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Case report: Successive ipsilateral and contralateral laryngeal nerve palsy as probable manifestation of neuroborreliosis

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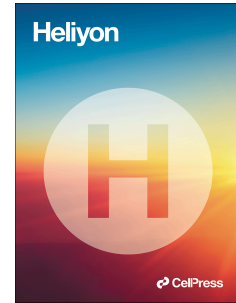
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Title:

Case report: Successive Ipsilateral and Contralateral Laryngeal Nerve Palsy as Probable Manifestation of Neuroborreliosis

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Recurrent nerve paralysis, Neuroborreliosis reinfection, Neuroborreliosis relapse.

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Abbreviations:

VF: Vocal fold

VFP: Vocal fold paralysis

IgM: Immunoglobulin M

IgG: Immunoglobulin G

EM: Erythema migrans

CSF: Cerebrospinal fluid

BB: *Borrelia burgdorferi*

AI: Antibody index

LNB: Lyme neuroborreliosis

EFNS: European Federation of Neurological Societies

CLIA: Chemiluminescence immune assay

DGN: Deutsche Gesellschaft für Neurologie

## Abstract

Neuroborreliosis is part of advanced stage of Lyme disease and often characterized by damage to the cranial and/or peripheral nerves. Involvement of one or both recurrent nerves is rare. Diagnosis is often difficult and based on a set of clinical manifestations, biological arguments, and cerebrospinal fluid (CSF) analysis. A 70-year-old man was referred to our Voice Clinic with a 3-month history of dysphonia caused by right vocal fold paralysis (VFP) without any cutaneous symptoms of tick bite or erythema migrans in the previous weeks and normal initial radiological examination (neck and thorax CT). Methylprednisolone had already been prescribed but without any clinical improvement. Late biological investigation 3 months after initial symptoms of VFP showed high IgG (93 U/mL; reference <10 U/mL) against *Borrelia burgdorferi* (BB), which was confirmed by two immunoblot markers (VIsE, p39 antigens). Therefore, a possible manifestation of Lyme disease with involvement of the right inferior laryngeal nerve was suspected, namely Lyme neuroborreliosis. However, given the spontaneous recovery of the patient after 7 months without any adapted antimicrobial regimen treatment, the diagnosis of neuroborreliosis was not confirmed by a lumbar puncture. Nineteen months later, the patient presented again for the same symptomatology but as left VFP. High IgG (68 U/mL) and IgM (>6, reference <0.90) levels against BB were confirmed by immunoblot. Subsequently, lumbar puncture was performed and revealed IgG against BB at 46.1 UA/mL (reference <5.5 UA/mL) in the CSF, with an extremely high IgG intrathecal synthesis antibody index (281.33, positive if >1.5). Intrathecal antibody synthesis is the gold standard for Lyme neuroborreliosis demonstrating a specific immune response to BB in the central nervous system, but with the limitation of persistence for years after eradication. Our patient did not exhibit pleocytosis in the CSF. Therefore, two criteria of the European Federation of Neurological Societies (EFNS) guidelines are fulfilled for possible neuroborreliosis. Doxycycline treatment led to rapid recovery in less than 8 weeks and normal mobility of the left vocal fold. Because of this very uncommon clinical presentation with two successive episodes of VFP for no other obvious reason and serological evidence from the serum and CSF during the second episode, we consider it

possible that the first episode of VFP could also have been a manifestation of neuroborreliosis. This case is the first report of possible relapse of laryngeal palsy successively on the right, and then the left side as a manifestation of Lyme neuroborreliosis.

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## Case report

### Introduction

Lyme borreliosis is a multisystem, tick-borne, infectious disease caused by *Borrelia* bacteria<sup>2 3 4 5 6</sup>, with a clinical course progressing in stages involving skin, joints, eye, heart and nervous system<sup>5</sup>.

Cranial nerve paralysis is mostly involving facial nerve<sup>4 5</sup>. Paralysis of laryngeal nerves is extremely rare and unusual<sup>3 4 9</sup>.

