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Review article

Role of phrenic nerve in respiratory distress secondary to Lyme neuroborreliosis

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ABSTRACT

Introduction: Critical importance of phrenic nerve, in patients with Lyme disease is discussed.
Aim: This paper addresses the critical importance of phrenic nerve and Lyme disease.
Material and methods: Medline searches were conducted in context of phrenic nerve, Lyme neuroborreliosis, thoracic diaphragm, and respiratory distress.
Results and discussion: The advancements in treatment options in Lyme disease were reviewed using current literature. Applied anatomy of the phrenic nerve and its dysfunction in neuroborreliosis is described in the article.
Conclusion: This paper reviews the literature pertaining to the importance of the phrenic nerve in Lyme disease.

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1. Introduction

The phrenic nerve descends from the 3rd, 4th, and 5th cervical nerves to innervate the lung, heart and diaphragm. This nerve carries motor, sensory and sympathetic nerve fibers for diaphragmatic function that is essential in respiration. Breathing occurs because sensory and motor information are exchanged between the phrenic nerve and the diaphragm. Diseases and dysfunction of phrenic nerves result in respiratory distress. One of the most rare manifestations of phrenic nerve disorder is neuroborreliosis, which may present itself with Lyme disease.[1]

2. Aim

This paper addresses the critical importance of phrenic nerve and Lyme disease.

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Abbreviations: DHI, diaphragmatic height index; CDC, Centers of Disease Control and Prevention.

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3. Material and methods

Medline searches were conducted in context of phrenic nerve, Lyme neuroborreliosis, thoracic diaphragm, and respiratory distress.

4. Results and discussion

4.1. Anatomy

Large contribution of the phrenic nerve comes from the C4's ventral ramus, but the nerve receives contributions from the C3 and C5 as well. The accessory phrenic nerve serves as the branch to the subclavius and joins the phrenic nerve in the thorax. Due to phrenic nerve's extensive anatomy, it can be divided into the cervical and thoracic portions. The cervical portion of the nerve stretches from the cervical plexus to the anterior surface of the scalenus anterior muscle. The right phrenic nerve descends through mediastinum, parietal pleura and the pericardial sac. It passes along the superior vena cava, travels next to the right atrium, and leaves through the inferior vena cava opening. The nerve may pass near the right superior pulmonary vein. The left phrenic nerve descends behind the innominate vein, passes near the aortic arch, pulmonary trunk, left atrial appendage, and then travels along the lateral border of the left ventricle to innervate the diaphragm.[2]

4.2. Relation to Lyme disease (Lyme neuroborreliosis)

Lyme neuroborreliosis is defined as neurological involvement of manifested Lyme disease. Lyme disease is a bacterial infection elicited by tick-borne bacteria spirochete, *Borrelia burgdorferi*. This double-membrane bacterium is primarily injected into the skin by bites of the genus *Ixodes* ticks. Thus, the disease is commonly diagnosed in patients who reside in densely wooded area, where human to deer contact often occurs. During the early-localized infection stage, the infection is detected by skin rash.

The early disseminated stage of Lyme disease infection comes weeks to months after the bite. The infection typically spreads through hematological or lymphatic routes to distant sites. Weeks to months after the infection, about 15% of untreated patients exhibit neurological conditions such as meningitis and cranial neuritis. In 5–10% reported cases, patients exhibit Lyme neuroborreliosis. The chronic stage symptoms primarily arise from rheumatologic and neurological disturbances.

Lyme neuroborreliosis is divided into categories of early, late, or chronic stages. It is in later stages of the disease that neurological symptoms begin to manifest. Three to six weeks after infection, Lyme neuroborreliosis results as lymphocytic meningoradiculoneuritis.[3]

Diaphragmatic complications from Lyme neuroborreliosis are unusual cases of Lyme disease. Diaphragmatic or respiratory disturbances in the presence of Lyme neuroborreliosis are recorded in only a few published cases. Most of these cases involve elderly patients with a few middle-aged patients who exhibit respiratory weakness or failures. *B. burgdorferi* infection was detected through serological testing for Lyme disease.

