Registered Charity: 19588

"Encouraging awareness, prevention & treatment of Lyme Disease (Borreliosis) in Ireland."

'There is no Lyme Disease in Ireland?'

Dear Sirs,

I am writing to you with sincere concerns about the recognition, testing & treatment of Lyme Disease in Ireland. Current figures suggest that 50-100[i] cases of Lyme are diagnosed each year. With such a rare illness why would we be concerned? The fact is that doctors AND consultants are still not recognising that Lyme Disease exists in Ireland. Therefore they are not thinking to test for it, they are not clinically diagnosing patients early & patients are very often misdiagnosed leading to a chronic, difficult to treat illness. For a mild illness this may not be alarming but this disease can inflict major damage to the brain, joints, muscles, organs, tissues & in extreme cases cause paralysis, which is why lack of recognition can be alarming, especially where it involves children.

What is Lyme?

Lyme is transmitted by the bite of an infected tick. In the 1990s Prof Gray identified that various sites throughout Ireland showed an infection rate of *borrelia* in 11-29%[ii] amongst ticks (the lyme causing bacteria). In the same study Gray showed that **50% of those ticks carried a currently untested strain of VS116**. This strain is not capable of being picked up in current testing which are designed to seek antibodies for the most common strains including *b. afzellii*, *b. garinii* & *b.sensu stricto*. If 50% of infected ticks are carrying this alternative strain shouldn't we be testing for it? Despite some studies showing VS116 to be non pathogenic, other studies have shown the strain in spinal fluid[iii] & EM[iv] rashes from Lyme patients. Prof Gray identified that ticks can carry a multitude of infections including various strains of Lyme Disease in a single tick. Other studies have looked at co-infections that ticks may carry, which could also be of significance in Ireland.[v]

Concern One: Recognition –

- Doctors are still not recognizing that Lyme exists in this country & are not happy to initiate testing even when a patient asks for it.
- The clinical criteria are too narrow. Many doctors expect to see a typical bulls-eye rash. The rash maybe uniform in nature or may not appear at all. Doctors need to be aware that some patients may skip stage one of the disease & become chronically ill with late stage Lyme.

If doctors & consultants aren't recognising Lyme is here, then they won't be on the lookout for signs & symptoms. However those who do know about Lyme tend to look for a very narrow definition – do you have a bulls-eye rash, do you have a swollen knee, did you see the tick that bit you? Sadly this is too simplistic; rashes can show up in a variety of forms & sometimes not at all. In a 2010 paper they stated that "**The classic EM, originally described as a slowly expanding bull's eye lesion, is now recognized to be present in only the minority of cases (9%);** the dominant morphologic

lesion of EM is now recognized to be the diffusely homogenous red plaque or patch, which occurs in over 50% of cases."[vi] Additionally Lyme Disease can show up in the form of migratory joint pain rather than joint swelling. Ticks hide in tucked away places such as in the groin area so often times patients may not even notice the tick at all. We were recently told of a doctor who had an engorged tick in his groin area that had been feeding there for days. He had no knowledge of it until the area started to itch & on further investigation he found the offending tick. In most cases there would be no itching at all so you can see that many times doctors would be reliant on the patient mentioning they had a tick bite. To help this happen therefore patients need to be aware of the dangers of tick bites so they can keep an eye out for them, keep a check for early symptoms, make sure any ticks are removed as soon as possible & be aware that any early unusual signs should be reported to their doctor immediately. But the only way they can do this is if they have knowledge that lyme disease exists. The best way is to place notices in public areas such as GP offices, schools or at the very least national park areas**, an informed patient plus an informed medical system can ensure prompt treatment at the outset** which is the best time to treat with fairly cheap antibiotics (doxycycline). Lack of treatment can lead to months & years of debilitating symptoms & often renders the patient immobile, unable to work or contribute to society.

Concern Two: Testing –

- The current method of testing is to use a 2 tier system (Elisa & Western Blot). ELISA is the 1st tier **indirect** antibody test which is not specific to a *borellia* & can be affected by the stage of the disease, the strain of *borrelia* infection & the level of immune response in the body.

- Trinity Biotech states that early Lyme & some manifestations of late Lyme can result in a negative result & **should not be used to exclude diagnosis**. The use of antibiotics early in treatment can abrogate immune response also creating false negative serology.[vii]

Testing issues are of grave concern to us. Trinity Biotech also state that "serological tests for antibodies to B. burgdorferi are known to have low sensitivity and specificity, and because of such inaccuracy, **these test cannot be relied upon for establishing a diagnosis of Lyme disease**". Despite this consultants who see a negative result will often REFUSE to give treatment to any patient. Some patients, due to concerns over the current testing, seek private testing such as the Elispot LTT[viii], a CE approved test. This look at T cell activity against borrelia, however consultants are trained to only accept positive 2 tier testing & are therefore unwilling or unable to consider another test even if it is more accurate.

A second tier test, the Western Blot is offered to patients who 'are' positive or borderline to rule out false positives. But what about the patients who are false negative in the first tier? They are tested no further & are not offered any treatment, despite in some cases patients claiming they had a rash & flu like symptoms & reported having a tick bite.