We herein describe the history of a 70-year-old man with successive ipsilateral and contralateral laryngeal nerve palsy due to two distinct episodes of possible Lyme neuroborreliosis.

### Case report

A 70-year-old man was referred to the Voice Clinic of the ENT Department of the CHU of Liège to consult a phoniatrician (first author) for dysphonia (vocal weakness without any swallowing disorder) that appeared suddenly 3 months prior without any other associated symptom. The patient gave his informed consent to publish his medical data, story, and management as a case report.

The general ENT examination was unremarkable and right vocal fold paralysis (VFP) was diagnosed by video-fibro-stroboscopy (figure 1). A 9-day treatment with methylprednisolone had previously been prescribed by the referent ENT specialist without any clinical improvement.

The postoperative context was femoro-popliteal bypass, and the patient had a history of smoking, hypothyroidism, and non-insulin-dependent diabetes that was properly controlled (HbA1c 6.5%). A cervico-thoracic scan and cerebral MRI were performed and did not show any lesion along the path of the vagus and recurrent nerves.

Three months after the beginning of the complaints, chemiluminescence immunoassay (CLIA, by DiaSorin) for *Borrelia burgdorferi* (BB) showed an IgG level of 93 U/mL (reference <10 U/mL), which was confirmed by immunoblotting two markers (Euroline

Borrelia-RN-AT), VIsE and P39 antigens, but no IgM was detected on CLIA and immunoblot, which could be compatible with a recent or old infection by BB.

To improve the patient's vocal quality, temporary medialization with hyaluronic acid (Juvederm Ultra 2°, Allergan) was performed twice, one under local anesthesia and one under general anesthesia, which was effective. A referral to the Department of Neurology was planned but, at the time of the neurological consultation, the patient had spontaneously and completely recovered from his right VFP. Given the atypical and isolated presentation and spontaneous recovery, the diagnosis of neuroborreliosis was not retained, the explorations were cancelled, and the patient was not treated with an adapted antibiotic regimen.

Nineteen months later, the patient came back due to recurrence of dysphonia. This time, video-fibro-stroboscopy revealed left VFP (figure 2). A new workup with MRI, cervico-thoracic scan, and biology was prescribed. The BB serology was positive for IgG at 68 U/mL (reference <10 U/mL), IgM index >6 (reference <1.10), and both confirmed by immunoblot with four positive markers for IgG (Euroline RN-AT; VIsE ba, VIsE bb, P39, and OspC antigens) and IgM (Euroline RN-AT-adv; four types of OspC bands), which once again suggests the presence of an active Lyme disease infection. Other serological tests for potential causes were negative (i.e., syphilis, toxoplasmosis, EBV). A lumbar puncture and CLIA revealed the presence of IgG against BB at a level of 46.1 UA/mL (reference <5.5 UA/mL). An extremely high antibody index (AI) of IgG intrathecal synthesis was calculated (281.33, positive if >1.5). We observed a massive intrathecal secretion of IgG against BB, evoking the high probability of Lyme neuroborreliosis (LNB).

The other CSF characteristics were normal cell count (no pleocytosis) and normal level of sodium, potassium, total protein, glucose, and albumin. The patient was treated with oral doxycycline 200 mg daily for 21 days. A progressive recovery of vocal fold mobility was observed and was complete after 8 weeks. Since then, the patient has been asymptomatic with normal laryngeal mobility (figure 3).

Therefore, this is a case of successive VFP, first on the right side and then on the left side, with serological evidence of Lyme disease in both episodes.

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## Discussion

The etiology of unilateral VFP is established by a diagnostic work-up comprising diagnosis of tumoral compression/invasion of the vagus or laryngeal nerves, mainly via CT of the neck and thorax and cerebral MRI; neurological conditions (e.g., SLA, multiple sclerosis, Guillain-Barré, Parsonage and Turner); and medical illness comprising thyroiditis, diabetes, infection due to viral illness, neurosyphilis, or infection by BB. In the case of our patient, our diagnostic exploration revealed well-balanced type 2 diabetes, strong serological positivity for BB during both episodes, confirmation of intrathecal secretion of specific IgG against BB during the second episode of VFP, and the absence of other obvious causes of unilateral VFP.