Lyme neuroborreliosis symptoms are caused by painful radiculitis. The pathogenesis is axonal injury of nerve segments caused by lymphocytic perineuritis. Lymphocytic inflammation is confirmed by the presence of meningeal and root inflammation in cerebrospinal fluid. The central nervous system becomes more involved in the late stage of Lyme neuroborreliosis (Tables 1 and 2).[3]

4.3. Epidemiology

Analyses of cases between 1991 and 2005 in the Northeastern United States had high incidence of Lyme disease.[40] Another region of high incidence of Lyme disease was prevalent in Nova Scotia, Canada.[41]

4.4. Clinical presentation

Patients who suffer from phrenic dysfunction secondary to Lyme neuroborreliosis manifest with severe pain in their abdominal, neck, or upper back. Dyspnea, diplopia, dysuria and flu-like symptoms have been presented as well. Tick head or bite marks were recovered from some, while others had no tick bites. Unilateral or bilateral facial palsy indicates cranial symptoms. In children, the primary symptoms are of meningitis (Table 3).[3]

4.5. Treatment

Treatment of phrenic nerve dysfunction in relation to Lyme neuroborreliosis is intravenous ceftriaxone that ranges up to 30 days. Depending on the severity of the patient's respiratory performance, mechanical or non-invasive ventilation is also administered as necessary. Tetracyclines (such as doxycycline) are used extensively because of their various antimicrobial uses and relatively safe properties. Oral doxycycline has also been used as a treatment option and is preferred over

Table 1 – Diagnosis of phrenic dysfunction and Lyme neuroborreliosis.

Diagnosis of phrenic dysfunction	Diagnosis of Lyme neuroborreliosis – eMedicine
• Diaphragmatic height index (DHI)[4]	• Early stage, clinical presentation
• Introcardiac echocardiography (early detection during cryoballoon pulmonary isolation)[5]	○ History of tick exposure or bite
• Fluoroscopy[6]	○ Presence of erythema migrans
• Electrophysiological phrenic nerve testing after cardiac surgery[7]	• Positive anti-*B burgdorferi* antibody index
• Hemidiaphragm elevation	

Table 2 – Etiology of phrenic dysfunction.

Etiology of phrenic dysfunction	References
Adult	
• Mechanical injury during artery harvesting	Deng et al.[8]
• Cardiac surgery	Aguirre et al.[9]
• Pacemaker pulse generator replacement	Harris et al.[10]
• Internal jugular venous catheter placement	Ahn et al.[11]
• Open-heart surgery	Ataka et al.[12]
• Coronary artery bypass	Alexander[13]
• Cold-induced injury	Brodaty et al.[14]
Ablation methods	
◦ Cryoballoon	Andrade et al.[15]
◦ Radiofrequency	Bunch et al.[16]
◦ Epicardial and endocardial	Sánchez-Quintana et al.[17]
Pediatric	
• Erb's palsy	Al-Qattan et al.[18]
Cardiac surgery	
• Dissection near phrenic nerve	Georgiev et al.[19]
• Blalock Taussing shunt-surgical method	de Jong and Manni[20]
• Brachial plexus avulsion	Karaoğlu et al.[21]
• Thoraenthesis for TPM effusion	Ozdemir et al.[22]
During delivery	
• Traumatic delivery	Stramrood et al.[23]
• Birth trauma	Shiohama et al.[24]
Thoracic interventions	
• Lung transplant	Ferdinande et al.[25]
• Thymectomy	Ostrowska and de Carvalho[26]
• Thoracotomy	Helps et al.[27]
Other procedures	
• Catheterization	Işlek et al.[28]
• Laparotomy	Taşkınlar et al.[29]
• Neck dissection	de Jong et al.[20]
• Tracheoesophageal fistula repair	Henderson and Spigland[30]
• Interscalene block	De and Hayes[31]
• Liver transplantation	McAlister et al.[32]
• Intercostal drainage	Odita et al.[33]
Traumatic injury	
• Chronic cervical spinal cord injury	
• Blunt trauma	Ulku et al.[34]
Disease and medical condition	
• Lyme neuroborreliosis	Abbott et al.[1]
• Diabetes	Fisher et al.[35]
• Turner syndrome	Odell et al.[36]
• Charcot–Marie–Tooth disease	Abboud et al.[37]
• Brachial neuritis	Barraclough et al.[38]
• Benign thyroid goiter	Manning et al.[39]

