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REVIEW ARTICLE

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The ALSUntangled Group

The first ALSUntangled, published in 2009, reviewed the possibility of a link between ALS and Lyme disease (1). We found no evidence for an increased frequency of positive Lyme tests in our cohort of 4000 patients with confirmed diagnoses of ALS. We found no evidence that any of the patients in our cohort with a positive Lyme test had their ALS cured by appropriate treatment for Lyme disease. Nonetheless, rumours of a connection have persisted and a number of "Lyme literate" clinics continue to advertise their controversial testing and treatments for patients with ALS (PALS). One source of these persistent rumours appears to be an online manuscript called "When ALS Is Lyme" written by Sarah and John Vaughter (2) and available on their marketing website (3). Here, on behalf of PALS who requested it, we review this manuscript.

Arguments made for a connection between Lyme and ALS

The Vaughters attempt to demonstrate that "Lyme is a frequent cause of ALS" using the following arguments: a similarity of symptoms and anatomic abnormalities in chronic Lyme and ALS, an overlap between the geographic and occupational distributions of Lyme and that of ALS, an increased frequency of positive serologic testing for Lyme in PALS, and cases of ALS and Lyme in which the former was said to improve with treatment of the latter. We will now review each of these arguments.

First, the Vaughters state that PALS have generalized brain damage including cognitive changes, and that those patients with Lyme disease also have generalized brain damage and cognitive changes. They go on to conclude from this "therefore most ALS patients have classical symptoms of neuroborreliosis". This is one of many examples of flawed logic that appear in the manuscript. Post mortem and neuroimaging studies show that ALS targets specific motor and non-motor brain regions; involvement of frontal and temporal regions leads to specific (not general) cognitive deficits such as verbal fluency (4). Whether or not Lyme can cause brain damage in these same regions is controversial; if so, it is exceedingly rare (5). Even if there is overlap in the brain regions affected by ALS and Lyme, a very general coincidence/overlap between two conditions such as this does not mean that they are causally related. The Vaughters fail to mention that 90% of patients with Lyme report or have a specific type of rash called erythema migrans (6); PALS rarely, if ever, do. The most common symptoms and signs of nervous system Lyme disease are headache, stiff neck, photosensitivity and fever (from lymphocytic meningitis), reversible facial nerve palsy, eye movement abnormalities, and mono- or oligo-radiculopathy that produces dermatomal pain and sensory loss in addition to weakness (5). PALS do not present with headache, stiff neck, photosensitivity, fever or reversible facial weakness, and rarely have eye movement abnormalities, dermatomal pain or sensory loss. Thus, in reality, there is little overlap between the typical clinical picture of ALS and that of nervous system Lyme disease. Very rarely, Lyme has been reported to cause encephalomyelitis and/or polyradiculopathy. If these occurred together they could produce upper and lower motor neuron signs (the hallmark of ALS), but again they should be accompanied by clinical and laboratory features that are not part of ALS such as pain, sensory loss, and focal inflammatory changes on neuroimaging and/or spinal fluid (5,7).

Secondly, the Vaughters argue that geographic locations and occupations with a high incidence of Lyme disease diagnosed by Centers for Disease Control (CDC) criteria also have a high incidence of ALS. Again, here we see coincidence being accepted as causality. The authors downplay other potential explanations for geographic and occupational clusters of ALS (8). Furthermore, they again fail to mention information that contradicts their hypothesis (including information in some of the very references they cite): the incidence of Lyme

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disease in Italy is almost 30 times higher than in Ireland (9), yet ALS incidence in these countries is similar (10); Hawaii had no Lyme reported between 2000 and 2010 (11) yet certainly has had patients diagnosed with ALS; Guam, which historically has had one of the highest incidences of ALS in the world (12) has a very low incidence of Lyme (13).

