6. Frigas E, Nzeako UC. Angioedema. Pathogenesis, differential diagnosis, and treatment. Clin Rev Allergy Immunol. 2002;23: 217–231.
7. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981;30: 239–245.
8. Available at: https://api.fda.gov/drug/event.json?search=quetiapine.angioedema+&count=reactionmeddrapt.
9. Tatar ZB, Oflaz S, Baran B. A case of late-onset angioedema associated with clozapine and redevelopment of angioedema with olanzapine. J Clin Psychopharmacol. 2014;34:523–525.
10. Yücel A, Yücel N, Özcan H, et al. Dose-dependent paliperidone associated with angioedema. J Clin Psychopharmacol. 2015;35:615–616.
11. Mishra B, Sahoo S, Sarkar S, et al. Clozapine-induced angioneurotic edema. Gen Hosp Psychiatry. 2007;29:78–80.
12. Palombaro JF, Klingelberger CE. Angioedema associated with droperidol administration. Ann Emerg Med. 1996;27:379–381.
13. Honma M, Minami-Hori M, Tsuji H, et al. Olanzapine-induced limb edema simulating episodic angioedema with eosinophilia. J Dermatol. 2012;39:1105–1106.
14. Chen HJ, Lin ST, Hsu HC, et al. Paliperidone-related peripheral edema: a case report and review of the literature. J Clin Psychopharmacol. 2014;34:269–271.
15. Soumya RN, Grover S, Dutt A, et al. Angioneurotic edema with risperidone: a case report and review of literature. Gen Hosp Psychiatry. 2010;32:646.e1–646.e3.
16. Lamer V, Lipozencić J, Turcić P. Adverse cutaneous reactions to psychopharmaceuticals. Acta Dermatovenerol Croat. 2010;18:56–67.
17. Warnock JK, Morris DW. Adverse cutaneous reactions to antipsychotics. Am J Clin Dermatol. 2002;3:629–636.

Post-Lyme Syndrome–Associated Polyneuropathy Treated With Immune Immunoglobulin and a Luteolin-Containing Formulation

To the Editors:

Outbreaks of transient erythema and migratory seronegative arthritis in the town of Lyme in Connecticut had puzzled physicians until Dr Alan Steere, at Yale University School of Medicine, then discovered that it was due to an infection by the spirochete Borrelia burgdorferi transmitted by female ticks.[1,2]

Lyme disease affects 10 to 100 of 100,000 individuals per year depending on the study and the region.[3–5] Prompt administration of tetracyclines or lactam antibiotics treats the infection and may halt the associated symptoms.[2] However, during the years, it became apparent that many patients continue to experience lingering neurologic and musculoskeletal symptoms of unknown etiology that have eluded diagnosis and therapy.[6,7] Repeated courses of antibiotics for prolonged treatment periods have proven to be unsuccessful. The Centers for Disease Control and Prevention has estimated that 10% to 20% may experience "posttreatment Lyme disease (PTLD) syndrome."[8]

Responses from 2024 patients indicated that it took them visiting at least 7 physicians and more than 10 years before proper diagnosis was made.[8] One study estimated the annual Lyme-associated cost to be approximately 25 million Euros in Germany.[9] Another study compared 52,795 individuals treated for Lyme disease with 263,975 matched controls and found that those with PTLD were associated with $3798 higher total health care costs and 66% more outpatient visits for a 12-month period; the annual cost in the United States was estimated to be more than $1 billion in 2015.[10]

Prominent symptoms in patients with PTLD have included peripheral neuropathy, headaches, chronic fatigue, transient diffuse musculoskeletal pain and defects in cognition, memory, focus, and ability to multitask.[11,12] These symptoms mimic fibromyalgia syndrome[13] and "brain fog."[12] The lack of distinct pathogenesis and biomarkers of such post-Lyme cases, as well as the recognition that mouse models are now considered to poorly reflect human inflammatory diseases,[14] has hampered the development of effective management.

Here, we report the case of a 56-year-old white woman who presented with 6-year duration of diffuse arthralgia, migratory neuropathies, and progressive severe weakness of both the upper and lower extremities. The patient also described a chronic state of fatigue and depression with loss of short-term memory and difficulty finding the right words. Electromyography studies showed normal nerve conduction. Extensive evaluation including brain computed tomography, magnetic resonance imaging, and lumbar puncture were not contributory and ruled out multiple sclerosis, Guillain-Barre syndrome, or paraneoplastic syndrome. Western blot analysis was negative for viral or bacterial presence, except for Borrelia P.61 component IgG. Patient recalls having had a tick removed as a teenager, but she was never treated.

Her medical and family history was otherwise unremarkable. Treatment with antibiotics, nonsteroidal anti-inflammatory agents, corticosteroids, and anti–tumor necrosis factor agents, as well as gabapentin and pregabalin, was unsuccessful.