In a study in Poland 2011 they say '"The IIFA screening test used for diagnosing Lyme borreliosis produced the highest percentage of positive results, which were then confirmed by immunoblot, but not by ELISA. **Therefore using only ELISA as a screening test or for diagnosing Lyme borreliosis seems debatable**." [ix]

Even the Western Blot can have its problems due to the restricted number of bands present & the fact that some patients do not exhibit enough antibodies. A study showed that antibodies may be sequestered in immune complexes where they state that "**Binding to the 23-kDa protein was more intense in ICs [immune complex] than in the FA [free antibodies] fraction, FA immunoblot reactivity would have been classified as negative, according to the manufacturer's instructions**. [x]

The Western Blot approved by the CDC for disseminated lyme is as follows:
For IgG 5 out of 10 bands are required for a positive - bands 31 & 34* are not included since restricted criteria was introduced in the 90s.[xi] These bands are however Lyme specific & removing them from the criteria renders the screening much less sensitive. In fact the CDC state that this criterion is for **surveillance purposes only & should not be used for clinical diagnosis**.[xii] Despite this the insensitive ELISA & restricted Western Blot are often being used SOLELY for making a diagnosis here in Ireland making under diagnosis very likely. Trinity Biotech says ***Negative results (either first tier or second-tier) should not be used to exclude Lyme disease**. **Igenex labs in the States do include bands 31 & 34 & yet consultants here are not willing to accept those results.*

More recently a new band VlsE (variable major protein-like sequence) was introduced to try & improve sensitivity, however studies have also shown mixed results. One explains that "**not all patients who had IgM or IgG responses with 2-tiered testing had reactivity with the VlsE band**, and the VlsE test had slightly lower specificity in the control groups than standard 2-tiered testing"[xiii]

Another study stated "**Reactivity of the *B. garinii* strain PBi OspC was remarkably poor, especially for the neuroborreliosis panel.** The reasons for this remain unclear, but failure of ACA sera to bind PKo VlsE **could be due to atypical protein folding where epitopes are not accessible and possibly be related to immune evasion during the late stages of Lyme disease.**"[xiv] In fact this immune invasion can cause many problems with Lyme disease testing, especially where production of antibodies are being measured.

If consultants aren't acknowledging that patients can have a false negative result & are also not accepting alternative labs that maybe more sensitive then where does that leave the patient?

Ho Yen's lab in Scotland have been striving to improve their in house testing to provide a higher chance of diagnosing patients.[xv] In their paper they stated that antigenic strains of *borrelia* can affect testing & had the following concerns "**Although false negatives may be a result of treatment, or of testing a patient too soon after infection, the strain of *B. burgdorferi* used in diagnostic assays has been shown to influence test sensitivity**." (Hauser et al., 1997; Kaiser 2000; Robertson et al., 2000).

Maybe we could learn from them & look at ways to improve testing for Irish Lyme patients, with particular attention paid to strain VS116, mentioned at the start of this letter?

Concern Three: Guidelines –

In the year 2000, the IDSA (Infectious Disease Society of America) decided to issue some guidelines on how to manage Lyme disease. The recommendation of 2-4 weeks treatment is based on acute cases of Lyme disease. Little thought is given to persistence of infection & chronicity of the disease.[xvi] Due to the problems with early recognition, patients are not being diagnosed & treated immediately (as Lyme is not on the doctor's radar) & so patients develop chronic & at times serious symptoms. Those that do manage to get tested find that the consultant will not treat them without a positive 2 tier result, due to the inherent problems with testing detailed above. If they DO find they're positive & get lucky then they still have problems getting treated due to the restrictive guidelines issued by the IDSA, which are closely followed by the HSE (Ireland) & HPA (UK). This fails the patient many times over, during the early recognition stage, during the testing stage & later during the treatment stage. All too often patients who seek help with further treatment are turned away from disbelieving practitioners. Physicians in the U.S. who do treat further are being bullied by IDSA members or insurance companies for daring to treat beyond the recommended guidelines.

Dr. Kenneth Liegner, an MD treating a large number of Lyme patients in Armonk, New York, summarized the plight of Lyme physicians:

"Physicians who have cared for persons with chronic Lyme disease have faced harassment at a minimum and for some, their careers have been ruined. Researchers who have seriously dedicated themselves to the scientific study of chronic Lyme disease in humans and/or animals have often found themselves attacked or marginalized. To persist in their researches would have resulted in virtual career suicide and some have been forced, by exigencies of survival, to leave the field."

Despite physicians being 'bullied' for not adhering to IDSA/CDC guidelines, the IDSA have this to say: http://www.idsociety.org/Guidelines_Patient_Care/

Quote: "It is important to realize that guidelines cannot always account for individual variation among patients**. They are not intended to supplant physician judgment with respect to particular patients or special clinical situations**. IDSA considers adherence to the guidelines listed below to be **voluntary**, with the ultimate determination regarding their application to be made by the physician in the light of each patient's individual circumstances."

Sadly, despite this infectious disease consultants in UK & Ireland have cited they are also afraid to treat long term for fear of repercussion. This creates a serious situation whereby sick patients who have already been let down by the system cannot ever be made better; Lyme is a complex illness & requires much more than 'treatment in a box' mentality.

