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# 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 heneslae*, 8% *Babesia microti*, and 2% *Anaplasma phagocytophila*. Multiple other surveys of the tick population have documented the high prevalence of coinfected 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.

## References

1. Swedo SE, Leonard HL, Kiessling LS. Speculations on antineuronal antibody-mediated neuropsychiatric disorders of childhood. Pediatrics. 1994 Feb;93(2):323-6. PMID: 8121747.
2. Swedo SE, Seidlitz J, Kovacevic M, Latimer ME, Hommer R, Lougee L, Grant P. Clinical presentation of pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections in research and community settings. J Child Adolesc Psychopharmacol. 2015 Feb;25(1):26-30. doi: 10.1089/cap.2014.0073. PMID: 25695941; PMCID: PMC4340334.
3. Chang K, Frankovich J, Cooperstock M, Cunningham MW, Latimer ME, Murphy TK, Pasternack M, Thienemann M, Williams K, Walter J, Swedo SE; PANS Collaborative Consortium. Clinical evaluation of youth with pediatric acute-onset neuropsychiatric syndrome (PANS): recommendations from the 2013 PANS Consensus Conference. J Child Adolesc Psychopharmacol. 2015 Feb;25(1):3-13. doi: 10.1089/cap.2014.0084. Epub 2014 Oct 17. PMID: 25325534; PMCID: PMC4340805.
4. Frankovich J, Thienemann M, Rana S, Chang K. Five youth with pediatric acute-onset neuropsychiatric syndrome of differing etiologies. J Child Adolesc Psychopharmacol. 2015 Feb;25(1):31-7. doi: 10.1089/cap.2014.0056. PMID: 25695942; PMCID: PMC4442568.
5. Tisi G, Marzolini M, Biffi G. Pediatric acute onset neuropsychiatric syndrome associated with Epstein–Barr infection in child with Noonan syndrome. Europ Psychiatry. 2017;41:S456. doi: 10.1016/j.eurpsy.2017.01.492.
6. Breitschwerdt EB, Greenberg R, Maggi RG, Mozayeni BR, Lewis A, Bradley JM. Bartonella henselae Bloodstream Infection in a Boy With Pediatric Acute-Onset Neuropsychiatric Syndrome. J Cent Nerv Syst Dis. 2019 Mar 18;11:1179573519832014. doi: 10.1177/1179573519832014. PMID: 30911227; PMCID: PMC6423671.
7. https://www.mayoclinic.org/diseases-conditions/lyme-disease/symptoms-causes/syc- 20374651 (Accessed February 14, 2021)
8. https://www.columbia-lyme.org/signs-and-symptoms (Accessed February 14, 2021)
9. Lawrence C, Lipton RB, Lowy FD, Coyle PK. Seronegative chronic relapsing neuroborreliosis. Eur Neurol. 1995;35(2):113-7. doi: 10.1159/000117104. PMID: 7796837.
10. Logigian EL, Kaplan RF, Steere AC. Chronic neurologic manifestations of Lyme disease. N Engl J Med. 1990 Nov 22;323(21):1438-44. doi: 10.1056/NEJM199011223232102. PMID: 2172819.
11. Shadick NA, Phillips CB, Logigian EL, Steere AC, Kaplan RF, Berardi VP, Duray PH, Larson MG, Wright EA, Ginsburg KS, Katz JN, Liang MH. The long-term clinical outcomes of Lyme disease. A population-based retrospective cohort study. Ann Intern Med. 1994 Oct 15;121(8):560-7. doi: 10.7326/0003-4819-121-8-199410150-00002. PMID: 8085687.
12. Liegner KB, Rosenkilde C, Campbell G, Quan T, Dennis D. Culture confirmed treatment failure of cefotaxime and minocycline in a case of Lyme meningoencephalomyelitis in the United States; Proceedings of the Program and Abstracts of the 5th International Conference on Lyme Borreliosis; Arlington, VA, USA. 1992 June 30.
13. Embers ME, Barthold SW, Borda JT, Bowers L, Doyle L, Hodzic E, Jacobs MB, Hasenkampf NR, Martin DS, Narasimhan S, Phillippi-Falkenstein KM, Purcell JE, Ratterree MS, Philipp MT. Persistence of Borrelia burgdorferi in rhesus macaques following antibiotic treatment of disseminated infection. PLoS One. 2012;7(1):e29914. doi: 10.1371/journal.pone.0029914. Epub 2012 Jan 11. Erratum in: PLoS One. 2012;7(4):10.1371/annotation/4cafed66-fb84-4589-a001-131d9c50aea6. Erratum in: PLoS One. 2013;8(9). doi:10.1371/annotation/f84663e3-0a2c-4243-8f97-3a58133c1b0f. PMID: 22253822; PMCID: PMC3256191.
14. Embers ME, Hasenkampf NR, Jacobs MB, Tardo AC, Doyle-Meyers LA, Philipp MT, Hodzic E. Variable manifestations, diverse seroreactivity and post-treatment persistence in non-human primates exposed to Borrelia burgdorferi by tick feeding. PLoS One. 2017 Dec 13;12(12):e0189071. doi: 10.1371/journal.pone.0189071. PMID: 29236732; PMCID: PMC5728523.
15. Hodzic E, Imai D, Feng S, Barthold SW. Resurgence of persisting non-cultivable Borrelia burgdorferi following antibiotic treatment in mice. PLoS One. 2014 Jan 23;9(1):e86907. doi: 10.1371/journal.pone.0086907. PMID: 24466286; PMCID: PMC3900665.
16. Oksi J, Kalimo H, Marttila RJ, Marjamäki M, Sonninen P, Nikoskelainen J, Viljanen MK. Inflammatory brain changes in Lyme borreliosis. A report on three patients and review of literature. Brain. 1996 Dec;119 ( Pt 6):2143-54. doi: 10.1093/brain/119.6.2143.