Cranial nerve examination was grossly intact. Further neurologic examination revealed severe, symmetrical, weakness of both the upper and lower extremities bilaterally and heightened sensitivity to touch throughout. There were no positive trigger points, but the patient reported a pain level of 7 out of 10. The patient seemed tired, depressed, and hopeless.

The patient was treated with intravenous immune immunoglobulin injections (20 mg) every 21 days, together with the dietary supplement BrainGain (2 capsules 2 times a day, containing a combination of the anti-inflammatory flavone luteolin and the antibacterial berberine sulfate) for 9 months. The patient had progressive improvement after 2 to 3 months and was entirely symptom free at 9 months. The patient continues on the same regimen, but the immune immunoglobulin has been reduced to 10 mg per infusion every 25 days. No adverse effects were reported.

Spirochete components have been reported to stimulate microglia[15–17] and induce the expression of toll-like receptors.[18] Microglia communicate with mast cells,[19] which have recently emerged as master immunoregulatory cells that participate in allergies, mastocytosis, and mast cell activation,[20] as well as other conditions or symptoms that involve neuroinflammation, associated with post-Lyme syndrome.[21] Borrelia stimulates mast cells,[18,22] which also express toll-like receptors.[23] The neuropeptide substance P augments Borrelia-induced prostaglandin E_2 from murine microglia[24] and stimulates mast cells.[25] In fact, mast cells have recently been linked to disruption of the blood-brain barrier[26] and to brain inflammation.[27]

Efforts to treat post–Lyme syndrome have proven futile. Intravenous immunoglobulin has been shown to improve polyneuropathies.[28–30] Moreover, certain naturally occurring flavonoids with anti-inflammatory properties[31] have been increasingly used in neurologic diseases[32,33] including "brain fog."[12] Luteolin inhibits mast cells[34] and microglia.[35] Luteolin is safe.[36] In fact, a different luteolin-containing formulation (NeuroProtek) was recently shown to improve communication and sociability in children with autism.[37] Interestingly, luteolin also improves cognition and memory in animal models.[38,39]

AUTHOR DISCLOSURE INFORMATION

T.C.T. is the developer of BrainGain and NeuroProtek, which have been trademarked in the United States. He has also been awarded US patent no. 8,268,365 —"Anti-inflammatory compositions for treating brain inflammation."

The authors declare they have no other competing interests.