The following questions need to be addressed: Are both episodes possible expression of LNB? If so, are we confronted with relapse or re-infection by BB?

Borreliosis is a zoonosis caused by a spirochete bacterium (i.e., BB) transmitted by the bite of a female tick, *Ixodes ricinus*<sup>2 3 4 5 6</sup>. The probability of developing borreliosis after a tick bite is less than 5%.

The mean incidence of Lyme disease in Belgium between 2015 and 2017 was estimated to be 5.9 cases/100,000 inhabitants/year for late/or disseminated Lyme disease and 97.6 cases/100,000 inhabitants/year for early cutaneous manifestations as erythema migrans (EM), mostly in humid and wooded areas<sup>5 7</sup>.

Lyme disease can affect many systems and organs (skin, joints, heart and ophthalmologic manifestations), including the central and peripheral nervous systems<sup>5</sup>. In the case of neurological involvement, it is most commonly called neuroborreliosis or LNB, which may appear rapidly or late after the tick bite and is not always associated with the eruption of EM<sup>5</sup>. Neurological manifestations are the second most common manifestation after cutaneous manifestations (6.5%-15% in France), appear mostly early (<6 months), and represent 6-15% of untreated borreliosis cases<sup>2 6 8 5</sup>. The manifestations include lymphocytic meningitis, encephalopathy, mononeuritis, and polyneuropathy<sup>5</sup>. The LNB reported in Europe is caused by *Borrelia garinii* in two-thirds of cases and *Borrelia afzelii* in one-quarter of cases<sup>5</sup>.

When a cranial nerve is involved, in most cases it is the facial nerve with the development of unilateral or bilateral peripheral facial paralysis (36% of neuroborreliosis)<sup>4 5</sup>. Vagus nerve involvement is unusual; rare clinical cases have reported unilateral cord paralysis or bilateral cord paralysis, but never a successive right and left VFP as observed in our case<sup>3 4</sup><sup>9</sup>. The physiopathology of peripheral mononeuropathy in LNB is still not completely elucidated. Questions remains as to whether there is direct nerve infiltration by the pathogen, an auto-immune response, or inappropriate production of inflammatory cytokines<sup>2</sup>.

Neurological symptoms are classified into early manifestations and late manifestations of LNB. The early manifestations of LNB touching the nervous system comprise Bannwarth syndrome (meningo-radiculo-neuritis), which is the most common manifestation of acute borreliosis in adult patients in Europe and associated with segmental pain, paresis, and cephalalgia; cranial neuropathy, mostly facial paralysis (bilateral in 40% of the cases); and Guillain-Barré syndrome<sup>10</sup>. In the rare condition of late neuroborreliosis, symptoms may be mononeuropathy, radiculopathy, or polyneuropathy. In Europe, polyneuropathy with variable paresthesia is typically accompanied by acrodermatitis chronica atrophicans<sup>10 11</sup>.

Diagnosis of borreliosis, and in our case of neuroborreliosis, can be difficult and is clearly underestimated. Laboratory diagnosis of LNB is challenging and a diagnostic algorithm is lacking<sup>12</sup>. Serological testing is an initial screening test (ELISA or CLIA) based on antibodies against BB: anti-Borrelia IgM (positive after 2 weeks) and anti-Borrelia IgG (positive after 6 weeks), which has good sensitivity but lower specificity, resulting in false positives. When the initial test is positive or doubtful, another more specific test, immunoblot, is performed to confirm the positivity<sup>6 13 10 12</sup>. Immunoblotting detects and identifies antigens specific to Borrelia. Ten markers are known to confirm and characterize the infection (Table 1). The serological standards and markers tested may vary between laboratories.

