in referenced publications.
Abbreviations: LD, Lyme disease; NS, not significant; PANDAS, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections.

Neuropsychiatric signs and symptoms

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

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 severity[57] have been attributed to genomic variations of bacterial strains[58] 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 al[66] and Moriarty et al[67] 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 al[23] collaborated with the US Army to photograph atypical and cystic states which were then successfully cultured in growth media. Weis et al[69] 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 al[73] 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 al[77] 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 al[79] 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 al[84] 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 al[54] 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.

GAβHS 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 sera[90] 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 al[91] 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 al[90] 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 GAβHS cell wall epitope *N*-acetyl-beta-*D*-glucosamine.

Resulting neuropsychiatric pathology seen in PANDAS meeting the 1998 criteria[7] is episodic and acute OCD and/or neurologic tics (defined by the outdated *DSM-IV*®[5] criteria) in temporal relation with GAβHS 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*®,[5] 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 al[96] 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 others[55] 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 GAβHS 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 scoring[105] 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 GAβHS-induced neuropsychiatric disorder remains controversial, protocols are provisional at best. Irregardless of PANDAS diagnosis, children with evidence of GAβHS 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. GAβHS infection occurring temporally with OCD or neurologic tics may be coincidental, given the high incidence of GAβHS 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 GAβHS-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 GAβHS 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 GAβHS 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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