



# Does Lyme Disease Cause PANS?

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In 1994, Susan Swedo and colleagues described children who developed mental health issues following infection with Group A *Streptococcus* (GAS) infections, and in a subsequent report coined the term Pediatric Autoimmune Neuropsychiatric Disorders Associated with *Streptococcal* Infections (PANDAS) [1,2]. In short order it was discovered that multiple microbes have the potential of triggering mental health issues in children and adolescents, and the nomenclature was updated to Pediatric Acute-Onset Neuropsychiatric Syndrome (PANS) [3]. The microbes that thus far have been associated with PANS include herpes simplex virus, influenza A virus, varicella virus, HIV, recurrent sinusitis, Epstein-Barr virus, the common cold, *Mycoplasma pneumoniae* and *Bartonella henselae* [4-6].

The criteria for PANS include the abrupt onset of severely restricted food intake or Obsessive-Compulsive Disorder (OCD) without an underlying medical disorder, accompanied by at least two of the following seven conditions [3]:

- Depression and/or emotional lability
- Anxiety
- Irritability, aggression and/or oppositional behavior
- Developmental (behavioral) regression
- Deterioration in school performance, cognitive changes
- Motor or sensory abnormalities, including choreiform movements and tics
- Somatic signs or symptoms, such as sleep disorders and enuresis

Lyme disease is an infection caused by the *Borrelia burgdorferi* (*B. burgdorferi*) bacterium. It is transmitted by the *Ixodes* tick and can generate multisystem complaints. Persistent infection generating chronic neurological symptoms is well documented [7-16]. It is now appreciated that *B. burgdorferi* can cause a host of psychiatric issues [17-24]. Lyme disease in children has been reported to cause anxiety, panic attacks, depression, irritability/oppositional disorders, personality disorders, attention deficit hyperactivity disorder, psychosis, OCD, eating disorders, cognitive difficulties with decline in school performance, and many somatic symptoms such as sleep disorder, musculoskeletal pain as well as tics [17,25-31].

It is clear that children with PANS manifest symptoms that parallel those with neurological Lyme disease. PANS appears to be caused by immune cross-reactivity between microbes and host tissues generating neuroinflammation. Children with PANS often have elevations in antineuronal antibodies against lysoganglioside [32], tubulin [33], and dopamine receptors [34-36], as well as activation of calcium Calmodulin-Dependent Protein Kinase II (CaMKII) [37]. CaMKII alters dopamine pathways, which in turn can lead to neuropsychiatric symptoms [37,38]. The Cunningham Panel, which includes levels of these antibodies as well as CaMKII activity, was developed to assess patients with PANS-like syndromes.

The utility of the Cunningham Panel in the diagnosis of PANDAS/PANS has been demonstrated by multiple investigators. Shimasaki, et al. [39] tested 58

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subjects who met criteria for PANS, both pre- and post-treatment, and found that the changes in Cunningham Panel assays paralleled changes in patients' symptoms with a 90% accuracy. Chain, et al. [40] found that 28 of 35 (91.4%) acute onset PANDAS patients were positive for one or more antineuronal antibodies compared to 9 of 28 (32.1%) healthy controls. Cox, et al. [32] found a significant correlation between GAS, tics and OCD with antibodies to lysoganglioside and dopamine receptor D1 as well as higher activation of CaMKII compared to healthy controls. Multiple other studies have documented the association between autoimmune neuropsychiatric conditions such as PANDAS/PANS and antineuronal antibodies included in the Cunningham Panel [41-51]. Bejerot and Hesselmark have challenged the utility of the Cunningham Panel in the diagnosis of PANS, as they did not find a difference in the Cunningham Panel biomarkers in PANS patients vs. healthy controls [52]. However, their findings have been refuted by Frye and Shimasaki because, among other issues, they used invalid collection tubes [53].

Two recent reports suggest a causal connection between Lyme disease and PANS. Fallon, et al. [54] tested 32 patients with a recent episode of acute Lyme disease (exhibiting erythema migrans rashes), eight of whom had prior episodes of Lyme disease, as well as 119 patients who had chronic symptoms following treatment for acute Lyme disease. These were compared to 28 seronegative controls without a prior history of Lyme disease. The two groups of patients who had previous episodes of Lyme disease had higher antibody levels against lysoganglioside, tubulin and dopamine receptors as well as increased activation of CaMKII compared to those with recent acute Lyme disease and the controls. The subjects in this study were adults with a mean age of 56, and there was no report of neuropsychiatric symptoms other than cognitive impairment. Nevertheless, the clear association of an elevation of antineuronal antibodies and CaMKII activation, i.e., abnormal Cunningham Panels, in patients with a history of Lyme disease suggests the capacity of *B. burgdorferi* to trigger PANS.

The second article, by Cross, et al. [55] is a case report of a seven-year-old girl who began having physical, neurological, and psychiatric symptoms following a vacation in a tick endemic area. She tested positive for GAS and was treated with repeated courses of amoxicillin without relief. Subsequent testing revealed a Centers for Disease Control and Prevention (CDC) positive Western blot for Lyme disease, and later she exhibited a significant elevation in IgM to *Babesia duncani* (*B. duncani*), a coinfection of Lyme disease that is also transmitted by the *Ixodes* tick. She was treated with intravenous ceftriaxone as well as several oral antibiotics. A Cunningham Panel revealed significant elevations in antibodies to dopamine receptors D1 and D2 and tubulin, and the patient was treated with Intravenous

Immunoglobulin (IVIG) for three months. After three years of treatment the patient became asymptomatic, labs normalized, and treatment was discontinued; she has stayed in remission five years later.