The variable major protein-like sequence, expressed (VlsE) antigen is a surface protein of BB that plays a key role in the survival strategy of Borrelia. In acute Borrelia infections, antibodies against OspC are the most important serological marker and highly specific for IgM detection. P39 is also a highly specific Borrelia antigen. However, serological

evaluation and interpretation of patients with Lyme disease is difficult because the dynamics of antibody levels are highly variable and unpredictable in the future, especially in cases with successive extracutaneous symptoms. Furthermore, reversion to seronegativity is rare even after correct antibiotic treatment<sup>14</sup>. Prolonged seropositivity with persistently high levels of IgG and IgM has been described for months to years in patients with Lyme disease, rendering it difficult to conclude if the infection is recent or old<sup>14 6</sup>. IgM may not be observed if biological screening is delayed as in the case of our patient's first episode of VFP. Without any other demonstrated etiology explaining the first episode of right VFP, we initially concluded it was of idiopathic origin.

Notably, a diabetic cranial neuropathy has been considered but there are no cases described in the literature and this is usually associated with pain<sup>15</sup>. However, the serological evidence of high IgG levels against BB confirmed by two positive markers for BB on immunoblot (VIsE, p39) can be a solid argument for the first episode of LNB in our patient.

In cases of suspected LNB with serology suggestive of BB infection, lumbar puncture is indicated to calculate the AI for IgG<sup>5 8</sup>. Calculation of the AI for specific antibodies demonstrates a specific immune response to *Borrelia* in the central nervous system (not just passive diffusion of antibodies from serum into the CSF). This index is calculated by dividing the CSF antibody concentration by the serum antibody concentration corrected by the CSF/serum albumin quotient to avoid false positives due to rupture of the blood-brain barrier. This index is highly reliable because it has high specificity and sensitivity but can still be negative if it is done too early (<6 weeks of infection)<sup>2 6</sup>. When positive, it is usually associated with lymphocytic meningitis (pleocytosis and protein in the CSF).

Unfortunately, lumbar puncture was not performed in our case during the first episode of VLP due to spontaneous recovery and CSF analysis could not be performed according to the European Federation of Neurological Societies (EFNS) guidelines. When our patient presented again 19 months later with a VLP on the opposite side, we observed IgM seropositivity and a persistence of anti-*Borrelia* IgG. A lumbar puncture revealed the presence of IgG against BB. A very high, unusual AI for IgG was calculated, confirming massive intrathecal secretion of IgG against BB and evoking the high probability of LNB.

In Europe, most authors consider the production of intrathecal antibodies against BB as a keystone for the diagnosis of LNB<sup>5 8 10 12 18 16</sup>.

The albumin quotient (Qalb) was normal in our case; thus, the hemato-encephalic barrier was preserved, though dysfunction of the blood-CSF barrier has been observed frequently in LNB<sup>16 10 17</sup>. European guidelines for LNB (2010) are strict and include three criteria to conclude “definite” LNB: the presence of suggestive neurological symptoms, pleocytosis, and intrathecal antibody production against BB<sup>1 11 3 5 6</sup>. If two criteria are fulfilled, the EFSN guidelines consider the diagnosis of LNB as “possible”.

CSF findings in adults with acute LNB usually show elevated cell counts (pleocytosis), together with intrathecal immunoglobulin production, usually with an IgM dominance and blood-CSF dysfunction<sup>17</sup>. In our case, the CSF analysis varied from this description: no IgM, no pleocytosis, no blood-CSF dysfunction. Rare cases of neuroborreliosis without CSF pleocytosis have been described, but these are controversial. Three situations have been highlighted, the first of which is a previous history of infection by BB or a long history of illness, suggesting that the presence of an initial pleocytosis resolved itself with time. Conversely, it may also be a very brief illness with a test performed too early. In these cases, antibiotic treatment was still prescribed and all patients improved their symptoms<sup>19</sup>.