Thirdly, the Vaughters argue that there is an increased frequency of positive Lyme tests in patients with ALS. In order to review this it is necessary to define what is meant by a "positive Lyme test". An abundance of evidence suggests that Lyme testing of any variety should only be performed when there is a high clinical suspicion because false positives are so common (5,6,14). In our opinion this means that PALS who do not have typical Lyme features such as rash, headache, stiff neck, photosensitivity, fever, reversible facial weakness, eye movement abnormalities, dermatomal pain or sensory loss should not be tested at all. For patients with a clinical suspicion for Lyme disease, credible experts such as the Centers for Disease Control (15) agree that testing should start with an Elisa (enzyme linked immunoabsorbent assay) and if that test is positive or equivocal then a Western immunoblot should be performed. There are very specific bands that define a positive Western blot (6,14). In the appropriate clinical setting, if both tests are positive, a patient can be considered "positive for Lyme". With this highly reliable (16) approach, false negatives (concluding that a patient does not have Lyme when they actually do) are vanishingly rare unless a patient is in the first month of their illness (6,14); in these cases testing can be repeated. In CNS Lyme there will be abnormalities in the spinal fluid including elevated white blood cell counts and protein (5,7,14). The Vaughters claim that this approach is "unreliable," that the Elisa has "up to 95% false negatives (depending upon which expert you ask)" and that the Western blot has "up to 60% false negatives". No references are given to support these statements. They argue for a urine assay for Lyme, which clearly has been shown to be unreliable in peer reviewed literature (16). They claim that there is "no such thing as a false positive" Lyme test; this statement contradicts multiple published reports (6,14,16,17).

Against this background the Vaughters review the results of Lyme testing in various groups of patients reported to have ALS. There is a group of 150 described in an online post by Atkinson-Barr (18). Here the Lyme testing is described as "a panoply of tests-including Western blot, LUAT, PCR. Not one patient has been found to be negative across all tests. Many have been shown to be PCR positive" (18); details of the clinical presentation/ALS diagnoses are not provided except that "the prognosis and disease development of these patients is entirely consistent with ALS" (18). Without details on exactly how the diagnoses of Lyme or ALS were made, and in light of the high false positive rate of unselected Lyme tests (6,14,16,17), this post cannot be considered useful scientific evidence. Next is a group of 414 described by Qureshi (19). Here the testing for Lyme included the above described Elisa and Western blots. The diagnosis of ALS was made at one of the USA's best hospitals (MGH). The Vaughters report "this study found 5.8% of ALS patients positive for Lyme, which is 67 times higher" than the background population. They are referring to the frequency of positive Lyme Elisa tests (not those confirmed by Western blot) and they are comparing this to the background frequency of Lyme defined by CDC criteria for the entire United States (without regard for the marked regional variation in Lyme). In actuality, the study found four out of 414 PALS to be positive for Lyme by the two-step method (0.97%) and this is similar to the background rate of positive Lyme tests in the north-eastern United States where these patients came from (19). Next they report on a study by Halperin (20). The Vaughters interpret this paper as showing "21 out of 24 ALS patients that tested Lyme-positive, making it 88%, or almost nine out of ten patients". They go on to say "since the false negative rate of the tests used is notoriously high, we are justified in concluding that, most likely, every single ALS patient in their study was Lyme-positive". This interpretation is inaccurate for multiple reasons. We have already discussed that the false negative rate of the CDC recommended Lyme testing is very small. Halperin performed a variety of Lyme tests on 56 (not 24) patients with motor neuron disease. While some had classic ALS (upper and lower motor neuron signs), others had other motor neuron diseases that would not meet accepted criteria for ALS (patients with pure lower motor neuron signs or pure upper motor neuron signs) or had atypical features for ALS such as sensory loss. Unfortunately, the tables in the Halperin paper that list clinical characteristics do not include all 56 patients so it is not possible to clearly determine how many had classical ALS versus another motor neuron disease. However, the paper does show that, in one very small sample from an area with a high background rate of Lyme disease, a larger percentage of patients with motor neuron disease tested positive for Lyme (9/19 or 47%) compared to patients without motor neuron disease (4/38 or 11%). Halperin correctly concludes in this and subsequent papers that there are multiple possible explanations for his finding, including random chance (especially since the sample size is so small and the elevated frequency was oddly seen almost exclusively in men). The Vaughters dismiss these suggestions, but not for a scientific reason; rather they present the following baseless personal accusation: "The paper's authors-possibly afraid of the consequences to their careers if they were to pursue an 'ALS is Lyme' angle, decided to 'cook the books'." The Vaughters dismiss other reports in peer reviewed literature that failed to find an increased frequency

of positive Lyme tests in groups of patients with ALS (1,17), again electing to launch personal attacks against the authors rather than critique the science.