PMID: 9010017.

17. Bransfield RC. Neuropsychiatric Lyme Borreliosis: An Overview with a Focus on a Specialty Psychiatrist's Clinical Practice. Healthcare (Basel). 2018 Aug 25;6(3):104. doi: 10.3390/healthcare6030104. PMID: 30149626; PMCID: PMC6165408.

18. Fallon BA, Nields JA. Lyme disease: a neuropsychiatric illness. Am J Psychiatry. 1994 Nov;151(11):1571-83. doi: 10.1176/ajp.151.11.1571. PMID: 7943444.

19. Fallon BA, Nields JA, Burrascano JJ, Liegner K, DelBene D, Liebowitz MR. The neuropsychiatric manifestations of Lyme borreliosis. Psychiatr Q. 1992 Spring;63(1):95-117. doi: 10.1007/BF01064684. PMID: 1438607.

20. Fallon BA, Nields JA. Lyme disease: a neuropsychiatric illness. Am J Psychiatry. 1994 Nov;151(11):1571-83. doi: 10.1176/ajp.151.11.1571. PMID: 7943444.

21. Fallon BA, Kochevar JM, Gaito A, Nields JA. The underdiagnosis of neuropsychiatric Lyme disease in children and adults. Psychiatr Clin North Am. 1998 Sep;21(3):693-703, viii. doi: 10.1016/s0193-953x(05)70032-0. PMID: 9774805.

22. Bransfield RC. Aggressiveness, violence, homicidality, homicide, and Lyme disease. Neuropsychiatr Dis Treat. 2018 Mar 9;14:693-713. doi: 10.2147/NDT.S155143. PMID: 29576731; PMCID: PMC5851570.

23. Mattingley DW, Koola MM. Association of Lyme Disease and Schizoaffective Disorder, Bipolar Type: Is it Inflammation Mediated? Indian J Psychol Med. 2015 Apr-Jun;37(2):243-6. doi: 10.4103/0253-7176.155660. PMID: 25969618; PMCID: PMC4418265.

24. Rhee H, Cameron DJ. Lyme disease and pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS): an overview. Int J Gen Med. 2012;5:163-74. doi: 10.2147/IJGM.S24212. Epub 2012 Feb 22. PMID: 22393303; PMCID: PMC3292400.

25. Greenberg R. Infections and childhood psychiatric disorders: tick-borne illness and bipolar disorder in youth. Bipolar Disord. 2017;3:113.

