Carbamazepine in the Treatment of Lyme Disease–Induced Hyperacusis

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Lyme disease–induced hyperacusis can be an intensely disabling, chronic condition that is accompanied by posttraumatic stress disorder–like psychobehavioral sequelae. The authors describe effective treatment of 2 patients with carbamazepine. Speculations regarding a mode of action are offered.

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As many as 48% of patients with late-stage neurologic Lyme disease may develop hyperacusis,[1] defined as a lowered threshold for sound tolerance (100 dB hearing level [HL] or less). In severe cases, discomfort can occur at volumes of 60 dB HL or lower; that is, below the range of normal human speech. Other causes of hyperacusis include trauma, severe sound exposure leading to inner ear damage, congenital disorders such as Williams syndrome, and, less commonly, pervasive developmental delay, endocrine or metabolic disorders, cerebrovascular changes, and some other infectious diseases. Although in most cases Lyme disease–induced hyperacusis resolves with antibiotic treatment, occasionally it may become chronic, precluding participation in normal social activities and causing occupational disability.

The authors describe 2 patients whose Lyme disease–induced hyperacusis persisted following antibiotic treatment and whose symptoms were mitigated by treatment with carbamazepine.

CASE REPORTS

Case 1. A 35-year-old woman developed vertigo, nystagmus, headaches, nausea, lancinating pains, migrating arthralgia, fasciculations, focal autonomic neuropathy, mild photophobia, mental confusion, new-onset dyslexia, and hyperacusis. Vertigo, nausea, and nystagmus intensified with sound stimulation (the Tullio phenomenon).[2] A pencil scratching against paper was painfully loud. Normal household sounds caused an intense startle response, nausea, and sometimes retching. Previous medical history was negative except for recurrent flu-like illnesses over the previous 2 years and an episode of knee pain requiring the use of crutches. Lyme disease was diagnosed on clinical grounds and confirmed by serum enzyme-linked immunosorbent assay (ELISA) and Western blot. Six weeks of intravenous ceftriaxone produced remission of all symptoms except mild arthralgias and fatigue; however, neurologic symptoms subsequently returned.

Photophobia and hyperacusis worsened to such an extent that she wore glacier glasses and airport headphones even in the house. Hyperacuities of taste, smell, and vibration sense developed as well. Certain foods, such as strawberries, tasted intolerably bitter; odors only mildly unpleasant to others would induce reflex retching. The vibration of her car while driving seemed highly magnified, an effect that intensified during prolonged car trips and was accompanied by nausea and feelings of alarm. Exposure to one modality—light, vibration, or, most markedly, sound—led to a generalized heightening of hypersensitivity across other modalities as well. She evidenced short-term memory problems, right/left confusion, and a tendency to bump into things on the left side of her body and to drop things from her left hand.

When she was re-treated, this time with iv cefotaxime, most symptoms resolved gradually; however, her hyperacusis diminished but did not abate completely and indeed remained the main impediment to resumption of normal activities. Over the subsequent 2 years, the hyperacusis underwent daily and weekly fluctuations but remained on average unchanged. Most notably, prolonged exposure to a mildly uncomfortable level of sound led to a lowered sound tolerance threshold, so that previously tolerated sounds produced an intense startle response, extreme discomfort, and an "electric shock"–like sensation through her body. Prolonged or repeated sound exposure was followed by pervasive fear, increased irritability, hypervigilance, paranoia, and vivid nightmares. This lowered threshold and altered emotional state would last for hours or several days following return to a quiet environment. A trial of clonazepam led to a mild short-term attenuation of hyperacusis but was discontinued because of increased emotional lability.

A similarity to kindling was noted in that repeated subthreshold sound stimulation led to a lowered sound tolerance threshold and an altered neuropsychiatric state. On the basis of this similarity, carbamazepine was given and titrated to a blood level of 6 μg/ml. The kindling-like effects

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diminished, so that sound exposures no longer seemed to "add up"; the patient was able to recover more quickly, and her threshold for tolerance increased. The intense fear response and irritability were mitigated; nightmares were less frequent and less severe. She became able to participate in a broader range of activities: work in a quiet office environment, dinners in relatively quiet, carpeted restaurants. During her treatment with carbamazepine, audiometric testing revealed hyperacute hearing (ability to distinguish sounds below zero dB HL) and auditory hyperacusis with sound intolerance at 80 dB HL and above.

When carbamazepine was discontinued after 2 years, there was a significant decrease in sound tolerance threshold and a return of the kindling-like effect, almost but not quite to the level prior to treatment with carbamazepine. The previously noted posttraumatic stress disorder–like symptomatology returned as well: increased startle, pervasive fear, hypervigilance, irritability, paranoia, and nightmares. Audiometric testing showed sound intolerance at 60 dB HL and above. Resumption of carbamazepine or a trial of valproate is being contemplated.