Finally, the Vaughters attempt to show that "many people were initially diagnosed with ALS. But when they sought a second opinion from an infectious disease specialist knowledgeable about Lyme, they obtained the correct diagnosis of Lyme neuroborreliosis, received antibiotic treatment and their 'ALS' disappeared". Most of the cases they present along these lines are unpublished self-reports. ALSUntangled recognizes the potential value of these; indeed we have utilized information from the structured self-reports found on PatientsLikeMe in many of our prior reviews. However, in the self-reports described by the Vaughters, neither the diagnoses of ALS or Lyme, nor the response to treatment can be validated. Many describe vague outcomes of uncertain significance, and/or periods of plateaus or stabilization; the latter are well known to occur in patients with ALS regardless of what treatment they are receiving (21). The Vaughters also refer to a small number of published case reports from peer reviewed journals. One describes a patient with cervical myeloradiculopathy (lower motor neuron signs confined to the hands, and upper motor neuron signs to the legs) from an area with high Lyme incidence (7). His serum Lyme testing was positive and his spinal tap was markedly abnormal with evidence of inflammation. His doctors correctly determined that his atypical presentation was "not consistent with a diagnosis of ALS". Another (22) is summarized by the Vaughters as: "Swedish doctors found a Lyme causing ALS." In reality, the patient described in this paper had upper motor neuron signs restricted to his lower extremities with no lower motor neuron signs detectable on exam or EMG. This would not meet criteria for an ALS diagnosis. Finally, they cite a report (23) written by and also about a David Martz who at one time worked at a clinic that advertised treatments for "patients who had neurologic diseases created by Lyme" (24) and thus may have been biased. Martz reports that he developed rapidly progressive arm and leg weakness accompanied by extremity fasciculations and hyperreflexia. These ALS-like symptoms and signs were accompanied by "inflammatory polyarthritis", his "electrophysiological studies were non-diagnostic", and there was disagreement across four consulting neurologists as to his diagnosis; these features would be highly unusual in ALS. Martz reports that his Lyme Western blot was negative and that his CSF was normal, which, as described above, would preclude a CNS Lyme diagnosis. On the basis of a clinical suspicion and a urine test, chronic antibiotics were administered; improvement "was rapidly evident" and after a year of taking these he reports that he became free of symptoms or signs of motor neuron disease both subjectively and by his neurologist's exams. Martz stated that "spontaneous (ALS) remissions have not been reported" and as a result concluded that his "ALS" was actually Lyme, and that his improvement was due to antibiotics. However, spontaneous remissions have been reported in PALS not taking antibiotics (25–28). The Vaughters acknowledge that there are cases of patients with ALS who have been treated for Lyme and did not improve or even worsened. To explain these away they claim that the treatments did not go on long enough, or that the antibiotic dosages were not high enough, or that antifungals should have been added; these criticisms and suggested antibiotic regimens make little intuitive sense and contradict published, widely accepted and independently validated practice guidelines (29–31). They acknowledge that some patients with ALS treated with antibiotics have worsened, and they cite a published minocycline trial in which this occurred (32). They actually argue that these findings also support a connection between ALS and Lyme because "many different substances have been tried against ALS and never has any substance been identified that made ALS worse. Except two substances-totally different substances, but both antibiotics: minocycline and ceftriaxone. Why would that be? The best explanation-and so far the only one-is the Jarisch- Herxheimer effect, observed in both neurosyphilis and neuroborreliosis. Patients get worse, sometimes much worse, before they get better". Again, the Vaughters are apparently unaware of a number of facts here that contradict this statement: PALS taking topiramate (33) or lithium (34) also got worse faster than those taking placebo; a prior study of minocycline (35) showed no evidence of accelerating ALS; the Jarisch-Herxheimer effect consists of fever, rigors, fluctuations in body temperature and alterations in white blood cell counts (36), none of which was more common in patients taking minocycline compared to those taking placebo in the study they refer to (32).

Broader conspiracy theories

The Vaughters state a broader belief that many diseases besides just ALS are caused by Lyme including multiple sclerosis, Parkinson's disease, Alzheimer's disease, fibromyalgia, chronic fatigue syndrome, lupus, Crohn's disease, Pick's disease and frontotemporal dementia (2,3). They claim that a vast conspiracy is being purveyed by self-interested doctors, non-profits, pharmaceutical companies and government agencies who are withholding information, stealing donations, and even "cooking the books" to keep this information secret and withhold treatments from patients suffering from these diseases. They provide no evidence to support this. From a general standpoint, these accusations would require very large numbers of sociopathic physicians, researchers and charity staff, working in a highly coordinated manner for several years, without a single person who ever thought it was reprehensible

