PE1662/E
Lyme Disease Action submission of 27 October 2017

We support the petitioners' calls for action to improve the position with regard to awareness, diagnosis and treatment of Lyme disease. We would like to draw your attention to a few specific points where there is genuine uncertainty and complexity.

- NHS blood tests for Lyme disease have significant limitations[1] and do not identify all cases.
- There is no current test which can distinguish current disease from past disease.
- Lyme disease can persist beyond a course of antibiotics, particularly when treated late.
- What causes persisting symptoms, and the best way to treat them in any one individual, is currently unknown.
- The vast majority of UK doctors have insufficient experience of Lyme disease.
- The majority of UK doctors will only diagnose those with positive test results and, despite the absence of a gold standard test, will rule out Lyme disease as a possibility on the basis of test results.
- From a historical perspective, a small but highly influential group of doctors including some experts involved with the Health Protection Agency and British Infection Association actively promoted the (incorrect) view that Lyme disease is easy to diagnose and easy to treat, and tended to dismiss increasing public concern. Doctors rely heavily on such expert opinion, especially in areas of scientific uncertainty; they will believe their peers.
- Lyme disease is a complex disease with many areas of current scientific uncertainty.

However:

- The symptoms of Lyme disease do genuinely overlap those of many other conditions, some of which also have no definitive test and this can lead to difficulties in diagnosis.
- The blood tests from a few private German laboratories are not helpful. Some are not specific to Lyme disease and some not licensed for Lyme disease diagnosis. These tests are not used by official German laboratories.
- Social media encourages patients to use these laboratories, they receive positive blood test results and may then believe the NHS negative test is "useless". Patients will believe sources of information in which they have faith, including their peers.
- Private doctors in Germany and the USA will diagnose patients clinically and treat patients empirically with long term and combinations of antibiotics. However, they publish no outcome studies so it is not known whether patients definitely had Lyme disease, how many recovered, or how far any recovery was related to a particular aspect of treatment or due to some other factor. They do not add to the scientific medical evidence base on which medicine generally relies.
- The test used for diagnosis in Scotland is designed to detect infections caused by all the Borrelia genospecies currently known to be present in Scottish ticks.

- The first reported case of Lyme disease in Scotland was 1977, so it is an emerging disease in the UK and not altogether surprising that doctors have little experience. They do not have time to read emerging science and, of course, believe those in authority and their peers.

Lyme Disease Action has argued for pilot specialist clinics for Lyme disease which would develop a new protocol, co-designed with patients, for assessing and reviewing patients. This was supported by the Minister for Health, Lord Prior, following a debate in the House of Lords in 2015. We are close to agreement on this in principle, with a proposal for 3 pilots, including one in Scotland.

Further detail

The NHS blood tests in use for Lyme disease aim to detect antibodies to a defined set of antigens (proteins) of the Borrelia bacteria. Manufacturers of test kits select those they believe are most likely to detect infection, and although the tests from different companies are broadly similar, they do have some differences. Each laboratory has to choose a test which they think will detect infections in their population. These are known as serology tests and are the main type of test used worldwide to help in the diagnosis of Lyme disease.

As an indirect test, serology has inherent limitations as it relies on the right antibodies being generated by the infected person and this does not always happen. The main reasons for not detecting Lyme disease when it is present is

a. testing too early before antibodies have developed fully and
b. possible interference of medication with the immune system which means antibody generation may be inhibited.

But there are other reasons and the science is not yet fully understood. Antibodies last for years, even in people who have recovered from Lyme disease, so a positive test simply demonstrates exposure of the immune system to the bacteria.

Some other test techniques, such as PCR (Polymerase Chain Reaction) aimed at detecting the DNA of Borrelia, are used on tissue, synovial fluid and spinal fluid, but these are not routine and also have limitations due to the low numbers of bacteria present and the difficulty in obtaining samples.

As there is no test which can guarantee to detect Lyme disease, it is not possible to say how many cases are missed. Some patient groups state that as many as 50% of cases are missed, but this appears to be mainly based on figures which include early infections, possibly skewing the results.

There are 4 different genospecies of Borrelia present in Scotland of which 3 are pathogenic.[2] These have some antigens in common and the test in use at Raigmore[3] is aimed at detecting infections caused by all these 3 genospecies. It is possible that there are other pathogenic genospecies present in Scottish ticks, which are less likely to be detected by the current tests but this is speculation.

Other tests. Lyme disease can persist beyond a course of antibiotics, but there is currently no test which can distinguish between current and past infection. The **Lyme antigen** test mentioned is likely to become available in Europe in November 2017

via a Netherlands Laboratory which now has a European licence from the American developers. It has not yet been tested on European patients although small scale tests in America indicate that it may be able to discriminate between past and current disease. It needs first to be tried on people who definitely had Lyme disease and who have relapsed, and as a comparison on those who are now asymptomatic. As there is no proof that those who have relapsed still have symptoms due to Lyme disease, the difficulties in interpreting the results can be appreciated.