26. Bransfield RC, Wulfman JS, Harvey WT, Usman AI. The association between tick-borne infections, Lyme borreliosis and autism spectrum disorders. Med Hypotheses. 2008;70(5):967-74. doi: 10.1016/j.mehy.2007.09.006. Epub 2007 Nov 5. PMID: 17980971.

27. Bloom BJ, Wyckoff PM, Meissner HC, Steere AC. Neurocognitive abnormalities in children after classic manifestations of Lyme disease. Pediatr Infect Dis J. 1998 Mar;17(3):189-96. doi: 10.1097/00006454-199803000-00004. PMID: 9535244.

28. Fallon BA, Kochevar JM, Gaito A, Nields JA. The underdiagnosis of neuropsychiatric Lyme disease in children and adults. Psychiatr Clin North Am. 1998 Sep;21(3):693-703, viii. doi: 10.1016/s0193-953x(05)70032-0. PMID: 9774805.

29. McAuliffe P, Brassard MR, Fallon B. Memory and executive functions in adolescents with posttreatment Lyme disease. Appl Neuropsychol. 2008;15(3):208-19. doi: 10.1080/09084280802324473. PMID: 18726742.

30. 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 Fall;13(4):500-7. doi: 10.1176/jnp.13.4.500. PMID: 11748319.

31. Riedel M, Straube A, Schwarz MJ, Wilske B, Müller N. Lyme disease presenting as Tourette's syndrome. Lancet. 1998 Feb 7;351(9100):418-9. doi: 10.1016/S0140-6736(05)78357-4. PMID: 9482302.

32. Cox CJ, Zuccolo AJ, Edwards EV, Mascaro-Blanco A, Alvarez K, Stoner J, Chang K, Cunningham MW. Antineuronal antibodies in a heterogeneous group of youth and young adults with tics and obsessive-compulsive disorder. J Child Adolesc Psychopharmacol. 2015 Feb;25(1):76-85. doi: 10.1089/cap.2014.0048. Epub 2015 Feb 6. PMID: 25658702; PMCID: PMC4340634.

33. Kirvan CA, Cox CJ, Swedo SE, Cunningham MW. Tubulin is a neuronal target of autoantibodies in Sydenham's chorea. J Immunol. 2007 Jun 1;178(11):7412-21. doi: 10.4049/jimmunol.178.11.7412. PMID: 17513792.

34. Cunningham MW, Cox CJ. Autoimmunity against dopamine receptors in neuropsychiatric and movement disorders: a review of Sydenham chorea and beyond. Acta Physiol (Oxf). 2016 Jan;216(1):90-100. doi: 10.1111/apha.12614. Epub 2015 Nov 5. PMID: 26454143; PMCID: PMC5812018.

35. Cox CJ, Sharma M, Leckman JF, Zuccolo J, Zuccolo A, Kovoor A, Swedo SE, Cunningham MW. Brain human monoclonal autoantibody from sydenham chorea targets dopaminergic neurons in transgenic mice and signals dopamine D2 receptor: implications in human disease. J Immunol. 2013 Dec 1;191(11):5524-41. doi: 10.4049/jimmunol.1102592. Epub 2013 Nov 1. PMID: 24184556; PMCID: PMC3848617.

36. Brimberg L, Benhar I, Mascaro-Blanco A, Alvarez K, Lotan D, Winter C, Klein J, Moses AE, Somnier FE, Leckman JF, Swedo SE, Cunningham MW, Joel D. Behavioral, pharmacological, and immunological abnormalities after streptococcal exposure: a novel rat model of Sydenham chorea and related neuropsychiatric disorders. Neuropsychopharmacology. 2012 Aug;37(9):2076-87. doi: 10.1038/npp.2012.56. Epub 2012 Apr 25. PMID: 22534626; PMCID: PMC3398718.

37. Robison AJ. Emerging role of CaMKII in neuropsychiatric disease. Trends Neurosci. 2014 Nov;37(11):653-62. doi: 10.1016/j.tins.2014.07.001. Epub 2014 Jul 30. PMID: 25087161.