enough to blow the whistle on it or provide any evidence of it occurring, such as emails, meetings, or recorded phone calls. This is simply not logical. Furthermore, as with many of the Vaughters' other arguments listed above, there is obvious contradictory evidence for some of these accusations. For example, the Vaughters claim that the United States military is suppressing information relating to a purported cluster of ALS around Kelly Air Force Base because they are "not eager to assume legal responsibility for the deaths of over a hundred people". By awarding 100% service-connected disability to veterans with ALS the military has in fact accepted responsibility for far more than 100 people (37). The Vaughters report that "it isn't easy to find out" who the authors of ALSUntangled are, that we are "rumored to be run by ALS experts", that we are "a front for organizations that have a financial stake in ALS not being curable by antibiotics, because they're working on patentable symptom relievers" and that we "pay extra money to (our) registrar for anonymous listing". Those who have actually read one of our articles are aware that we always list our names at the end. Google search of our names reveals that members of ALSUntangled have ALS-specific medical and scientific training, relevant degrees from accredited universities, several years and hundreds of 'real world' experiences treating PALS, numerous ALS publications, and publicly available conflict of interest statements that disclose our funding sources (38). We do not pay extra for any anonymous listing; simply typing our domain name into the 'whois' function of any web hosting site reveals the name of our group's leader and his contact information (39).

Conclusions

The monograph "When ALS Is Lyme" is filled with errors in logic, misinterpretations of scientific papers, controversial statements that are either not referenced or refer to unverifiable anecdotes, and omissions of data contradicting its authors' opinions. It fails in its attempt to argue that there is a connection between ALS and Lyme disease. At this time ALSUntangled does not recommend Lyme testing for patients with classical ALS. We sincerely hope that the Vaughters' unqualified medical advice, baseless conspiracy theories and accusations do not alienate PALS from mainstream specialized multidisciplinary ALS clinics. Within these clinics appropriate patients with atypical motor neuron diseases (pure lower, pure upper, accompanied by rash, headache, stiff neck, photosensitivity, fever, reversible facial nerve palsy, eye movement abnormalities, dermatomal pain and sensory loss), especially those coming from Lyme-endemic areas, will be tested for Lyme according to CDC criteria, and also treated rationally according to validated guidelines if Lyme is diagnosed. More importantly for the vast majority, those who come to specialized ALS clinics will receive competent and caring healthcare teams that will work to optimize the length and quality of their lives, and facilitate their participation in research toward a cure.

The ALSUntangled Group currently consists of the following members: Richard Bedlack, Orla Hardiman, Terry Heiman-Patterson, Laurie Gutmann, Mark Bromberg, Lyle Ostrow, Gregory Carter, Edor Kabashi, Tulio Bertorini, Tahseen Mozaffar, Peter Andersen, Jeff Dietz, Josep Gamez, Mazen Dimachkie, Yunxia Wang, Paul Wicks, James Heywood, Steven Novella, L. P. Rowland, Erik Pioro, Lisa Kinsley, Kathy Mitchell, Jonathan Glass, Sith Sathornsumetee, Hubert Kwiecinski, Jon Baker, Nazem Atassi, Dallas Forshew, John Ravits, Robin Conwit, Carlayne Jackson, Alex Sherman, Kate Dalton, Katherine Tindall, Ginna Gonzalez, Janice Robertson, Larry Phillips, Michael Benatar, Eric Sorenson, Christen Shoesmith, Steven Nash, Nicholas Marigakis, Dan Moore, James Caress, Kevin Boylan, Carmel Armon, Megan Grosso, Bonnie Gerecke, Jim Wymer, Bjorn Oskarsson, Robert Bowser, Vivian Drory, Jeremy Shefner, Noah Lechtzin, Melanie Leitner, Robert Miller, Hiroshi Mitsumoto, Todd Levine, James Russell, Khema Sharma, David Saperstein, Leo McClusky, Daniel MacGowan, Jonathan Licht, Ashok Verma, Michael Strong, Catherine Lomen-Hoerth, Rup Tandan, Michael Rivner, Steve Kolb, Meraida Polak, Stacy Rudnicki, Pamela Kittrell, Muddasir Quereshi, George Sachs, Gary Pattee, Michael Weiss, John Kissel, Jonathan Goldstein, Jeffrey Rothstein, and Dan Pastula.

Note: This paper represents a consensus of those weighing in. The opinions expressed in this paper are not necessarily shared by every investigator in this group.

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