The LTT test was referred to by the petitioners. There are several tests (LTT, ELISPOT etc) using techniques which aim to measure the reaction of a patient's T cells to Borrelia. This technique has been used successfully in TB and many researchers are working to develop similar tests for Lyme disease. However, they have not yet been successful because of technical issues, including the need to process samples within a relatively short time frame and the challenge of ensuring sufficient test accuracy. The tests so far developed can give positive results in healthy people (false positives) as well as those who are ill, and do not necessarily identify those with Lyme disease (false negatives).

There are a few private laboratories in Germany offering T cell based tests as well as other tests which are not specific for Lyme disease. Given the reluctance of any UK doctor to diagnose someone without a positive test result, it is not surprising that many people look for and find alternative tests.

Much of the on-line patient community supports these private laboratories, and indeed specifically recommends them, because they have a reputation of providing positive test results. This fuels the perception that NHS tests are poor and German tests are better. Note that official German laboratories use the same type of test as the NHS, and in some cases exactly the same test. The test in use at Raigmore is from a German manufacturer.

These private German Laboratories also use tests for common infections to which many people have antibodies and this tends to make patients believe that co-infections are common. Our help desk has many patients seeking help following a blood test result from these laboratories positive for "Lyme disease and co-infections" which they believe explains their ill health. It may do, but equally it may not.

Because there is no currently available test that can distinguish current infection, it is not possible to know in any one case whether persisting symptoms following treatment are due to persistent disease, tissue damage, an autoimmune process or some other condition.

The epidemiology of Lyme disease in the UK is not fully known. The petitioners rightly say that only positive blood tests are counted in the annual figures and cases are likely to be considerably greater and the study on Scottish blood donors[4] supports this, finding 4.2% of donors had had exposure to the bacteria. They could have had a mild form from which they recovered without treatment or serious disease for which they had treatment and also recovered.

This Scottish seroprevalence is very low compared with many European countries. Background seroprevalence tends to be higher in countries with a higher recorded incidence of Lyme disease and tends to increase as Lyme disease becomes more endemic. Although seroprevalence in lowland areas of Scotland was zero it should be noted that the data is old, from 2010/2011 blood donor sessions, so we might expect the seroprevalence to have risen. To introduce another uncertainty, we do not know whether the in-house test used in this study would detect any antibodies to non-pathogenic genospecies nor how sensitive it would have been to minority pathogenic genospecies not represented in that test.

The infection rate in Scottish ticks varies from place to place and year to year. Published figures tend to include all genospecies, including one that is not pathogenic, so it is often difficult to get an accurate idea of the % of infected ticks likely to pass disease to humans. The infection rate varies from place to place and year to yea. Published data in a 2016 paper[2] showed a maximum of 6% and zero at some sites. This compares, for example, with about 20% in Sweden.

It should be noted that where there have been surveys **other tick-borne infections** are far less common in England and Wales than on mainland Europe or in North America, though there is a lack of information on other infections in Scottish ticks. Human Granulocytic Anaplasmosis, a tick-borne infection of white blood cells which was acquired in Scotland, was confirmed in a returning traveller to Germany in 2013[5]. The UK is surrounded by sea and this has protected us to some extent and delayed the introduction of many pathogens. There are several Scottish researchers studying ticks, and the committee would do well to seek information from them.

Polarisation of opinion

LDA's help desk provides evidence that UK doctors do not know enough about Lyme disease. They may not recognise the characteristic "bull's eye" rash, called erythema migrans, seen in around two thirds of cases, so an important window for effective antibiotic treatment of early Lyme disease may be missed. They may be unaware of their lack of knowledge and experience of genuine areas of uncertainty around testing, diagnosis and treatment of Lyme disease.

The list of conditions with overlapping symptoms and without definitive tests includes a wide range of neurological and autoimmune conditions as well as ME and fibromyalgia, complicating diagnosis. There is also a tendency amongst doctors to view subjective "medically unexplained symptoms" as evidence of some form of psychiatric disorder, often called a "functional" disorder, if a physical cause cannot be determined.

There is a risk of prematurely foreclosing on a correct diagnosis of Lyme disease and discharging the duty of care. We believe this has an impact on patient safety and leaves more complex cases abandoned by NHS services on which they would normally depend as a "life-line". Lyme disease can be incredibly debilitating in both adults and children and people may have little choice but to seek private care, often abroad, in order to try and regain their health and restore their lives.

Between 2010 and 2012, Lyme Disease Action worked with the James Lind Alliance on a Priority Setting Partnership for Lyme disease which resulted in publication of the known uncertainties at systematic review level and identified research priorities[6]. It was very difficult to engage doctors in this process as many of them believed (and indeed stated) that there were no uncertainties.

On the other hand, patients value the care and treatment provided by the private doctors who are referred to as LLMDs (Lyme Literate Medical Doctors). Some private clinics use a wide range of therapies (eg hyperthermia, homeopathy, supplements, immune therapy, Rife machines etc.) in addition to, or instead of, antibiotics. Their concept of Lyme disease is controversial, being wider and more inclusive than a single bacterial infection. It can be challenging for patients to make an informed decision on treatment which often involves considerable financial cost and may involve a degree of risk.

We include with our response a presentation given by a member of the Health Protection Research Unit at Liverpool to our annual conference in July 2017. This reports on a workshop held in Edinburgh in June 2017 and gives details of current UK research as well as key unanswered challenges and uncertainties.

Lyme Disease Action, October 2017

References

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