38. Liu XY, Mao LM, Zhang GC, Papasian CJ, Fibuch EE, Lan HX, Zhou HF, Xu M, Wang JQ. Activity-dependent modulation of limbic dopamine D3 receptors by CaMKII. Neuron. 2009 Feb 12;61(3):425-38. doi: 10.1016/j.neuron.2008.12.015. PMID: 19217379; PMCID: PMC2650276.

39. Shimasaki C, Frye RE, Trifiletti R, Cooperstock M, Kaplan G, Melamed I, Greenberg R, Katz A, Fier E, Kem D, Traver D, Dempsey T, Latimer ME, Cross A, Dunn JP, Bentley R, Alvarez K, Reim S, Appleman J. Evaluation of the Cunningham Panel™ in pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection (PANDAS) and pediatric acute-onset neuropsychiatric syndrome (PANS): Changes in antineuronal antibody titers parallel changes in patient symptoms. J Neuroimmunol. 2020 Feb 15;339:577138. doi: 10.1016/j.jneuroim.2019.577138. Epub 2019 Dec 15. PMID: 31884258.

40. Chain JL, Alvarez K, Mascaro-Blanco A, Reim S, Bentley R, Hommer R, Grant P, Leckman JF, Kawikova I, Williams K, Stoner JA, Swedo SE, Cunningham MW. Autoantibody Biomarkers for Basal Ganglia Encephalitis in Sydenham Chorea and Pediatric Autoimmune Neuropsychiatric Disorder Associated With Streptococcal Infections. Front Psychiatry. 2020 Jun 24;11:564. doi: 10.3389/fpsyt.2020.00564. PMID: 32670106; PMCID: PMC7328706.

41. Cunningham MW, Cox CJ. Autoimmunity against dopamine receptors in neuropsychiatric and movement disorders: a review of Sydenham chorea and beyond. Acta Physiol (Oxf). 2016 Jan;216(1):90-100. doi: 10.1111/apha.12614. Epub 2015 Nov 5. PMID: 26454143; PMCID: PMC5812018.

42. Cox CJ, Sharma M, Leckman JF, Zuccolo J, Zuccolo A, Kovoor A, Swedo SE, Cunningham MW. Brain human monoclonal autoantibody from sydenham chorea targets dopaminergic neurons in transgenic mice and signals dopamine D2 receptor: implications in human disease. J Immunol. 2013 Dec 1;191(11):5524-41. doi: 10.4049/jimmunol.1102592. Epub 2013 Nov 1. PMID: 24184556; PMCID: PMC3848617.

43. Dale RC, Merheb V, Pillai S, Wang D, Cantrill L, Murphy TK, Ben-Pazi H, Varadkar S, Aumann TD, Horne MK, Church AJ, Fath T, Brilot F. Antibodies to surface dopamine-2 receptor in autoimmune movement and psychiatric disorders. Brain. 2012 Nov;135(Pt 11):3453-68. doi: 10.1093/brain/aws256. Epub 2012 Oct 11. PMID: 23065479.

44. Kirvan CA, Swedo SE, Heuser JS, Cunningham MW. Mimicry and autoantibody-mediated neuronal cell signaling in Sydenham chorea. Nat Med. 2003 Jul;9(7):914-20. doi: 10.1038/nm892. PMID: 12819778.

45. Kirvan CA, Cox CJ, Swedo SE, Cunningham MW. Tubulin is a neuronal target of autoantibodies in Sydenham's chorea. J Immunol. 2007 Jun 1;178(11):7412-21. doi: 10.4049/jimmunol.178.11.7412. PMID: 17513792.

46. Kirvan CA, Cox CJ, Swedo SE, Cunningham MW. Tubulin is a neuronal target of autoantibodies in Sydenham's chorea. J Immunol. 2007 Jun 1;178(11):7412-21. doi: 10.4049/jimmunol.178.11.7412. PMID: 17513792.

47. Ellis NM, Kurahara DK, Vohra H, Mascaro-Blanco A, Erdem G, Adderson EE, Veasy LG, Stoner JA, Tam E, Hill HR, Yamaga K, Cunningham MW. Priming the immune system for heart disease: a perspective on group A streptococci. J Infect Dis. 2010 Oct 1;202(7):1059-67. doi: 10.1086/656214. PMID: 20795820.