conventional tetracyclines because of its lipid solubility characteristics and ability to cross the blood-brain barrier.[46] The length of doxycycline treatment is about 21 days. A study was conducted on 29 patients with Lyme neuroborreliosis, facial nerve palsy, and meningitis who were treated with oral doxycycline. The cerebrospinal fluid in these patients show a decrease in inflammatory cells and protein concentrations compared to pretreatment levels, thus suggesting that doxycycline is an effective and convenient therapy for Lyme disease-associated facial palsy.[47]

Table 3

Patient	Symptoms	Reference
Female, 59 years old	– Tick head recovered from patient – Abdominal pain – Weakness in the right side of the body (fell often resulting in bruises) with back twitches for a month – Flu-like symptoms – Day of presentation, cough, reduced appetite, abdominal distension, constipation and dysuria (painful or difficult urination) – Some epigastric (upper mid-abdomen) tenderness	Abbott et al.[1]
Female, 64 years old	– Severe neck and upper back pain – Severe sinus-like frontal headaches – Erythematous papular rash on the forearm that became gradually larger – Facial palsy	Ishaq et al.[42]
Male, 68 years old	– Severe dyspnea, lancinating cervical pain, drowsiness – Several tick bites reported	Winterholler and Erbguth[43]
Male, 67 years old	– Severe dyspnea, diplopia and headache	van Egmond et al.[44]
Male, 30 years old	– Flu-like symptoms with dyspnea present a few months earlier – Back pain after fall at construction work	van Egmond et al.[44]
Male, 74 years old	– Severe, bilateral, thoracic shooting pain – Pain spread to the back, shoulder blades and C6 dermatome – Dyspnea – Tick bites and erythema migrans reported yet never was treated for Lyme disease	van Egmond et al.[44]
Huntsman, 87 years old	– Severe headache – Shooting pain on the left sided thoracic pain – Fatigue, vertigo – Facial weakness resulted in right facial palsy, dysarthria (trouble with speaking) and dysphagia (problem with swallowing) – Reported tick bites with absence of erythema migrans	Djukic et al.[45]

Studies have stated that ceftriaxone, cefotaxime and penicillin are also effective in the treatment of neuroborreliosis. One particular study followed 21 patients with severe Lyme neuroborreliosis radiculitis. The patients were given a

10-day treatment with either penicillin or cefotaxime. It was found that cerebrospinal fluid antibiotic concentrations increased the most with cefotaxime use, which offered the most hope for long-term prognosis of the disease. Ceftriaxone was also found to be effective in children with a recommended treatment of 14–28 days.[48] Administration of oral doxycycline was conducted for the duration of three weeks. Palsies of the face and diaphragm were resolved within eight weeks.[49]

4.6. *Centers of Disease Control (CDC) and Prevention recommendations for Lyme disease*

CDC's recommendation for diagnosing Lyme disease is based on identifying the signs and symptoms the patient presents regarding Lyme disease. Another useful method for diagnosing Lyme disease is the use of laboratory blood tests. However, this test should only be used when patients show symptoms of Lyme disease.[50]

CDC recommends the use of oral administration of antibiotics in the early stage of the disease, which results in rapid recovery. Patients with neurological and cardiac forms of the disease require intravenous treatment. Patients generally recover within a few weeks of antibiotic treatment.[51]

5. Conclusion

Neuroborreliosis and its relationship to phrenic nerve dysfunction are discussed and pertinent literature is reviewed.

Conflict of interest

The authors declare that they have no conflict of interest.

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