This child's symptoms and abnormal Cunningham Panel clearly indicate that she suffered from PANS. She manifested a polymicrobial infection including GAS, *B. burgdorferi*, and *B. duncani*, and eventually responded to multiple antibiotics and immunomodulation with IVIG. This case illustrates the difficulty in determining whether *B. burgdorferi* can cause PANS. Any one of these pathogens could have triggered a PANS syndrome, or perhaps a combination of microbes stimulated neuroinflammation and autoimmune encephalitis. The authors of this case history note that her improvement began when clindamycin was added to her regimen, suggesting infection with *Babesia* significantly contributed to her condition (Clindamycin along with quinine was the mainstay protocol for treating babesiosis until 2000 when Krause, et al. [56] described the efficacy of atovaquone and azithromycin).

In fact, it is likely that the preponderance of patients with persistent symptoms of Lyme disease despite treatment for *B. burgdorferi* have coinfections [57-61]. Coinfection of ticks is now "the rule rather than the exception", as highlighted by Moutailler, et al. [62] who found that coinfections occurred in almost half of all infected *Ixodes* ticks in the French Ardennes; single ticks had up to five different pathogens. Similarly, Adelson, et al. [63] analyzed *Ixodes* ticks in New Jersey and found that while 34% harbored *B. burgdorferi*, 34% had *Bartonella henselae*, 8% *Babesia microti*, and 2% *Anaplasma phagocytophila*. Multiple other surveys of the tick population have documented the high prevalence of coinfecting ticks [64-66].

Most reports of patients with Lyme disease have not included evaluations for coinfections. In a survey of 3,000 individuals who continued to be symptomatic at least six months following treatment for Lyme disease, 50% were diagnosed with coinfections, and 30% with two or more coinfections. The most common coinfections were *Babesia* and *Bartonella* [67]. A similar survey of 102 patients in Canada found only 40 who were diagnosed with only Lyme disease; 28 with one coinfection, 22 with two coinfections, and 16 with three or more coinfections [68]. Garg, et al. [58] analyzed the sera of from 432 patients who satisfied CDC surveillance criteria for Lyme disease, and reported that there is an 85% probability that patients with Lyme disease have tick-borne coinfections. In other words, persistent Lyme disease is most often a polymicrobial event, and it is unclear how many of the symptoms are generated by *B. burgdorferi*. Coinfections could be directly responsible for causing neuropsychiatric symptoms and triggering PANS.

It is noteworthy that 15% of those 3000 patients in the survey cited above were diagnosed with *Mycoplasma*. This microbe is capable of triggering autoimmune disorders and neuropsychiatric symptoms including acute psychosis [69,70], OCD [71], and mania [72], as well as PANS [73-75]. *Bartonella*, a common coinfection, can cause a plethora of neuropsychiatric symptoms similar to the ones described above in children with Lyme disease [76-79], as well as a host of autoimmune conditions [80-94]. In fact, *Bartonella* is a documented cause of PANS [6].

In the report by Fallon, et al. [54] patients were not tested for coinfections. It is entirely possible that the antineuronal antibodies detected in patients with previous Lyme disease were actually triggered by coinfecting microbes. At this time, there is insufficient evidence to indict *B. burgdorferi* as a cause of PANS.

On the other hand, the study by Fallon, et al. [54] raises another important issue. Is PANS limited to those with the acute onset of neuropsychiatric symptoms in the pediatric population? Neuropsychiatric symptoms are a prominent manifestation of persistent Lyme disease, with the same manifestations in adults as in children (described above) and then some. Rhee and Cameron have outlined the similarities of neuropsychiatric symptoms in adults with Lyme disease and children with PANDAS [24]. Specialized Positron Emission Tomography (PET) scans have demonstrated cerebral glial activation in patients with chronic symptoms following treatment for Lyme disease [95]. Chandra, et al. [96] found that antibodies against *B. burgdorferi* cross-reacted with several antineuronal proteins in 41 of 83 (49.4%) patients who continued to be symptomatic following treatment for Lyme disease. The identification of antineuronal antibodies and activation of CaMKII in adults by Fallon, et al. [54] suggests that microbial induced neuroinflammation resulting in neuropsychiatric symptoms is not limited to the pediatric population. Furthermore, the onset of these symptoms, as described in multiple case studies, can be gradual, variable, and intermittent, and not limited to acute presentations.

I suggest that it is time to broaden the nomenclature of PANS to include adults. I suggest Microbe-induced Autoimmune Neuropsychiatric Syndrome (MANS).

**Acronyms:** GAS: Group A *Streptococcus*; PANDAS: Pediatric Autoimmune Neuropsychiatric Disease Associated with Streptococcal Infections; PANS: Pediatric Acute-Onset Neuropsychiatric Syndrome; *B. burgdorferi*: *Borrelia burgdorferi*; CaMKII: Calcium Calmodulin-Dependent Protein Kinase II; CDC: Centers for Disease Control and Prevention; IVIG: Intravenous Immunoglobulin; *B. duncani*: *Babesia duncani*; PET: Positron Emission Tomography; MANS: Microbe-Induced Autoimmune Neuropsychiatric Syndrome.

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