48. Cunningham MW. Autoimmunity: an infection-related risk? Curr Opin Rheumatol. 2013 Jul;25(4):477-9. doi: 10.1097/BOR.0b013e3283621bd5. PMID: 23689638; PMCID: PMC5812263.

49. Ben-Pazi H, Stoner JA, Cunningham MW. Dopamine receptor autoantibodies correlate with symptoms in Sydenham's chorea. PLoS One. 2013 Sep 20;8(9):e73516. doi: 10.1371/journal.pone.0073516. PMID: 24073196; PMCID: PMC3779221.

50. Lotan D, Benhar I, Alvarez K, Mascaro-Blanco A, Brimberg L, Frenkel D, Cunningham MW, Joel D. Behavioral and neural effects of intra-striatal infusion of anti-streptococcal antibodies in rats. Brain Behav Immun. 2014 May;38:249-62. doi: 10.1016/j.bbi.2014.02.009. Epub 2014 Feb 20. PMID: 24561489; PMCID: PMC4000697.

51. Singer HS, Mascaro-Blanco A, Alvarez K, Morris-Berry C, Kawikova I, Ben-Pazi H, Thompson CB, Ali SF, Kaplan EL, Cunningham MW. Neuronal antibody biomarkers for Sydenham's chorea identify a new group of children with chronic recurrent episodic acute exacerbations of tic and obsessive compulsive symptoms following a streptococcal infection. PLoS One. 2015 Mar 20;10(3):e0120499. doi: 10.1371/journal.pone.0120499. PMID: 25793715; PMCID: PMC4368605.

52. Bejerot S, Hesselmark E. The Cunningham Panel is an unreliable biological measure. Transl Psychiatry. 2019 Jan 31;9(1):49. doi: 10.1038/s41398-019-0413-x. PMID: 30705260; PMCID: PMC6355775.

53. Frye RE, Shimasaki C. Reliability of the Cunningham Panel. Transl Psychiatry. 2019 Apr 8;9(1):129. doi: 10.1038/s41398-019-0462-1. PMID: 30962420; PMCID: PMC6453973.

54. Fallon BA, Stobino B, Reim S, Stoner J, Cunningham MW. Anti-lysoganglioside and other anti-neuronal antibodies in post-treatment Lyme disease and erythema migrans after repeat infection. Brain Behav Immun. 2020;2: 100015. doi: 10.1016/j.bbih.2019.100015

55. Cross A, Bouboulis D, Shimasaki C, Jones CR. Case Report: PANDAS and Persistent Lyme Disease With Neuropsychiatric Symptoms: Treatment, Resolution, and Recovery. Front Psychiatry. 2021 Feb 2;12:505941. doi: 10.3389/fpsyt.2021.505941. PMID: 33603684; PMCID: PMC7884317.

56. Krause PJ, Lepore T, Sikand VK, Gadbaw J Jr, Burke G, Telford SR 3rd, Brassard P, Pearl D, Azlanzadeh J, Christianson D, McGrath D, Spielman A. Atovaquone and azithromycin for the treatment of babesiosis. N Engl J Med. 2000 Nov 16;343(20):1454-8. doi: 10.1056/NEJM200011163432004. PMID: 11078770.

57. Owen DC. Is Lyme disease always poly microbial?--The jigsaw hypothesis. Med Hypotheses. 2006;67(4):860-4. doi: 10.1016/j.mehy.2006.03.046. Epub 2006 Jun 30. PMID: 16814477.

58. Garg K, Meriläinen L, Franz O, Pirttinen H, Quevedo-Diaz M, Croucher S, Gilbert L. Evaluating polymicrobial immune responses in patients suffering from tick-borne diseases. Sci Rep. 2018 Oct 29;8(1):15932. doi: 10.1038/s41598-018-34393-9. PMID: 30374055; PMCID: PMC6206025.

59. Berghoff W. Chronic Lyme Disease and Co-infections: Differential Diagnosis. Open Neurol J. 2012;6:158-78. doi: 10.2174/1874205X01206010158. Epub 2012 Dec 28. PMID: 23400696; PMCID: PMC3565243.

