

INTRODUCTION

Lyme disease is a complicated disease that has been under-reported, and sometimes unknown. A recent surge in Lyme disease -focused publications has resulted in a much needed growth in Lyme disease awareness. The National Institute for Health and Care Excellence (NICE) has published a guideline with an overview of the main issues with regard to Lyme disease;¹ Rayment and O'Flynn have written a summary for the *BJGP* covering some important points;² and Cruickshank *et al*, have also published a recent summary of the disease in the *BMJ*.³

In the last 40 years, Lyme disease has rapidly become the most common tick-borne infection in many parts of Europe and the US. The US Centers for Disease Control and Prevention (CDC) estimate that there are around 300 000 new cases of Lyme disease per year in the US.⁴ For all of Western Europe an estimate was published of around 232 000 cases per year, but this was based on data collected many years ago, and so is now likely to be an underestimate.⁵ A study of data from the Clinical Practice Research Datalink, a primary care database covering about 8% of the population in the UK has shown that the number of cases of Lyme disease recorded by GPs increased rapidly over the years 2001–2012, leading to an estimated UK total of nearly 8000 cases in 2012.⁶ GP medical notes were no longer recorded in the database after 2012, and so estimates are not available for recent years. If the number of cases has continued to rise since the end of the study period, then there could have been over 8000 cases in 2019.

Lyme disease was detected in every region throughout the country, but the highest incidence rate and largest number of cases were seen in Scotland followed by the south and south west of England. It was also seen at all times of year, although particularly in the summer months when people tend to go out walking.

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DIAGNOSIS OF LYME DISEASE

An erythema migrans (EM) is considered definitive for a diagnosis of Lyme disease, and is described in the NICE Guideline¹ and in the *BJGP* summary;² however, many patients with Lyme disease do not have this distinctive rash, and so they need to be diagnosed using other criteria. Only 25% of the cases had an EM in the original study in 1977 when Lyme disease was first identified.⁷ That study, unlike some others, did not have the rash as one of the criteria for being included in the study. Many recent studies of Lyme disease have a higher proportion of cases with the rash.⁸ However, sometimes having the rash was one of the main reasons the patients were included, in which case they may not provide a reliable estimate of the proportion with a rash, particularly if some Lyme disease cases were not part of the inclusion criteria, and so were not counted in the denominator, leading to an overestimate.

Along with many cases not having the rash is the added difficulty that laboratory testing for Lyme disease has inherent limitations, and both false positive and false negative results can occur.¹ If the test is performed too early (within 4 weeks of symptom onset) then the person may not have developed antibodies to the bacteria that causes Lyme disease, resulting in a false negative result. Negative laboratory test results, therefore, do not exclude active infection. Furthermore, Lyme disease can lead to a very wide range of symptoms, which is why it has been called ‘the great imitator’. The early symptoms

of Lyme disease often mimic flu or other diseases. There is no single distinctive pattern of symptoms to help with the diagnosis. It is therefore a challenge for doctors to make a confident diagnosis.

The oral antibiotic doxycycline is usually effective for early stage Lyme disease, and is a relatively benign treatment. Given the difficulty in diagnosis, oral antibiotic treatment may be appropriate in the early stages even if there is some uncertainty about the diagnosis, since rapid treatment is important to prevent long-term morbidity. Oral antibiotics, however, may not be effective if the infection has reached the later stages of the disease, when intravenous ceftriaxone may be recommended. Some patients with late stage Lyme disease may have had oral antibiotics but may still need intravenous ceftriaxone.

LONG-TERM PROBLEMS FOLLOWING LYME DISEASE

If it is left untreated or inadequately treated for some time, Lyme disease can lead to multiple problems. One of the long-term problems that can result from Lyme disease is what is known as post-treatment Lyme disease syndrome (PTLDS). Risk factors for PTLDS include a delay in treatment and increased severity of the initial illness. One study found that most of the patients with PTLDS had had a misdiagnosis or a delay in treatment.⁹ The authors wrote that, for those patients with a delay in treatment, the symptoms of PTLDS were more likely to have been overlooked or attributed to a viral illness. Allen Steere, who first identified Lyme disease in Lyme Connecticut in the US, has written:

‘... it is hypothesized that Borrelia burgdorferi may trigger immunologic or neurohormonal processes in the brain that cause persistent pain, neurocognitive, or fatigue symptoms, despite spirochaetal killing with antibiotic therapy.’¹⁰

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“... the charity Lyme Disease Action, which is working with the RCGP, provides resources for people at risk of Lyme disease and also their clinicians.”

This syndrome is mentioned in the NICE supplementary document on the evidence review for the management of ongoing symptoms.¹

A meta-analysis on this has provided strong evidence that some Lyme disease patients have fatigue, musculoskeletal pain, and neurocognitive difficulties that can persist for years.¹¹ The pattern of symptoms appears to be different from that seen with fibromyalgia, depression, and chronic fatigue syndrome. The fatigue from PTLDS has been described as profound and debilitating, and not as a vague symptom of tiredness. The musculoskeletal pain from this syndrome is often a roving, asymmetrical pain in the limbs, and is different from fibromyalgia, which is characterised by widespread, symmetrical pain at many sites over the whole body. Memory problems, particularly verbal memory, have also been observed as well as poor concentration, particularly auditory attention. In confirmation of this neurocognitive pattern, Fallon *et al*¹² observed significantly reduced blood flow in certain white matter areas of the brain in patients with PTLDS compared with healthy subjects, and the flow reductions were significantly associated with deficits in memory and visuospatial organisation. This could sometimes be misdiagnosed as Alzheimer's disease.