If we look at the clinical presentation of our patient’s second episode of VFP (isolated VFP, strong serological evidence of Lyme disease, extremely high AI index for IgG in the CSF without pleocytosis), this case possibly corresponds to the description of late LNB<sup>5 11</sup>. However, it is always difficult to distinguish early and late manifestations of Lyme disease for patients who have only extracutaneous symptoms such as LNB<sup>14</sup>. Guidelines note that late LNB cases have higher intrathecal IgG rates than early LNB<sup>10</sup>. According to EFSN guidelines, our case has diagnostic characteristics of “possible” LNB<sup>1</sup>.

Differences in guidelines from scientific societies show how difficult it is to establish a definitive diagnosis of LNB because of the constellation of clinical findings and laboratory data. The clinical history, serological findings with very high specificity tests, and the very high value of the IgG intrathecal production index are, in our opinion, arguments in favor of a probable diagnosis of LNB<sup>1 10 11</sup>.

The treatment of LNB consists of antibiotic therapy to accelerate eradication, improve healing, and prevent the emergence of late Lyme disease<sup>6</sup>. In the case of early neurological involvement, treatment with intravenous antibiotic therapy with ceftriaxone (2 g/day) for 14 days has been proposed by the EFSN guidelines<sup>1 10</sup>. However, recent research has shown that treatment with oral doxycycline (100 mg 2x/day) for 14 days is equally effective<sup>2 6 13</sup>.

For late LNB with peripheral neuropathy, the EFSN guidelines propose doxycycline (200 mg daily) or intravenous ceftriaxone (2 gr IV) for 3 weeks<sup>1 10</sup>. The prognosis after antibiotic treatment is very good as long as there is no severe initial deficit<sup>4</sup>. Oral treatment with doxycycline (200 mg daily) for 3 weeks in our case resulted in excellent evolution and the patient regaining normal laryngeal mobility in less than 8 weeks. Rapid disappearance of VFP after antibiotic treatment is, for some authors, a solid argument for LNB diagnosis<sup>2</sup>.

The observation of this unusual case leads to another important question: If these two episodes of VFP are manifestation of neuroborreliosis, is it a reinfection by BB or reactivation of latent Lyme disease? This case is the first report of probable relapse of laryngeal palsy successively on the right and then left side as a manifestation of Lyme disease. Unilateral and bilateral VFP have been described in the literature but never as separate and successive episodes affecting alternatively one side and then the other<sup>2 3 4</sup>. Successive episodes of facial palsy have been described in a 11-year-old girl in Germany; as in our case, facial palsy touched one side and then the contralateral side, but with a longer time elapsed between the two episodes (5 years), and reinfection was proven in this case, developing after a recognized tick bite. IgM antibodies were detected in both serum and CSF specimens<sup>20 21</sup>. Regarding the distinction between early and late manifestations, the distinction between relapse and re-infection is difficult in the absence of cutaneous symptoms<sup>14</sup>.

Reinfections are common in endemic areas and are usually cutaneous manifestations as EM. These reinfections are caused by species of *Borrelia* distinctly different from the one causing the original infection or by different strains within a particular species of *Borrelia*. In the United states, at least 17 subtypes of BB are associated with clinical illness (strains

classified according to the allele of the highly variable outer-surface protein (OspC) encoding gene)<sup>22</sup>. These frequent reinfections are explained by the weak immune response generated by a skin manifestation that cannot protect against future recurrent infections, in contrast to more severe and extracutaneous manifestations, such as neuroborreliosis<sup>14 22 23</sup>. As for reactivation of Lyme disease, this is an understudied concept, especially in patients who were not correctly treated during the first episode, as in our case. There is a rarity of reports of recurrent cases of LNB because the first episode could give a partial to complete protective immune response. However, reactivation has been described for other diseases caused by another spirochetes, such as syphilis or relapsing fever, which leads us to believe that it could also be possible for borreliosis<sup>24 25</sup>.