60. Sinco G, Bergamo S. Impact of Co-infections in Lyme Disease. Open Dermatol J. 2016 March 28;10:255-261. doi: 10.2174/1874372201610010055

61. Stricker RB, Gaito A, Harris NS, Burrascano JJ. Coinfection in patients with lyme disease: how big a risk? Clin Infect Dis. 2003 Nov 1;37(9):1277-8; author reply 1278-9. doi: 10.1086/378893. PMID: 14557980.

62. Moutailler S, Valiente Moro C, Vaumourin E, Michelet L, Tran FH, Devillers E, Cosson JF, Gasqui P, Van VT, Mavingui P, Vourc'h G, Vayssier-Taussat M. Co-infection of Ticks: The Rule Rather Than the Exception. PLoS Negl Trop Dis. 2016 Mar 17;10(3):e0004539. doi: 10.1371/journal.pntd.0004539. PMID: 26986203; PMCID: PMC4795628.

63. Adelson ME, Rao RV, Tilton RC, Cabets K, Eskow E, Fein L, Occi JL, Mordechai E. Prevalence of Borrelia burgdorferi, Bartonella spp., Babesia microti, and Anaplasma phagocytophila in Ixodes scapularis ticks collected in Northern New Jersey. J Clin Microbiol. 2004 Jun;42(6):2799-801. doi: 10.1128/JCM.42.6.2799-2801.2004. PMID: 15184475; PMCID: PMC427842.

64. Tokarz R, Tagliafierro T, Sameroff S, Cucura DM, Oleynik A, Che X, Jain K, Lipkin WI. Microbiome analysis of Ixodes scapularis ticks from New York and Connecticut. Ticks Tick Borne Dis. 2019 Jun;10(4):894-900. doi: 10.1016/j.ttbdis.2019.04.011. Epub 2019 Apr 15. PMID: 31023629.

65. Holden K, Boothby JT, Kasten RW, Chomel BB. Co-detection of Bartonella henselae, Borrelia burgdorferi, and Anaplasma phagocytophilum in Ixodes pacificus ticks from California, USA. Vector Borne Zoonotic Dis. 2006 Spring;6(1):99-102. doi: 10.1089/vbz.2006.6.99. PMID: 16584332.

66. Halos L, Jamal T, Maillard R, Beugnet F, Le Menach A, Boulouis HJ, Vayssier-Taussat M. Evidence of Bartonella sp. in questing adult and nymphal Ixodes ricinus ticks from France and co-infection with Borrelia burgdorferi sensu lato and Babesia sp. Vet Res. 2005 Jan-Feb;36(1):79-87. doi: 10.1051/vetres:2004052. PMID: 15610725.

67. Johnson L, Wilcox S, Mankoff J, Stricker RB. Severity of chronic Lyme disease compared to other chronic conditions: a quality of life survey. PeerJ. 2014 Mar 27;2:e322. doi: 10.7717/peerj.322. PMID: 24749006; PMCID: PMC3976119.

68. Sperling J, Middelveen M, Klein D, Sperling F. Evolving perspectives on lyme borreliosis in Canada. Open Neurol J. 2012;6:94-103. doi: 10.2174/1874205X01206010094. Epub 2012 Oct 5. PMID: 23091570; PMCID: PMC3474999.

69. Banerjee B, Petersen K. Psychosis following mycoplasma pneumonia. Mil Med. 2009 Sep;174(9):1001-4. doi: 10.7205/milmed-d-00-8209. PMID: 19780379.

70. Moor S, Skrine H. Psychosis in mycoplasma infection. Postgrad Med J. 1989 Feb;65(760):96-7. doi: 10.1136/pgmj.65.760.96. PMID: 2780471; PMCID: PMC2429129.

71. Ercan TE, Ercan G, Severge B, Arpaozu M, Karasu G. Mycoplasma pneumoniae infection and obsessive-compulsive disease: a case report. J Child Neurol. 2008 Mar;23(3):338-40. doi: 10.1177/0883073807308714. Epub 2007 Dec 13. PMID: 18079308.