Patients seeking help with the treatment abroad scheme also find difficulties. They are being told they don't need more treatment here & therefore are not given the approval to seek treatment abroad under the terms of the scheme..As their disease progress due to under treatment or lack of it the patient then becomes more & more dependent on benefits for a longer period of time. It is therefore important to see a change in direction with regards to this disease.

We feel that more needs to be done to improve the lives of patients & that Lyme specialists should be protected, as their knowledge is invaluable. The NHS & HSE are under so much pressure as it is & often do not have the knowledge to deal with this insidious disease. In fact we need more help not less, the more that consultants are pressured not to treat, the more that patients end up back where they started & putting their own pressure on the system.

Anyone can be next, a close friend, a neighbour, the local priest, the farmer down the road, a hard working business man who likes to spend time in the country at the weekend. We owe it to them to make sure things improve & we owe it to all the current patients who have been ridiculed, told it is in their heads, that they can't possibly have Lyme disease as Lyme doesn't exist in Ireland.

Ways forward –

- Ensure signs are show in prominent places to warn members of the public to be 'tick aware'.
- Advise doctors & consultants that not everyone has a typical bulls-eye rash (it can be uniform in nature or no rash at all).
- Allow consultants to accept overseas testing until in house ones can be significantly improved.
- Encourage consultants to attend workshops & keep an open mind when it comes to Lyme disease cases.

- Provide consultants with a means to treat patients (without fear) for the length of time they feel is most beneficial to the patient – Lyme is far too complex to treat all cases the same way.

- Arrange a hearing as a forum for scientists, consultants, doctors, family members, advocates & patients to speak together & achieve a common goal, on ways to improve the Lyme testing & care of patients. Some patients require long term care & their needs are currently not being met by the system.

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[i] http://www.ndsc.ie/hpsc/A-Z/Vectorborne/LymeDisease/Factsheet/

[ii] Local variations in the distribution and prevalence of Borrelia burgdorferi sensu lato genomospecies in Ixodes ricinus ticks. Kirstein, Rijpkema, Molkenboer, Gray: Appl Environ Microbiol. 1997 March; 63(3): 1102–1106.

[iii] *Borrelia valaisiana* in cerebrospinal fluid [letter]. Emerg Infect Dis. 2004 Sep [*date cited*]. Diza E, Papa A, Vezyri E, Tsounis S, Milonas I, Antioniadis A. http://wwwnc.cdc.gov/eid/article/10/9/03-0439.htm

[iv] Detection of *Borrelia afzelii, Borrelia burgdorferi sensu stricto, Borrelia garinii* and group VS116 by PCR in skin biopsies of patients with erythema migrans and acrodermatitis chronica atrophicans. Rijpkema et al. Clinical Microbiology & Infection 1997 Feb;3(1):109-116.

[v] http://ticktalkireland.files.wordpress.com/2011/04/coinfections-uk-ireland.doc

[vi] An update on the diagnosis and treatment of early Lyme disease: "focusing on the bull's eye, you may miss the mark". Stonehouse A, Studdiford JS, Henry C J Emerg Med. 2010 Nov;39(5):e147-51. Epub 2007 Oct 18.

[vii] http://www.trinitybiotech.com/Product%20Documents/2346580-29%20EN.pdf

[viii] http://elispot.com/Elispot_Kits.htm

[ix] Serodiagnosis of Borreliosis: Indirect Immunofluorescence Assay, Enzyme-Linked Immunosorbent Assay and Immunoblotting Wojciechowska-Koszko et al, 2011. Arch Immunol Ther Exp (Warsz). Feb;59(1):69-77.

[x] Immune complexes from serum of patients with Lyme disease contain Borrelia burgdorferi antigen and antigen-specific antibodies: potential use for improved testing**.** Brunner, Sigal J Infect Dis. (2000)182(2):534-539.

[xi] http://www.cdc.gov/mmwr/preview/mmwrhtml/00038469.htm

[xii] http://www.cdc.gov/osels/ph_surveillance/nndss/casedef/lyme_disease_current.htm

[xiii] 2-tiered antibody testing for early and late Lyme disease using only an immunoglobulin G blot with the addition of a VlsE band as the second-tier test. Branda et al 2010 *Clinical infectious diseases* 50(1), pp.20-6.

[xiv] Improvement of Lyme borreliosis serodiagnosis by a newly developed recombinant immunoglobulin G (IgG) and IgM line immunoblot assay and addition of VlsE and DbpA homologues. Goettner et al 2005 *Journal of clinical microbiology*, 43(8), pp.3602-9

[xv] The use of local isolates in Western blots improves serological diagnosis of Lyme disease in Scotland Mavin, Milner, Evans, Chatterton, Joss and Ho-Yen UK, Journal of Medical Microbiology (2007), 56, 47–51

[xvi] http://foreignaffairs.house.gov/hearings/view/?1455 Dr Stricker on persistence of infection studies - part of the hearing: Global Challenges in Diagnosing and Managing Lyme Disease—Closing Knowledge Gaps July 2012