Knowing the pattern of symptoms that is seen with PTLDS can help with the diagnosis. It is important for doctors to be aware of the disorder and the published data. It will help patients and may reassure them to hear that it is known⁹ and that, once the patients have had effective antibiotic treatment, it usually resolves, although very slowly. The symptoms of profound fatigue, musculoskeletal pain, and neurocognitive difficulties can continue for months or years, but many people recover with time. Nevertheless, some patients with Lyme disease do have ongoing problems.

After the free-living bacteria have been eradicated, some debris may remain that can activate inflammatory processes and host immune responses¹³ which can explain some of the long-term symptoms. Studies suggest that the debris cannot be removed by further antibiotic treatment¹⁴ although there can be a gradual recovery over time.

This highlights again the importance of avoiding a delay in treatment.

CONCLUSION

Lyme disease is seen throughout the UK and is more prevalent than many people realise. If left untreated, or if treated very late, Lyme disease can result in years of disability. It is to be hoped that an increased awareness of the problem will lead to an increase in preventive measures, such as avoiding dense vegetation, particularly wooded or grassy areas with moist and humid environments, using tick repellents and pesticides on skin and clothing, tucking trousers into socks, and searching the body for ticks after potential exposure. Greater awareness of the risks may also lead to more rapid diagnosis and treatment, which is important to prevent long-term morbidity.

RESOURCES FOR FURTHER INFORMATION ABOUT LYME DISEASE

The RCGP has prepared a Lyme disease toolkit, which includes links for resources on education, training, and other information for clinicians, patients, and the general public.¹⁵ Included is also a link for the RCGP e-learning course, which may help clinicians to recognise the clinical features of this easily missed condition. It also provides links to other evidence-based guidelines on Lyme disease, and highlights some scientific uncertainties and ongoing research into this complex disease. Information for the general public focuses on disease prevention and early recognition of symptoms and includes advice on tick-bite avoidance and correct tick removal. In addition, the charity Lyme Disease Action, which is working with the RCGP, provides resources for people at risk of Lyme disease and also their clinicians.

Victoria Cairns,
Consultant Statistician, Oxford, UK.

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ADDRESS FOR CORRESPONDENCE

Victoria Cairns
Email: v.cairns@outlook.com

REFERENCES

1. National Institute for Health and Care Excellence. Lyme disease. *NICE guideline [NG95]*. 2018. <https://www.nice.org.uk/guidance/NG95> [accessed 3 Feb 2020].
2. Rayment C, O'Flynn N. Diagnosis and management of patients with Lyme disease: NICE guideline. *Br J Gen Pract* 2018; DOI: <https://doi.org/10.3399/bjgp18X699713>.
3. Cruickshank M, O'Flynn N, Faust SN, Guideline Committee. Lyme disease: summary of NICE guidance. *BMJ* 2018; **361**: k1261.
4. Centers for Disease Control and Prevention. How many people get lyme disease? 2018. <http://www.cdc.gov/lyme/stats/humancases.html> [accessed 3 Feb 2020].
5. Sykes RA, Makiello P. An estimate of Lyme borreliosis incidence in Western Europe. *J Public Health [Oxf]* 2017; **39(1)**: 74–81.
6. Cairns V, Wallenhorst C, Rietbrock S, Martinez C. Incidence of Lyme disease in the UK: a population-based cohort study. *BMJ Open* 2019; **9(7)**: e025916.
7. Steere AC, Malawista SE, Snyderman DR, *et al*. Lyme arthritis: an epidemic of oligoarticular arthritis in children and adults in three Connecticut communities. *Arthritis Rheum* 1977; **20(1)**: 7–17.
8. Cairns V. Scrutinising Lyme disease in the UK — Aspiro reply. *Lancet Infect Dis* 2020 (in press).
9. Rebman AW, Bechtold KT, Yang T, *et al*. The clinical, symptom, and quality-of-life characterization of a well-defined group of patients with posttreatment Lyme disease syndrome. *Front Med [Lausanne]* 2017; **4**: 224.
10. Steere AC, Coburn J, Glickstein L. The emergence of Lyme disease. *J Clin Invest* 2004; **113(8)**: 1093–1101.
11. Cairns V, Godwin J. Post-Lyme borreliosis syndrome: a meta-analysis of reported symptoms. *Int J Epidemiol* 2005; **34(6)**: 1340–1345.
12. Fallon BA, Keilp J, Prohovnik I, *et al*. Regional cerebral blood flow and cognitive deficits in chronic Lyme disease. *J Neuropsychiatry Clin Neurosci* 2003; **15(3)**: 326–332.
13. Jutras BL, Lochhead RB, Kloos ZA, *et al*. Borrelia burgdorferi peptidoglycan is a persistent antigen in patients with Lyme arthritis. *Proc Natl Acad Sci U S A* 2019; **116(27)**: 13498–13507.
14. Sapi E, Kasliwala RS, Ismail H, *et al*. The long-term persistence of borrelia burgdorferi antigens and DNA in the tissues of a patient with Lyme disease. *Antibiotics [Basel]* 2019; **8(4)**: pii: E183.
15. Royal College of General Practitioners. Lyme disease toolkit. <https://www.rcgp.org.uk/clinical-and-research/resources/toolkits/lyme-disease-toolkit.aspx> [accessed 3 Feb 2020].