72. Becker MA, Cannon J, Certa K. A Case of Mycoplasma Pneumoniae Encephalopathy Presenting as Mania. Psychosomatics. 2020 Feb 22:S0033-3182(20)30045-1. doi: 10.1016/j.psym.2020.02.004.

73. Piras C, Pintus R, Pruna D, Dessì A, Atzori L, Fanos V. Pediatric Acute-onset Neuropsychiatric Syndrome and Mycoplasma Pneumoniae Infection: A Case Report Analysis with a Metabolomics Approach. Curr Pediatr Rev. 2020;16(3):183-193. doi: 10.2174/1573396315666191022102925. PMID: 31642785.

74. Frankovich J, Thienemann M, Rana S, Chang K. Five youth with pediatric acute-onset neuropsychiatric syndrome of differing etiologies. J Child Adolesc Psychopharmacol. 2015 Feb;25(1):31-7. doi: 10.1089/cap.2014.0056. PMID: 25695942; PMCID: PMC4442568.

75. Toufexis MD, Hommer R, Gerardi DM, Grant P, Rothschild L, D'Souza P, Williams K, Leckman J, Swedo SE, Murphy TK. Disordered eating and food restrictions in children with PANDAS/PANS. J Child Adolesc Psychopharmacol. 2015 Feb;25(1):48-56. doi: 10.1089/cap.2014.0063. Epub 2014 Oct 20. PMID: 25329522; PMCID: PMC4340640.

76. Greenberg R. The Role of Infection and Immune Responsiveness in a Case of Treatment-Resistant Pediatric Bipolar Disorder. Front Psychiatry. 2017 May 22;8:78. doi: 10.3389/fpsyt.2017.00078. PMID: 28588506; PMCID: PMC5439003.

77. Schaller JL, Burkland GA, Langhoff PJ. Do bartonella infections cause agitation, panic disorder, and treatment-resistant depression? MedGenMed. 2007 Sep 13;9(3):54. PMID: 18092060; PMCID: PMC2100128.

78. Breitschwerdt EB, Sontakke S, Hopkins S. Neurological Manifestations of Bartonellosis in Immunocompetent Patients: A Composite of Reports from 2005-2012. J Neuroparasitol. 2012;3:1-15. doi: 10.4303/jnp/235640.

79. Flegr J, Preiss M, Balátová P. Depressiveness and Neuroticism in Bartonella Seropositive and Seronegative Subjects-Preregistered Case-Controls Study. Front Psychiatry. 2018 Jul 13;9:314. doi: 10.3389/fpsyt.2018.00314. PMID: 30061846; PMCID: PMC6055045.

80. Chiuri RM, Matronola MF, Di Giulio C, Comegna L, Chiarelli F, Blasetti A. Bartonella henselae infection associated with autoimmune thyroiditis in a child. Horm Res Paediatr. 2013;79:185-8. doi: 10.1159/000346903. Epub 2013 Feb 22. PMID: 23446023.

81. Van Audenhove A, Verhoef G, Peetermans WE, Boogaerts M, Vandenberghe P. Autoimmune haemolytic anaemia triggered by Bartonella henselae infection: a case report. Br J Haematol. 2001 Dec;115(4):924-5. doi: 10.1046/j.1365-2141.2001.03165.x. PMID: 11843827.

82. Tsukahara M, Tsuneoka H, Tateishi H, Fujita K, Uchida M. Bartonella infection associated with systemic juvenile rheumatoid arthritis. Clin Infect Dis. 2001 Jan;32(1):E22-3. doi: 10.1086/317532. Epub 2000 Dec 11. PMID: 11112671.

83. Cozzani E, Cinotti E, Ameri P, Sofia A, Murialdo G, Parodi A. Onset of cutaneous vasculitis and exacerbation of IgA nephropathy after Bartonella henselae infection. Clin Exp Dermatol. 2012 Apr;37(3):238-40. doi: 10.1111/j.1365-2230.2011.04177.x. Epub 2011 Oct 10. PMID: 21981612.

84. Hopp L, Eppes SC. Development of IgA nephritis following cat scratch disease in a 13-year-old boy. Pediatr Nephrol. 2004 Jun;19(6):682-4. doi: 10.1007/s00467-004-1432-1. Epub 2004 Mar 11. PMID: 15015065.