Case 2. A 33-year-old woman developed Lyme disease at age 25, manifested by an erythema migrans rash and positive Lyme serologies (Western blot, ELISA, and polymerase chain reaction). At age 28 she developed another erythema migrans rash, followed by severe fatigue, crushing headaches, sharp facial pain, lancinating pains, diffuse arthritis, weakness, weight loss, and severely debilitating neuropsychiatric symptoms. These included impaired short-term memory, word-finding problems, spatial disorientation, stuttering with intermittent expressive aphasia, insomnia, depression with suicidal ideation, photophobia, and hyperacusis. Normal household sounds, such as the sound of crickets, the purring of a cat, or the running of bath water, caused her intense discomfort. She resorted to wearing ear plugs and rifle range headphones for protection from unavoidable sound exposure. Because both light and sound caused a hyperstimulated, painful, and confused state, she led an extremely circumscribed life, avoiding social gatherings, markets, and restaurants. Four weeks of intravenous ceftriaxone led to a 50% to 60% improvement, although severe hyperacusis and mild photophobia remained, as did accompanying irritability and depression. For the latter, she was placed on nortriptyline 75 mg daily, which helped her mood and insomnia but did not alter the hyperacusis.

Sound tolerance increased after a period of relative quiet. Conversely, repeated or intense exposure to sound and, to a lesser degree, light, seemed to lower her tolerance threshold for hours or days. For example, after she was exposed to the multiple stimuli of a crowded urban train station, previously tolerated sounds such as a person scratching his arm nearby were intensely painful to her. In addition, previously unremarkable sounds now grabbed her attention, rendering her easily distractible. Such states were accompanied by stuttering, word-finding problems, and paranoia in which she perceived normal ambient sounds as being purposely aimed at her by hostile others. She also developed frequent nightmares and a chronically heightened startle.

Carbamazepine dosed to a blood level of 4–6 μg/ml resulted in significant improvement. She became less sound-sensitive, less isolated, and able to tolerate brief trips to town as long as the ambient sound was not excessive. The overload-related stuttering also decreased. One year later, after discontinuation of carbamazepine, her hyperacusis worsened, forcing a return to her former highly circumscribed life. A resumption of carbamazepine led to greater sound tolerance, as before, although significant limitations remained. Quiet conversation was now tolerable to her, but this woman's still markedly low sound tolerance threshold was a cause of significant social isolation, and while she was able to take great pleasure in some aspects of her life, she suffered bouts of significant depression because of the constrictions imposed by her hyperacusis as well as mild paranoia following unavoidable excessive sound stimulation. Audiometry while she was on carbamazepine revealed hyperacute hearing bilaterally, with sound intolerance starting at 50 dB HL.

DISCUSSION

Two patients with Lyme disease–induced hyperacusis benefited from a trial of carbamazepine. In both patients, hyperacusis emerged with other central nervous system symptoms: memory loss, new-onset dyslexia, photophobia, and disturbances in spatial orientation. Whereas most CNS symptoms remitted after antibiotic treatment, hyperacusis lessened to a degree but remained problematic; even the sound of normal human speech was painful. In each patient, a kindling-like phenomenon occurred such that repeated subthreshold sound stimulation effectively lowered the tolerance threshold for hours or days and resulted in increased arousal, irritability, and paranoia. After carbamazepine was initiated, both patients responded with increased baseline sound tolerance and some relief from the additive effects and psychobehavioral sequelae of repeated sound exposure. Case 1 suggests that carbamazepine treatment improved sound tolerance by 20 dB HL. Symptoms worsened on discontinuation of the drug and remitted again in the patient for whom it was restarted.

Although the rationale for a trial of carbamazepine was a presumed kindling-like effect, other possible mechanisms include "wind-up"[3] (frequency-dependent potentiation of neuronal response), sensitization, altered neurotransmitter effects, and/or neuronal irritability due to nerve damage. Neuroanatomically, hypersensitivity to sound can originate anywhere along the auditory pathways—from the ear, auditory nerve, brainstem nuclei, or limbic system to the cortex. The presence of multiple sensory hyperacuities in both patients suggests that the primary abnormality was not confined to the auditory system, and the intensely visceral and emotional response to sound stimulation suggests limbic system rather than cortical involvement. Stimulation in one sensory modality—sound, light, or vibration—led

in both patients to a lowered tolerance threshold in other sensory modalities, lending further support to the hypothesis of a central rather than peripheral locus of pathology.

Experimental activation of the amygdala is known to cause a clinical picture similar to that seen in our patients: prominent hyperacusis (R. Post, personal communication), tinnitus, heightened sensory experiences in other modalities (sight, smell, taste),[4] intense fearfulness and heightened startle.[5–7] The amygdala is particularly vulnerable to kindling[4] and has high levels of gamma-aminobutyric acid receptors,[8] which appear to mediate these psychophysiological effects.[4]

Although SPECT scans were not performed on our patients, preliminary data show that Lyme encephalopathy may preferentially involve frontal cortical and subcortical, including limbic system, structures.[9] Primary involvement of these structures in the production of both hyperacusis and tinnitus, previously hypothesized on theoretical grounds,[10] is further supported, at least in the case of tinnitus, by a recent study using PET that shows an abnormal auditory-limbic link in patients with tinnitus.[11]

Further research is necessary to describe more fully the phenomenology of Lyme disease–induced hyperacusis, to elucidate its mechanisms, and to determine under controlled conditions whether in fact anticonvulsant therapy is helpful for these patients.

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