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REFERENCES

1. Steere AC, Malawista SE, Snydman DR, et al. Lyme arthritis: an epidemic of oligoarticular arthritis in children and adults in three Connecticut communities. Arthritis Rheum. 1977;20:7–17.
2. Arvikar SL, Steere AC. Diagnosis and treatment of Lyme arthritis. Infect Dis Clin North Am. 2015;29:269–280.
3. Nelson CA, Saha S, Kugeler KJ, et al. Incidence of clinician-diagnosed Lyme disease, United States, 2005-2010. Emerg Infect Dis. 2015;21:1625–1631.
4. Mead PS. Epidemiology of Lyme disease. Infect Dis Clin North Am. 2015;29:187–210.
5. Hofhuis A, Harms M, Bennema S, et al. Physician reported incidence of early and late Lyme borreliosis. Parasit Vectors. 2015;8:161.
6. Miklossy J, Kasas S, Zurn AD, et al. Persisting atypical and cystic forms of Borrelia burgdorferi and local inflammation in Lyme neuroborreliosis. J Neuroinflammation. 2008;5:40.
7. Crowder LA, Yedlin VA, Weinstein ER, et al. Lyme disease and post-treatment Lyme disease syndrome: the neglected disease in our own backyard. Public Health. 2014;128:784–791.
8. Johnson L, Aylward A, Stricker RB. Healthcare access and burden of care for patients with Lyme disease: a large United States survey. Health Policy. 2011;102:64–71.
9. Lohr B, Müller I, Mai M, et al. Epidemiology and cost of hospital care for Lyme borreliosis in Germany: lessons from a health care utilization database analysis. Ticks Tick Borne Dis. 2015;6:56–62.
10. Adrion ER, Aucott J, Lemke KW, et al. Health care costs, utilization and patterns of care following Lyme disease. PLoS One. 2015; 10:e0116767.
11. Koedel U, Fingerle V, Pfister HW. Lyme neuroborreliosis-epidemiology, diagnosis and management. Nat Rev Neurol. 2015;11:446–456.
12. Theoharides TC, Stewart JM, Hatziagelaki E, et al. Brain "fog," inflammation and obesity: key aspects of neuropsychiatric disorders improved by luteolin.Front Neurosci. 2015;9:225.
13. Theoharides TC, Tsilioni I, Arbetman L, et al. Fibromyalgia, a syndrome in search of pathogenesis and therapy. J Pharmacol Exp Ther. 2015;355:255–263.
14. Seok J, Warren HS, Cuenca AG, et al. Genomic responses in mouse models poorly mimic human inflammatory diseases. Proc Natl Acad Sci U S A. 2013;110:3507–3512.
15. Myers TA, Kaushal D, Philipp MT. Microglia are mediators of Borrelia burgdorferi-induced apoptosis in SH-SY5Y neuronal cells. PLoS Pathog. 2009;5:e1000659.
16. 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.
17. Rasley A, Anguita J, Marriott I. Borrelia burgdorferi induces inflammatory mediator production by murine microglia. J Neuroimmunol. 2002;130:22–31.
18. Bernardino AL, Myers TA, Alvarez X, et al. Toll-like receptors: insights into their possible role in the pathogenesis of Lyme neuroborreliosis. Infect Immun. 2008;76:4385–4395.
19. Skaper SD, Facci L, Giusti P. Mast cells, glia and neuroinflammation: partners in crime? Immunology. 2014;141:314–327.
20. Theoharides TC, Valent P, Akin C. Mast cells, mastocytosis, and related disorders. N Engl J Med. 2015;373:163–172.
21. Theoharides TC. Atopic conditions in search of pathogenesis and therapy. Clin Ther. 2013;35: 544–547.
22. Talkington J, Nickell SP. Borrelia burgdorferi spirochetes induce mast cell activation and cytokine release. Infect Immun. 1999;67: 1107–1115.
23. Abraham SN, St John AL. Mast cell-orchestrated immunity to pathogens. Nat Rev Immunol. 2010;10:440–452.
24. Rasley A, Marriott I, Halberstadt CR, et al. Substance P augments Borrelia burgdorferi-induced prostaglandin E2 production by murine microglia. J Immunol. 2004;172:5707–5713.
25. Theoharides TC, Zhang B, Kempuraj D, et al. IL-33 augments substance P-induced VEGF secretion from human mast cells and is increased in psoriatic skin. Proc Natl Acad Sci U S A. 2010;107:4448–4453.
26. Esposito P, Chandler N, Kandere-Grzybowska K, et al. Corticotropin-releasing hormone (CRH) and brain mast cells regulate blood–brain-barrier permeability induced by acute stress. J Pharmacol Exp Ther 2002;303:1061–1066.
27. Polyzoidis S, Koletsa T, Panagiotidou S, et al. Mast cells in meningiomas and brain inflammation. J Neuroinflammation. 2015;12:170.
28. Crisp D, Ashby P. Lyme radiculoneuritis treated with intravenous immunoglobulin. Neurology. 1996;46:1174–1175.
29. Srivastava R, Ramakrishna C, Cantin E. Anti-inflammatory activity of intravenous immunoglobulins protects against West Nile virus encephalitis. J Gen Virol. 2015;96(pt 6): 1347–1357.
30. Kaveri SV, Lecerf M, Saha C, et al. Intravenous immunoglobulin and immune response. Clin Exp Immunol. 2014;178 (suppl 1):94–96.
31. Middleton EJ, Kandaswami C, Theoharides TC. The effects of plant flavonoids on mammalian cells: implications for inflammation, heart disease and cancer. Pharmacol Rev. 2000;52:673–751.
32. Grosso C, Valentão P, Ferreres F, et al. The use of flavonoids in central nervous system disorders. Curr Med Chem. 2013;20: 4694–4719.
33. Jones QR, Warford J, Rupasinghe HP, et al. Target-based selection of flavonoids for neurodegenerative disorders. Trends Pharmacol Sci. 2012;33:602–610.
34. Weng Z, Patel AB, Panagiotidou S, et al. The novel flavone tetramethoxyluteolin is a potent inhibitor of human mast cells. J Allergy Clin Immunol. 2014;14:1044–1052.
35. Jang S, Kelley KW, Johnson RW. Luteolin reduces IL-6 production in microglia by inhibiting JNK phosphorylation and activation of AP-1. Proc Natl Acad Sci U S A. 2008;105: 7534–7539.
36. Theoharides TC, Conti P, Economu M. Brain inflammation, neuropsychiatric disorders, and immunoendocrine effects of luteolin. J Clin Psychopharmacol. 2014;34:187–189.
37. Taliou A, Zintzaras E, Lykouras L, et al. An open-label pilot study of a formulation containing the anti-inflammatory flavonoid luteolin and its effects on behavior in children with autism spectrum disorders. Clin Ther. 2013;35:592–602.
38. Yoo DY, Choi JH, Kim W, et al. Effects of luteolin on spatial memory, cell proliferation, and neuroblast differentiation in the hippocampal dentate gyrus in a scopolamine-induced amnesia model. Neurol Res. 2013;35:813–820.
39. Liu R, Gao M, Qiang GF, et al. The anti-amnesic effects of luteolin against amyloid beta(25–35) peptide-induced toxicity in mice involve the protection of neurovascular unit. Neuroscience. 2009;162:1232–1243.