85. Giladi M, Maman E, Paran D, Bickels J, Comaneshter D, Avidor B, Varon-Graidy M, Ephros M, Wientroub S. Cat-scratch disease-associated arthropathy. Arthritis Rheum. 2005 Nov;52(11):3611-7. doi: 10.1002/art.21411. PMID: 16255053.

86. Maggi RG, Mozayeni BR, Pultorak EL, Hegarty BC, Bradley JM, Correa M, Breitschwerdt EB. Bartonella spp. bacteremia and rheumatic symptoms in patients from Lyme

disease-endemic region. Emerg Infect Dis. 2012 May;18(5):783-91. doi: 10.3201/eid1805.111366. PMID: 22516098; PMCID: PMC3358077.

87. Durey A, Kwon HY, Im JH, Lee SM, Baek J, Han SB, Kang JS, Lee JS. Bartonella henselae infection presenting with a picture of adult-onset Still's disease. Int J Infect Dis. 2016 May;46:61-3. doi: 10.1016/j.ijid.2016.03.014. Epub 2016 Mar 18. PMID: 27000538.

88. Stockmeyer B, Schoerner C, Frangou P, Moriabadi T, Heuss D, Harrer T. Chronic vasculitis and polyneuropathy due to infection with Bartonella henselae. Infection. 2007 Apr;35(2):107-9. doi: 10.1007/s15010-007-6021-3. PMID: 17401716.

89. Massei F, Gori L, Taddeucci G, Macchia P, Maggiore G. Bartonella henselae infection associated with Guillain-Barre syndrome. Pediatr Infect Dis J. 2006 Jan;25(1):90-1. doi: 10.1097/01.inf.0000195642.28901.98. PMID: 16395116.

90. Balakrishnan N, Ericson M, Maggi R, Breitschwerdt EB. Vasculitis, cerebral infarction and persistent Bartonella henselae infection in a child. Parasit Vectors. 2016;9(1):254. doi: 10.1186/s13071-016-1547-9.

91. Palumbo E, Sodini F, Boscarelli G, Nasca G, Branchi M, Pellegrini G. Immune thrombocytopenic purpura as a complication of Bartonella henselae infection. Infez Med. 2008 Jun;16(2):99-102. PMID: 18622151.

92. Ayoub EM, McBride J, Schmiederer M, Anderson B. Role of Bartonella henselae in the etiology of Henoch-Schönlein purpura. Pediatr Infect Dis J. 2002 Jan;21(1):28-31. doi: 10.1097/00006454-200201000-00006. PMID: 11791094.

93. Robinson JL, Spady DW, Prasad E, Mccoll D, Artsob H. Bartonella seropositivity in children with Henoch-Schonlein purpura. BMC Infect Dis. 2005Apr5;5(21). doi: 10.1186/1471-2334-5-21.

94. Kinderlehrer DA. Is Bartonella a Cause of Primary Sclerosing Cholangitis? A Case Study. Gastrointest Disord. 2020;2(1):48-57. doi: 10.3390/gidisord2010005

95. Coughlin JM, Yang T, Rebman AW, Bechtold KT, Du Y, Mathews WB, Lesniak WG, Mihm EA, Frey SM, Marshall ES, Rosenthal HB, Reekie TA, Kassiou M, Dannals RF, Soloski MJ, Aucott JN, Pomper MG. Imaging glial activation in patients with post-treatment Lyme disease symptoms: a pilot study using [11C]DPA-713 PET. J Neuroinflammation. 2018 Dec 19;15(1):346. doi: 10.1186/s12974-018-1381-4. PMID: 30567544; PMCID: PMC6299943.

96. Chandra A, Wormser GP, Klempner MS, Trevino RP, Crow MK, Latov N, Alaedini A. Anti-neural antibody reactivity in patients with a history of Lyme borreliosis and persistent symptoms. Brain Behav Immun. 2010 Aug;24(6):1018-24. doi: 10.1016/j.bbi.2010.03.002. Epub 2010 Mar 18. PMID: 20227484; PMCID: PMC2897967.

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