In an article treating reinfection with Lyme disease, the authors concluded that, considering the limited available data, no pattern of serological response has been identified that would differentiate re-infection from initial infection with BB and insist on the difficulty in distinguishing relapse from new infection if cutaneous symptoms are absent<sup>14</sup>.

In summary, our patient presented with an episode of VFP due to highly probable neuroborreliosis based on CLIA, immunoblot blot, and AI-positive CSF. This second episode makes us reconsider the "idiopathic" etiology of our first episode given the history of seroconversion for *Borrelia* IgG. Given the low probability of a patient presenting with recurrent idiopathic paralysis episodes, we suggest a possible relapse of a latent infection or the emergence of a new infection. The support for reactivation includes the absence of correct antibiotic treatment of the first episode of laryngeal palsy and a symptomatology of extracutaneous symptomatology, which could generate sufficient protection against re-infection. However, supporting the possibility of reinfection to explain the second episode of laryngeal palsy is the absence of IgM seropositivity during the first episode of laryngeal palsy and its appearance in the second, but we lack a serological algorithm<sup>14</sup>.

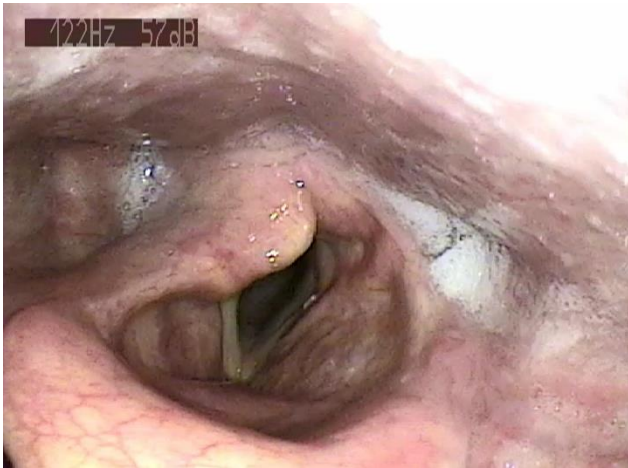
## Conclusion

We observed and treated a patient who presented with two episodes of possible LNB, both times manifesting as VFP. Unfortunately, the first episode of right cord paralysis lasting for several months with serological signs of infection by BB was not recognized as a manifestation of Lyme disease despite the absence of other possible etiologies for the laryngeal palsy. The patient recovered spontaneously without treatment. Nineteen months later, he presented a second episode of laryngeal paralysis on the contralateral side and possible neuroborreliosis was confirmed by lumbar puncture. Recovery was rapid after oral antibiotic treatment. To the best of our knowledge, this is the first case of successive laryngeal paralysis due to two distinct episodes of possible LNB. Unfortunately, the data in our possession does not permit us to conclude in favor of re-infection or re-activation of the illness.

This case and the rarity of clinical reports and serological findings in cases of Borreliosis in the literature warrant future investigations to better characterize the clinical symptoms and serological responses associated with separate episodes of Lyme disease.



**ANNEXES**



*Figure 1: Right vocal fold paralysis*



*Figure 2: Left vocal fold paralysis*



*Figure 3: Normal laryngeal mobility indicating total recovery*



| Marker | Description   |
|--------|---|
| P100   | Marker of old infection   |
| VlsE   | Variable major protein-like sequence, expressed antigen is a surface protein of BB that plays a key role in the survival strategy of Borrelia |
| p58    | Non-specific  |
| p41    | Flagellum protein common to all spirochetes, non-specific.  |
| p39    | Membrane protein and usually a marker of old infection  |
| OspA   | Surface protein and usually a marker of old infection   |
| OspC   | Outer surface protein C, marker of an early stage of infection; specific marker often associated with p41, highly specific for IgM detection  |
| P18    | Surface protein and marker of old infection, specific marker  |

*Table 1: Immunoblot markers and characteristics*

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**Declaration of interests**

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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